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Synaptic Control of Motoneuronal Excitability

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Rekling, Jens C., Gregory D. Funk, Douglas A. Bayliss, Xiao-Wei Dong, and Jack L. Feldman. Synaptic Control of Motoneuronal Excitability. *Physiol. Rev.* 80: 767–852, 2000.—Movement, the fundamental component of behavior and the principal extrinsic action of the brain, is produced when skeletal muscles contract and relax in response to patterns of action potentials generated by motoneurons. The processes that determine the firing behavior of motoneurons are therefore important in understanding the transformation of neural activity to motor behavior. Here, we review recent studies on the control of motoneuronal excitability, focusing on synaptic and cellular properties. We first present a background description of motoneurons: their development, anatomical organization, and membrane properties, both passive and active. We then describe the general anatomical organization of synaptic input to motoneurons, followed by a description of the major transmitter systems that affect motoneuronal excitability, including ligands, receptor distribution, pre- and postsynaptic actions, signal transduction, and functional role. Glutamate is the main excitatory, and GABA and glycine are the main inhibitory transmitters acting through ionotropic receptors. These amino acids signal the principal motor commands from peripheral, spinal, and supraspinal structures. Amines, such as serotonin and norepinephrine, and neuropeptides, as well as the glutamate and GABA acting at metabotropic receptors, modulate motoneuronal excitability through pre- and postsynaptic actions. Acting principally via second messenger systems, their actions converge on common

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effectors, e.g., leak K^+ current, cationic inward current, hyperpolarization-activated inward current, Ca^{2+} channels, or presynaptic release processes. Together, these numerous inputs mediate and modify incoming motor commands, ultimately generating the coordinated firing patterns that underlie muscle contractions during motor behavior.

I. INTRODUCTION

Motoneurons transform the internal actions of the brain into behavior, translating patterns of interneuronal activity into commands for skeletal muscle contraction and relaxation. Every movement, whether simple (knee-jerk reflex, postural maintenance), rhythmic (locomotion, respiration), or complex (playing the piano, hitting a baseball, speaking), is the consequence of a highly detailed and precise pattern of activity of many populations of motoneurons, convolved with the biomechanical properties of the skeletomuscle system. Although the signal processing underlying the distribution of inputs between and within motoneuron pools determines the basic features of any movement, the final arbiters of nervous system output are motoneurons. How motoneurons respond to their inputs, and how their responses are regulated, is of interest and the subject of this review.

Sherrington (1142) introduced the concept of motoneurons as the final common path, representing the penultimate link between the central nervous system (CNS) and motor behavior. Since then, motoneurons have attracted the attention of investigators studying the cellular physiology of central neurons for several reasons. *1*) The function of motoneurons is well defined, i.e., causing contraction of striated muscle. *2*) With the advent of intracellular recording techniques, it was possible to study the electrical properties of these large accessible neurons, which can be readily identified in physiological experiments by antidromic invasion from specific muscle nerves (141). *3*) Multisensorial inputs from muscles, joints, and skin produce synaptic potentials in motoneurons, and experimental access to these pathways paved the way for studies of synaptic transmission in the CNS and of simple reflex pathways in mammals (317, 436). Numerous major reviews have been published on motoneuron physiology; among the more notable are References 49, 107, 161, 162, 475.

From Sherrington to Eccles, motoneurons were the paradigmatic neurons of the brain. Many fundamental and general properties of neurons and synaptic transmission were first identified in motoneurons, e.g., quantal release, inhibitory transmission, and the consequent conclusion that chemical neurotransmission is the principal form of interneuronal communication. In the past decade, interest in motoneurons has waned as intense investigation of other regions of the brain has led to an encyclopedic identification of neuronal properties not typically associated with motor control, e.g., long-term potentiation observed in hippocampal neurons and proposed to be a component of learning. One difficulty in contextualizing all of this information is that many of these well-characterized properties have been identified in neurons in the absence of data concerning how these neurons process signals in actual behavior. Here, motoneurons have a unique advantage since we know precisely *1*) the information coding of their output signals, i.e., contraction of the innervated muscle fibers, and; *2*) in many cases, their activity during complex behaviors, either indirectly by observing movements or recording muscle activity, or directly by recording from their axons or better yet their cell bodies. This provides a context for understanding and interpreting data that should be more highly valued. One goal in this review is to emphasize this perspective. We review studies, with emphasis on recent work, describing the passive and active membrane properties of spinal and cranial motoneurons, anatomical organization of their synaptic input, and the actions of different transmitter systems on the control of motoneuronal excitability (see Fig. 1). Most of these studies were done without addressing issues that were and remain the focus of many studies of motoneurons, such as the physiological relevance and characterization of *1*) different motor unit types, e.g., fast

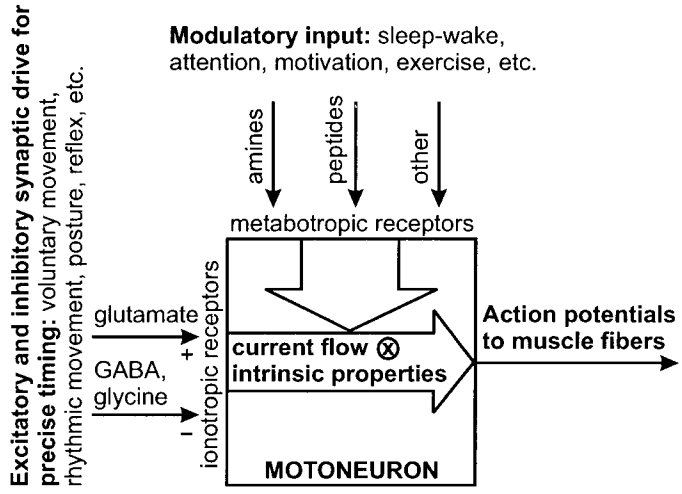

FIG. 1. Overview of control of motoneuronal excitability. Precise timing of voluntary movements, rhythmic movements, afferent reflexes, and other motor acts is mediated primarily by excitatory and inhibitory synaptic drive to motoneurons using glutamate, GABA, and glycine. These transmitters activate ionotropic receptors generating synaptic current in motoneurons, which is convolved with intrinsic membrane properties to produce action potentials, which trigger muscle contraction. Modulatory systems, using amines, peptides, and other transmitters, act (mostly) through metabotropic receptors to modify excitability via changes in postsynaptic ion channel function and presynaptic release processes. These various modulatory systems produce changes in excitability related to the sleep-wake cycle, motivation, and exercise.

fatigue resistant, fast fatigable, slow fatigue resistant; *2*) the mechanisms underlying their orderly recruitment, i.e., the size principle; and *3*) the synaptic inputs from multiple classes of afferent fibers. We refer the reader to several excellent reviews on these important issues (49, 107, 475, 1103). We further limit our discussion to mammalian α-motoneurons, with a few notable exceptions involving motoneurons from other vertebrates, where some motoneuronal properties have been studied in more detail. There are important differences between the properties of motoneurons in newborn compared with those in adult mammals, both with respect to cellular properties and actions of transmitters; where such differences may reflect on the control of excitability, we have separated the description of the two groups.

II. MOTONEURONS

A. Embryonic Development and Anatomical Organization of Motoneurons

Motoneurons are generated from progenitor cells in the ventral region of the neural tube early in embryonic development (145, 1230). The inductive signal in this process is the Sonic Hedgehog glycoprotein (SHH), which is secreted by axial mesodermal cells of the notochord (214, 319, 339, 340, 799, 1054, 1397). The extracellular matrix protein vitronectin may act as a downstream effector or a synergistic factor in SHH-induced motoneuron differentiation (803). The transcription factor MNR2 functions as a neural determination gene, and its expression initiates motoneuron differentiation (1233). Further motoneuronal differentiation requires expression of the LIM homeodomain transcription factor, Islet1 (*Isl-1*), since animals in which *Isl-1* function has been eliminated do not generate motoneurons (980). Diversification of motoneuron subtypes in the spinal cord is controlled by the differential expression of four LIM homeodomain proteins (*Isl-1*, *Isl-2*, *Lim-1*, *Lim-3*) (32, 763, 1230, 1254, 1276). At the time of their birth, all classes of motoneurons express *Isl-1* and *Isl-2*, but at the time of axon extension, the four LIM factors show a stereotyped expression pattern in functional subclasses of spinal motoneurons: *1*) motoneurons innervating axial muscles express *Isl-1*, *Isl-2*, and *Lim-3*; *2*) motoneurons innervating ventral limb muscles and body wall express *Isl-1* and *Isl-2*; and *3*) motoneurons innervating dorsal limb muscles express *Lim-1* and *Isl-2*. Early-born motoneurons in the lateral motor column (LMC) at the brachial and lumbar levels synthesize a retinoid that induces late-born LMC motoneurons to migrate past the early-born LMC motoneurons to the ventrolateral spinal cord (1172); this suggests that neuronally released retinoids may coordinate subtype identity of spinal motoneurons innervating limb muscles. Genes of the LIM homeodomain class are also expressed differentially among cranial motor nuclei (1307). Their function is presently unknown; they may regulate receptors for guidance cues that direct axons selectively along distinct pathways to regions outside the spinal cord (763). Thus inductive signals from the notochord establish the identity of motoneurons, and local signals (possibly from the paraxial mesoderm) induce a differential expression pattern of LIM factors determining the motoneuronal subtype. Once the induction and functional differentiation of motoneurons has occurred, survival of developing motoneurons depends on muscle-derived factors and/or functional changes in the state of the motoneurons, i.e., from growing cells to transmitting cells (440, 936). The nature of the muscle-derived growth molecules is largely unknown, but one, hepatocyte growth factor/scatter factor, is necessary for survival of a subpopulation of limb-innervating motoneurons (1399). The molecular basis for motoneuronal innervation of specific muscles is being elucidated in model systems such as chick hindlimb muscles, zebrafish axial muscle, and *Drosophila* abdominal body wall muscle (cf. Ref. 325). However, the genetic determinants controlling subtype-specific development of motoneuronal morphology, intrinsic electrical properties, and CNS connectivity are largely unknown.

In the fully developed mammal, motoneuron groups are somatotopically organized (475, 502, 822, 916, 1055). Spinal cord motoneurons are in lamina IX of the ventral horn, divided into a medial and a lateral column. Motoneurons in the medial column innervate axial muscles, and those in the lateral column, present at the cervical, upper thoracic, and lumbosacral levels, innervate limb muscles. In the lateral column, motoneurons innervating distal muscles are more dorsal. In the rostrocaudal direction, motoneuron groups innervating single muscles span one to several spinal segments. Cranial, i.e., brain stem, motoneurons are not organized in a continuous column as in the spinal cord but form distinct nuclei, with an intrinsic somatotopic organization (297, 664).

The size and dendritic arborization of spinal and cranial motoneurons vary considerably. Consider, for example, cat hindlimb motoneurons. They have medium to large somata with a diameter of 30–70 μm (246, 1287, 1298, 1435) and 5–20 stem dendrites, which have a diameter of 0.5–19 μm and ramify extensively over a mean path length of ~1,200 μm, giving rise to ~150 dendritic terminations. The dendrites tend to project in the longitudinal direction (247), a phenomenon seen in many types of spinal motoneurons (178, 283, 1189).

B. Passive Membrane Properties of Motoneurons

The dendritic membrane constitutes >97% of the total membrane surface area in cat spinal motoneurons

(246), with 61% of the stem dendrites and 12–33% of more distal dendrites covered by synaptic boutons (937). Consequently, the vast majority of synaptic inputs to motoneurons are dendritic, and integration of synaptic potentials is heavily influenced by the passive membrane properties of the dendrites (548, 1024). Synaptic current generated in a dendrite attenuates as it spreads electrotonically toward the soma, escaping through open channels in the membrane and charging the dendritic membrane capacitance. Determination of the geometrical features of the dendritic tree together with electrical parameters of the membrane [membrane resistance (R_m), membrane capacitance (C_m), and cytoplasmic resistivity (R_i)], provides an estimate of the attenuation of synaptic potentials. One useful parameter is the length constant, or space constant (λ), which is the distance over which a steady-state voltage is attenuated to 1/*e* (0.37) of its initial value.

Estimates of the electrotonic length of cat spinal motoneurons, based on recordings with sharp intracellular electrodes (which introduces an artifactual somatic shunt) and morphological reconstructions of the dendritic tree, are between 1.1 and 1.6 λ (63–65, 336, 369, 1288). Whole cell patch-clamp recordings (reducing somatic shunt artifacts) with two electrodes on the same soma from spinal cord motoneurons in juvenile rats estimates electrotonic length of uncut dendrites at 0.85 λ (1247). Thus a substantial fraction of a direct current in the dendrite reaches the motoneuronal soma, making the neuron relatively compact electrotonically for slowly changing currents. However, synaptic potentials have fast rise times, and the low-pass filtering properties (due to membrane charging) of dendrites distort and attenuate a synaptic signal more strongly than an applied steady-state voltage. This strong filtering property in cat motoneurons is mainly the result of a large membrane capacitance, and peak attenuations measured for fast synaptic currents in the distal dendrites range over 20- to 30-fold. A more direct approach to the measurement of dendritic attenuation is to study spinal motoneurons in culture (Fig. 2) (706, 1290). The electrotonic length of these neurons is ~0.7 λ; dual recordings (one electrode on the soma and one on a dendrite) give a 1/*e* attenuation corresponding to ~260 μm for excitatory postsynaptic potentials (EPSP) travelling from the dendrite to the soma (706). Interestingly, EPSP travelling from the soma to the dendrite are attenuated much less (1/*e* attenuation of ~710 μm), a result predicted by cable theory (188). The overall picture of the passive properties of motoneurons in culture is that the soma and dendrites are roughly isopotential for slowly varying potentials with fast voltage transients arising from synaptically generated currents more strongly filtered. Thus dendritic EPSP should produce smaller and more slowly changing somatic depolarization that could bring the membrane potential above threshold for firing but with a smeared temporal relation to underlying synaptic potentials. In contrast, EPSP in the somatic region should rise sufficiently fast that if they were above threshold, an impulse would be generated in close synchrony with the incoming synaptic potential.

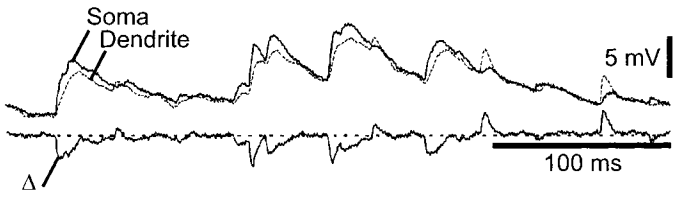

FIG. 2. Attenuation of synaptic potentials along a dendrite of a motoneuron in culture. *Top traces*: simultaneous recordings from 2 electrodes of spontaneous excitatory postsynaptic potentials (EPSP) from the soma and a dendrite. *Bottom trace*: difference of the 2 recordings. Note that early and late parts of the trace are dominated by somatic and dendritic EPSP, respectively. [Adapted from Larkum et al. (706).]

Spatial differences in the membrane resistivity will also affect integration of synaptic input. For example, in cat spinal motoneurons, the somatic membrane has a lower resistivity than the dendritic membrane (179, 369, 1288), perhaps due to the presence of somatic voltage-dependent K^+ channels (179). However, this difference may instead be due to a shunt induced by the recording pipette (1247). Ongoing synaptic input will also change the resistance of the dendritic membrane and the driving force for the synaptic current, and consequently affect synaptic integration. An estimated fivefold decrease in the membrane resistivity will result if all of the excitatory boutons impinging on a spinal motoneuron release transmitter at a rate of 30 quanta/s (107). The synaptically generated shunt of the motoneuronal membrane in an intact behaving animal has yet to be measured.

C. Active Membrane Properties of Motoneurons

The dynamic regulation of motoneuronal excitability is largely determined by voltage-gated channels, which also are the targets for several neuromodulators affecting excitability (Table 1).

1. Na^+ currents

All motoneurons have a fast inactivating Na^+ current ($I_{Na\,i}$), which underlies Na^+-dependent action potentials. The exact membrane distribution of inactivating Na^+ channels (Na_i channels) is presently unknown. Because action potentials initiate in the unmyelinated initial axon segment, this region may have a higher concentration of Na_i channels (34, 66, 141, 200, 240, 861, 1114). Normally, initial segment action potentials invade the somatodendritic membrane and give rise to action potentials, with inflections in typical intracellular recordings referred to as IS and SD spikes (66, 240, 454, 870, 919). Na^+ channels

TABLE 1. *Membrane currents in motoneurons, their proposed function, and modulation by transmitters*

Current (Ions)	Proposed Function	Transmitter Modulation	Transmitter Reference No.
$I_{Na\,i}$ (Na^+)	Action potential		
$I_{Na\,p}$ (Na^+)	Acceleration of membrane potential to spike threshold, amplify EPSP, linearize firing with increased current input	5-HT	527
$I_{K\,leak}$ (K^+)	Resting V_m	TRH, SP, NE, 5-HT, Glu (metabotropic)	77, 287, 302, 367, 526, 703, 958, 1039
I_{Kir} (K^+)	Resting V_m, stabilize V_m around rest		
I_{Kdr} (K^+)	Action potential repolarization, fAHP		
I_h (K^+, Na^+)	Resting V_m, stabilize V_m around rest, rebound potentials	5-HT, NE	526, 702, 959
I_A (K^+)	Resting V_m, control onset of firing	NE	958
$I_{Cl\,leak}$ (Cl^-)	Resting V_m		
$I_{K\,Ca(BK)}$ (K^+)	Action potential repolarization		
$I_{K\,Ca(SK)}$ (K^+)	AHP		
$I_{Ca\,HVA}$ (Ca^{2+})	ADP, AHP, plateau potentials	5-HT Adenosine, Glu (metabotropic)	73, 285, 287, 521, 796, 882
$I_{Ca\,LVA}$ (Ca^{2+})	ADP, action potential repolarization	5-HT	93
$I_{Na\,Ca}$ (Na^+)	Plateau potentials, afterdepolarization in specialized motoneurons		
$I_{K\,Na}$ (K^+)	Postdischarge hyperpolarization		

EPSP, excitatory postsynaptic potential; V_m, membrane potential; fAHP, fast afterhyperpolarization; AHP, afterhyperpolarization; ADP, afterdepolarization; 5-HT, 5-hydroxytryptamine; TRH, thyrotropin-releasing hormone; SP, substance P; NE, norepinephrine; Glu, glutamate.

in the dendritic membrane have not been demonstrated directly in motoneurons in vivo or in acute brain slices, but there is evidence for backpropagating Na^+-dependent spikes in dendrites of cultured spinal motoneurons (707, 766). The voltage dependence and kinetics of activation and inactivation of Na^+ channels in motoneurons are difficult to study, because motoneurons are not ideal for voltage-clamp techniques requiring a high time resolution. Because of their complex electrotonic structure, motoneuron membrane charging is slow; reliably controlling membrane voltage, i.e., obtaining a good "space clamp," is not possible. In two-electrode voltage-clamp recordings from spinal motoneurons, the somatic $I_{Na\,i}$ in spinal motoneurons activates and inactivates rapidly (τ ~1 ms; range, 0.1–1.3 ms depending on voltage) and exhibits some steady-state inactivation at resting membrane potential (66). The somatic membrane of neonatal rat spinal motoneurons has tetrodotoxin (TTX)-sensitive 14-pS conductance Na_i channels (1068). Activation occurs between −60 and −20 mV, and inactivation kinetics are fitted by a single exponential function (τ ~1–4 ms) with a half-maximal potential of −82 mV. Interestingly, recovery from inactivation is rather slow (τ ~154 ms), suggesting that control of firing frequency in motoneurons is affected by recovery time from Na_i channel inactivation. However, whether these values from the neonate are comparable to values in the adult CNS is unknown.

A persistent, i.e., noninactivating, Na^+ current ($I_{Na\,p}$) is present in facial, hypoglossal, and trigeminal motoneurons (205, 870, 919). $I_{Na\,p}$ activates below spike threshold, which would accelerate subthreshold membrane depolarization to spike threshold. $I_{Na\,p}$ may represent Na_i channels in a noninactivating gating mode, rather than a distinct type of Na^+ channels (148, 243).

2. K^+ currents

K^+ channels are principal determinants of the subthreshold membrane behavior, action potential shape, and firing properties of motoneurons and are also important targets for neuromodulators affecting motoneuronal excitability. Several distinct types of K^+ conductances are found in motoneurons (825).

The resting membrane potential of cat spinal motoneurons in vivo is typically between −65 and −75 mV (458, 459, 993, 1421), positive to the equilibrium potential for K^+ (E_K). This suggests that resting membrane potential is the result of balance between outward K^+-, inward Na^+-, and Cl^--leak conductances. The relative contribution of these leak currents in motoneurons under in vitro conditions is estimated as $g_{Na}/g_K = 0.13$ and $g_{Cl}/g_K = 0.25$ (372). Other ionic currents, such as the inward rectifier K^+ current (I_{Kir}), hyperpolarization-activated inward current (I_h), transient outward K^+ current (I_A), and Ca^{2+}-activated K^+ currents also contribute to the resting membrane potential (74, 525, 667, 701, 1261).

Inward rectifier currents, i.e., currents that reduce upon depolarization and increase with hyperpolarization, are mediated by Kir channels (481, 912, 1065). In some neurons, inward rectifiers are active at resting membrane potential, giving rise to a steady outward current, which is in balance with leak inward currents. When the membrane is relatively unperturbed, this equilibrium ensures that the membrane potential is stable near E_K. However,

if the membrane is depolarized, Kir channels close (due to a voltage-dependent block by polyamines and Mg^{2+}), releasing the membrane to depolarize further (anomalous rectification). Transmitters acting on the Kir channels (through second messenger systems) can have a powerful influence on neuronal excitability by reducing the stabilizing action of the Kir current. Recently, several novel inwardly rectifying K^+ channels ($Kir_{2.1}$, $Kir_{2.2}$, $Kir_{2.4}$, GIRK1–3) have been identified in brain stem motoneurons (607, 1261). Remarkably, expression of $Kir_{2.4}$ transcripts appears restricted to brain stem motor nuclei. Transcripts appear to be absent in higher brain structures. In hypoglossal motoneurons, block of $I_{Kir2.2}$ and $I_{Kir2.4}$ by extracellular Ba^{2+} leads to depolarization and firing, suggesting that these and related conductances indeed contribute to the motoneuronal resting membrane potential.

Delayed rectifier (I_{Kdr}), transient outward (I_A), Ca^{2+}-activated K^+ [$I_{K\,Ca(BK)}$, $I_{K\,Ca(SK)}$], and leak currents shape the membrane trajectory of action potentials and associated afterhyperpolarizations in motoneurons. The delayed rectifier is a sustained outward K^+ current (1065) activated by depolarization, with slower activation kinetics than $I_{Na\,i}$ (90% complete within 5 ms, Ref. 62). It contributes to the falling phase of the action potential and the fast afterhyperpolarization (fAHP). External tetraethylammonium (TEA) blocks the delayed rectifier, lengthening action potential duration and blocking fAHP in motoneurons (62, 205, 523, 870, 919, 1113, 1213, 1311). Unitary K^+ currents of the delayed rectifier type, observed in patches from the soma of neonatal spinal motoneurons (1068), have a ~10-pS channel conductance (in normal Ringer solution), activate between −70 and 0 mV, and deactivate slowly (60 ms at −60 mV).

I_A is a transient, i.e., rapidly inactivating, outward K^+ current activated by depolarization, that is deinactivated by hyperpolarization (481, 1065), affecting the onset and steady-state firing of motoneurons (525, 919, 1068, 1213, 1311). In trigeminal motoneurons (525), I_A activates around −55 to −60 mV (preceded by a "priming" hyperpolarization), peaks within 5 ms, inactivates with a time constant of 6–8 ms, and is partially activated at resting membrane potential (525). In spinal motoneurons of neonatal rat, I_A activates between −60 and −20 mV, quickly inactivates (τ ~15–60 ms), and has a conductance of ~19 pS in normal Ringer solution (1068). In motoneurons, 4-aminopyridine (4-AP) blocks I_A, prolonging spike repolarization, and reducing fAHP (525, 919, 1213, 1311, 1425). However, it is unclear whether I_A affects the interspike interval, since interspike hyperpolarizations in motoneurons may be too small to deinactivate I_A (525). If I_A indeed is active at resting membrane potential, it could affect the onset of firing by delaying the occurrence of the first spike in response to a strong depolarizing input.

Ca^{2+}-activated K^+ currents are ubiquitous, found in all neurons. They are the result of large (BK) and small conductance (SK) K^+ channels gated by a rise in intracellular Ca^{2+}, and in the case of the BK channels, also by voltage (1065). Both $I_{K\,Ca(BK)}$ and $I_{K\,Ca(SK)}$ are present in motoneurons (205, 463, 523, 647, 666, 667, 826, 870, 918, 919, 1070, 1213, 1291, 1311). $I_{K\,Ca(BK)}$, which also is called I_c, is selective for K^+ and activates after an influx of Ca^{2+} during an action potential. In the absence of $I_{K\,Ca(BK)}$, the falling phase of the action potential is prolonged (1213, 1291, 1311). In patches from cultured mouse motoneurons and with symmetrical K^+ concentrations (140 mM), BK channels have a large conductance (240 pS), a sigmoidal dependence on potential, an increased open probability with increased Ca^{2+} concentration, an inactivation time constant of 40 ms at low Ca^{2+} concentration (0.5 μM), and are blocked by external TEA (825, 826). Unitary Ca^{2+}-activated K^+ currents of the BK type in soma membrane patches of rat spinal motoneurons (1070) have a conductance of 82 pS in normal Ringer solution, are activated by intracellular Ca^{2+} and depolarization, activate rapidly (within 2–3 ms with 10^{-4} M Ca^{2+} internally and depolarization to −50 mV), do not inactivate in 100 μM internal Ca^{2+}, and are blocked by external TEA and charybdotoxin.

$I_{K\,Ca(SK)}$ is a Ca^{2+}-activated, voltage-independent K^+ current blocked by the bee venom apamin and is the dominant conductance underlying afterhyperpolarizations. Spike afterhyperpolarization in motoneurons is blocked by inorganic Ca^{2+} blockers, intracellular injection of Ca^{2+} chelators, and notably by apamin (7, 205, 523, 647, 1311, 1426), suggesting that motoneurons express SK channels and that they play a critical role in the repetitive firing behavior of motoneurons. In mouse motoneurons in culture, unitary currents from SK channels have a ~18-pS conductance, a 3.5-ms mean open time, and show no voltage dependency (825).

Na^+-activated K^+ channels ($I_{K\,Na}$) are found in membrane patches from spinal motoneurons (1069). $I_{K\,Na}$ does not appear to contribute to single action potentials but gives rise to the postdischarge hyperpolarization that follows trains of action potentials, due to accumulation of internal Na^+.

A hyperpolarization-activated current (I_h, or I_Q in some studies), which is a mixed cationic current carried by Na^+ and K^+, is found in motoneurons (7, 62, 74, 205, 523, 577, 870, 919, 957, 1214, 1313). I_h has relatively slow kinetics (τ ~100–400 ms, Ref. 74) and has a reversal potential positive to resting membrane potential (approximately −40 mV, Refs. 74, 1214), i.e., the net current is inward both at rest and at hyperpolarized potentials. Consequently, I_h opposes membrane hyperpolarizations, such as would be produced by inhibitory synaptic input. Activation-deactivation of I_h following hyperpolarizations gives rise to a postinhibitory rebound (PIR) and can lead to rebound bursts of action potentials. I_h may be partially active at rest, thereby contributing to the resting mem-

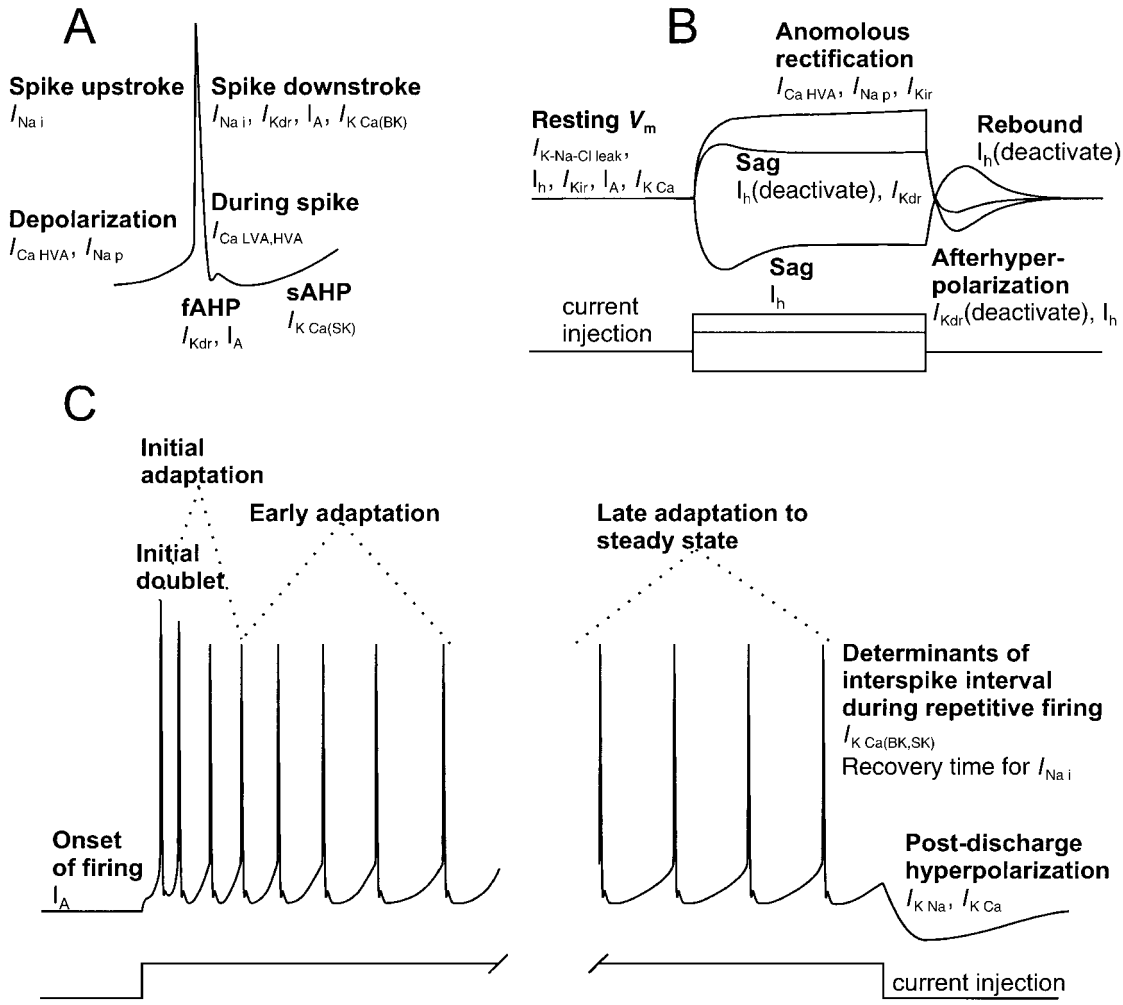

FIG. 3. Supra- and subthreshold membrane behavior of motoneurons. *A*: ionic currents underlying the action potential waveform. *B*: ionic currents underlying subthreshold membrane behavior, in this case, elicited by a short-lasting depolarizing/hyperpolarizing square current pulse. *C*: different phases of adaptation during repetitive firing and postdischarge hyperpolarization after a long-lasting current pulse. Unless noted, currents are activated at times indicated. For definitions, see Table 1 and section II*C*.

brane potential (74, 701). A steady activation at rest also means that I_h affects motoneuron responses to depolarizing inputs. During depolarization, I_h deactivation will increase neuronal input resistance. When the depolarizing current or synaptic input is relieved, steady outward currents repolarize the membrane, generating an afterhyperpolarization because of the increased input resistance. The afterhyperpolarization then activates I_h, and the membrane returns to rest. (Fig. 3; Refs. 870, 957). Thus I_h seems to stabilize the membrane potential around rest and also underlies rebound depolarizations and hyperpolarizations. Spinal motoneurons in the newborn rat receive phasic excitatory and inhibitory synaptic input during neurochemically induced fictive locomotion (486), and I_h may play a role in generating rebound burst firing following phasic inhibitory synaptic input (98).

3. Ca^{2+} currents

At least six types of voltage-gated Ca^{2+} channels (L, N, P, Q, R, and T types) are expressed in CNS neurons (1030, 1275). The pharmacological and single-channel properties of motoneuronal Ca^{2+} channel subtypes have been worked out in greatest detail in neonatal hypoglossal motoneurons (1291, 1293, 1310). Three types of high-voltage-activated (HVA; L, N, and P type) and one type of low-voltage-activated (LVA; T type) Ca^{2+} channel types are present (1291), with single-channel conductances (with 110 mM Ba^{2+} as charge carrier) of 28 pS (L type), 14 pS (N type), 20 pS (P type), and 7 pS (T type). L- and P-type channels do not inactivate, whereas T- and N-type channels do (τ ~20 and 58 ms, respectively). Whether adult hypoglossal motoneurons express all of these types of Ca^{2+} channels is not known. Neonatal facial motoneu-

rons also have HVA and LVA Ca^{2+} channel types in their somatic membrane (995). However, the HVA P-type channel is absent in the somatodendritic membrane, and a novel type (R_{slow}) carries a major component of the total HVA Ca^{2+} current (995). In this study, single-cell RT-PCR was used to detect mRNA for the α_{1A}-subunit of HVA Ca^{2+} channel subtypes, along with other α_1-subunit types. Because α_{1A}-subunits are thought to combine to form P/Q-type Ca^{2+} channels, the absence of P-type channels in the soma suggests that P-type channels may be present elsewhere in the membrane of facial motoneurons, most likely in axon terminals (995). LVA and HVA Ca^{2+} channel types are also present in spinal motoneurons (524, 881). Ca^{2+} conductances affect the falling phase of the action potential, spike afterdepolarization (ADP), and afterhyperpolarization (AHP), in the latter case via $I_{K\,Ca}$ (463, 523, 524, 647, 870, 1291, 1310, 1311). The Ca^{2+} channel subtypes underlying ADP, which is most prominent in neonatal animals, and AHP can be distinguished pharmacologically and result from both LVA and HVA as well as HVA Ca^{2+} channels, respectively (647, 1291, 1311). The L-type Ca^{2+} channels play a central role in some motoneurons that are capable of generating plateau potentials (521, 527). In the absence of modulatory transmitters, inward current flowing through L-type Ca^{2+} channels is curtailed by outward currents (524), effectively generating a small inward rectification just subthreshold to spike initiation (870, 1112, 1111). Perturbations of the balance of inward and outward currents, e.g., in form of transmitter-induced reduction in outward K^+ currents, can lead to plateau potentials and bistable membrane behavior by uncovering inward currents through L channels (121, 285, 521, 1200). In some specialized motoneurons, a separate mechanism operates to produce plateau potentials. Motoneurons in the rostral compact formation of the nucleus ambiguus, which innervate esophageal muscles, have a Ca^{2+}-activated Na^+ current ($I_{Na\,Ca}$) that produces prolonged plateaulike firing in response to brief afferent input or current injection. $I_{Na\,Ca}$ resembles the Ca^{2+}-activated nonspecific cationic current (I_{CAN}) found in other CNS neurons (962). Spinal motoneurons in the turtle also have an I_{CAN}, but in these motoneurons the current is not involved in generation of plateau potentials (970).

The spatial distribution of active conductances over the somatodendritic membrane is obviously important in determining the motoneuronal response to inputs. In turtle spinal motoneurons, Ca^{2+} conductances are present in dendrites (522), which may have important consequences for the transfer of synaptic input (1162), and in the generation and modulation of plateau potentials (521, 522, 524, 1200). In rat spinal motoneurons, L-type Ca^{2+} channels are present in the somatic and proximal dendritic membrane and N-type Ca^{2+} channels in both the dendritic and somatic membrane (1351).

D. Integration of Synaptic Input and Firing Modes of Motoneurons

The relationship between synaptic input to a motoneuron pool and the resulting muscle force, i.e., the motor pool input-output function, is generally described by a sigmoid curve (107). The initial upslope of the curve results from the orderly recruitment of motor units with increasing size, axonal conduction velocity, and fatigability, i.e., the size principle (107, 475). Rate modulation of the firing of motoneurons underlies further increases, with some contribution of continued recruitment. One of the main goals in the study of motoneuronal excitability is to understand how integration of synaptic input produces this input-output relationship, and how it is affected by neuromodulators. In broad terms, transformation of synaptic input to generation of impulses depends on the following: *1*) motor unit type (types S, FR, FI, FF), *2*) location of synaptic terminals, *3*) character and distribution of active and passive membrane properties, and *4*) effects of neuromodulators on synaptic transmission and on repetitive firing behavior.

In section IV, we discuss the mechanisms by which synaptic inputs affect the input-output relationship of motoneurons. In this section, we describe the basic firing properties of motoneurons.

Motoneurons fire repetitively in response to sustained suprathreshold excitatory input. This behavior has been studied mainly by injection of current pulses through an intracellular electrode. There are distinct phases of spike-frequency adaptation to such pulses, and a nonlinear rise in steady-state firing frequency with increasing current (Fig. 3; Refs. 437, 622, 625). At the onset of a long current pulse, an initial doublet [two spikes at short interval (<20 ms)] is often seen, which is part of the initial adaptation phase (0.5–1 s) during which the firing frequency drops sharply. A second phase of adaptation follows, which in some motoneurons (1087) is divided into an early (~2-s duration) and late phase (approaching steady state for long pulses). At the end of the current pulse, there is a postdischarge hyperpolarization followed by a return to resting potential.

Initial doublets, with instantaneous frequencies of 50–300 Hz, are seen in spinal motoneurons during endogenous motor behavior (488, 639, 673, 1417), suggesting that they are not an experimental artifact. Initial doublets may permit motoneurons to generate extra force at the onset of a contraction (476, 838), perhaps to overcome inertia, but the phenomenon is not necessarily correlated with a physiological need for strong contractions (639, 673). An increase in the magnitude and duration of spike AHP contributes to the initial adaptation (48, 62, 1312), dependent on Ca^{2+} entry (activating $I_{K\,Ca}$) during the first few spikes (1088, 1301). However, blockade of Ca^{2+} influx does not entirely abolish initial adaptation. Other pro-

cesses may contribute, such as deactivation of I_h at the onset of the depolarization, and changes in the threshold for action potential generation in the initial segment (1114). Late adaptation is also not abolished by Ca^{2+} channel blockers; in fact, it increases (1088, 1311), indicating that a number of Ca^{2+}-independent mechanisms contribute to late adaptation. During repetitive firing, spike duration lengthens, and spike amplitude and rate of rise decrease (1312); this suggests that conductances that shape impulses change during maintained firing, leading to late adaptation. Late adaptation may be produced by a progressive increase/decrease in an unidentified outward/inward current (1088). Postdischarge hyperpolarization is blocked by ouabain, suggesting that it is due to an outward current generated by a Na^+-K^+ pump driven by local accumulation of Na^+ (1088).

The relationship between steady-state firing rate and injected current (F-I relationship) increases in a linear fashion at low firing rates (primary range), then enters a steeper linear phase (secondary range) at higher firing rates (47, 623, 1109). In cat lumbosacral motoneurons, the secondary range starts when steady-state firing reaches ~50 spikes/s, with a slope 2–6 times that of the primary range (623). Many motoneurons lack the secondary range at steady state, with a linear F-I relationship over the entire firing range (573, 859, 870, 919). A persistent inward current (I_i, Ca^{2+} mediated) may underlie the secondary range (1003, 1114). The F-I relationship is highly dependent on the magnitude and duration of the spike AHP, since repetitive firing rate is directly related to the AHP duration (624). An effective way of modulating motoneuronal excitability is to modulate the magnitude of the AHP. For example, 5-hydroxytryptamine (5-HT) reduces the spike AHP (see sect. IV*E*) in cranial motoneurons, which leads to a dramatic increase in the slope of the F-I relationship (91, 526).

A particularly intriguing firing property of some motoneurons is the generation of repetitive firing that outlasts the period of excitatory input (239, 244, 326, 518–520, 527, 634, 1110). Plateau potentials underlie this behavior, which can be elicited in motoneurons by either short trains of excitatory synaptic input or current injection. Short-lasting inhibitory input can turn off the plateau potential, leading to bistable firing or membrane bistability under some circumstances. In most motoneurons, plateau potentials are not an endogenous membrane behavior but a latent property uncovered by activation of monoaminergic receptors (632, 634), and under modulatory control by other neurotransmitters (285, 1200). Thus motoneurons in spinalized cats (which are deprived of input from brain stem monoaminergic neurons) will exhibit plateau potentials when 5-HT and norepinephrine (NE) precursors are given intravenously (239, 244, 519), but not otherwise. A persistent Ca^{2+} current, possibly located in the dendrites, is the proposed ionic mechanism for generation of these plateau potentials in motoneurons (521, 522, 527, 720; see sect. IV*E*). During fictive locomotion (486, 1104) and in tonic muscle contractions associated with postural control (327, 633, 635), plateaulike firing is present in some motoneurons (486, 1104). Long-lasting plateau potentials are preferentially found in motoneurons with low thresholds for spike initiation and slow axonal conduction velocity, a hallmark of motoneurons of the S and FR type, which underlie most postural tasks (721, 722). The threshold for somatic activation (via current injection) of plateau potentials in cat spinal motoneurons is lowered by tonic excitatory afferent input (88). Because the plateau threshold can be lowered to the recruitment level of these motoneurons, plateau potentials under normal circumstances could play a role in amplifying the recruitment step rather than generating bistable behavior (88). An alternative view holds that plateau potentials serve to reduce the need for steady ongoing synaptic drive during maintained postural muscle contraction, through generation of self-sustained firing after transient synaptic input (634). Plateau generation in cat spinal motoneurons exhibits the phenomenon of "warm up," i.e., a progressive lowering of threshold for plateau activation with repeated activation (3- to 6-s intervals) (89). Plateau warm up may represent a form of short-term plasticity in motoneurons that ensures an increased motoneuronal output during sustained motor acts such as repetitive movements, e.g., locomotion. Specialized motoneurons in the compact formation of the nucleus ambiguus (innervating the esophagus) show plateau potentials in response to short-lasting synaptic input or current injection (1041). This plateau potential is carried by an I_{CAN}-like current and may generate prolonged spike activity in the ambiguus motoneurons during swallowing.

III. ORGANIZATION OF SYNAPTIC INPUT TO MOTONEURONS

Adult cat spinal motoneurons receive ~50,000–140,000 synaptic boutons (937), with >93% of the receptive membrane area in the dendrites. In L_7 cat motoneurons, 61% of this space is covered by synaptic boutons. GABA/glycine-immunoreactive boutons dominate the stem dendrites, covering 69% of the membrane; glutamate-like immunoreactive terminals comprise 18% (ratio ~4). In more distal dendrites, the GABA/glycine-to-glutamate ratio falls to 1.5. About 6% of the dendritic boutons are not immunoreactive for GABA, glycine, or glutamate. Presumably these boutons contain other transmitters (937).

The origins of these synaptic inputs are of considerable interest, since they encode the functional significance of the incoming signals. In the following section we briefly summarize the anatomical organization of synaptic inputs to spinal and cranial motor nuclei. The majority of

TABLE 2. *Major afferent inputs to brain stem and spinal motor nuclei*

Motor Nuclei	Reticular Formation/ Spinal Gray	NTS	Spinal V Complex	Vestibular Nuclei	Peri-ambiguual Region	Raphe Nuclei	Locus Coeruleus/ A7, A5	Pontine Nuclei	PH/ riMLF/ NIC	PAG	Location of Premotor Neuron Unknown*	Reference No.
Oculomotor, abducens, trochlear (III, VI, IV)	+			+ GABA					+		Angiotensin IV, bradykinin, endothelin, 5-HT, NE	225, 281, 653, 684, 685, 699, 816, 849, 877, 891, 1176, 1344, 1346, 1383, 1420
Trigeminal (V)	+ Met-Enk, ACh, GABA, Gly, Glu	+	+ Glu			+ 5-HT, SP, Met-Enk	+ NE	+			ACh, angiotensin II, IV, endothelin, PTHRP, TRH	83, 375, 451, 653, 737, 738, 740, 849, 982, 1210, 1263, 1277, 1278, 1315, 1342, 1416
Facial (VII)	+ GABA, Gly	+	+ GABA, Gly	+		+ 5-HT, SP, Met-Enk	+ NE	+		+	ACh, ADH, angiotensin IV, bombesin, prostaglandin, PTHRP, somatostatin, TRH	192, 273, 376, 451, 482, 739, 740, 849, 850, 964, 1019, 1208, 1315, 1342, 1416, 1418
Ambiguus	+ ACh	+		+	+			+		+	ACh, ADH, CRF, GABA, Leu-Enk, NE, 5-HT, oxytocin, somatostatin, SP, TRH	38, 159, 177, 281, 467, 574, 591, 698, 840, 892, 924, 998, 1096, 1144, 1315, 1393, 1427
Hypoglossal (XII)	+ GABA, Gly	+	+ GABA, Gly		+	+ 5-HT, SP, Enk	+ NE	+			ACh; adenosine; ADH; angiotensins II, III IV; ATP; DA; CRF; endothelin; NT; prostaglandin; PTHRP; somatostatin-28; TRH	12, 14, 85, 86, 122, 126, 235, 289, 399, 477, 653, 725, 739, 788, 789, 794, 836, 849, 935, 956, 1208, 1315, 1342, 1403
Spinal	+ Glu, Gly	+		+	+ GABA, Gly	+ 5-HT, SP, Enk, CCK, NKA, Galanin, Glu	+ NE Glu, Enk	+			Adenosine, Angiotensin IV, DA, vasopressin, CRF, NT, somatostatin	41, 49, 84, 134, 209, 248, 300, 331, 354, 398, 409, 497, 501, 502, 504, 508, 659, 792, 848, 907, 908, 925, 939, 1012, 1128, 1161, 1183, 1267

+, Projection from premotoneurons to motoneurons; CRF, corticotropin-releasing factor; DA, dopamine; Gly, glycine; INC, interstitial nucleus of Cajal; Met-Enk, methionine-enkephalin; NKA, neurokinin A; NT, neurotensin; PTHRP, parathyroid hormone-related peptide; PAG, periaquaductal gray; PH, prepositus hypoglossi; riMLF, rostral interstitial nucleus of the medial longitudinal fasciculus; SP, substance P; TRH, thyrotropin-releasing hormone; ADH, vasopressin. Periambigual region is defined here as a region around and within the ambiguus nucleus in the ventrolateral medulla; locus coeruleus is defined as locus coeruleus and subcoeruleus nucleus; pontine nuclei include nucleus of the Kölliker-Fuse, parabrachial nucleus, pontine medial reticular formation. * Column indicates receptor expression, immunoreactivity, or physiological effect of putative transmitters within a motor nucleus, but with unknown location of the premotor neuron somata.

the cited studies are based on tracing techniques combined with immunohistochemical detection of putative transmitters. We do not attempt to give a complete description of all the known pathways; rather, we emphasize the major anatomical pathways and the organizational principles (Table 2, Fig. 4).

A. Afferent Projections to Spinal Motor Nuclei

Monosynaptic input to spinal motoneurons from sources outside the neuraxis originate exclusively from muscle spindle Ia and group II afferents (147, 502, 543, 830, 1184). The Ia projection likely uses glutamate as a

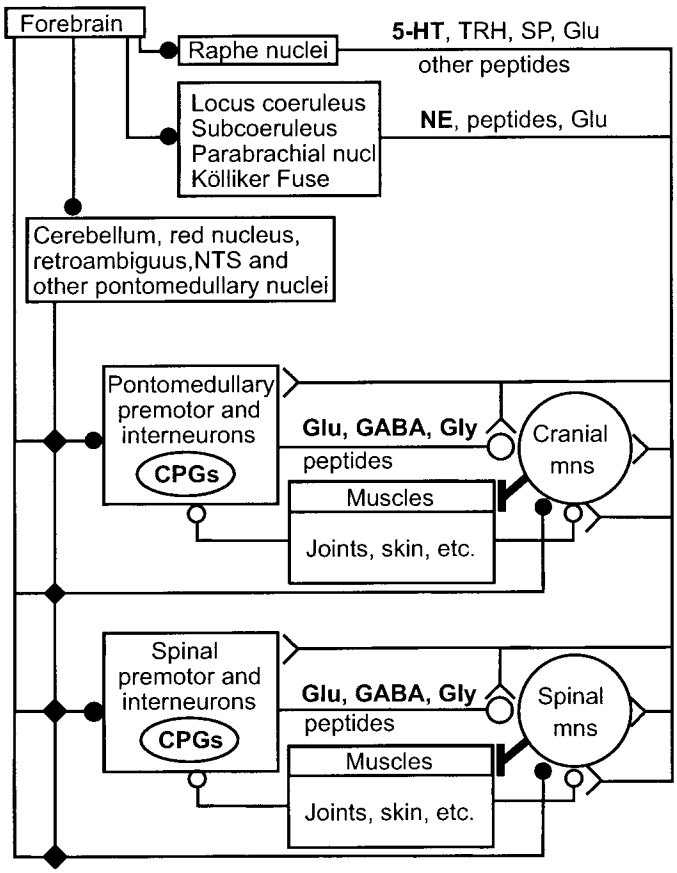

FIG. 4. Anatomical organization of synaptic input to motoneurons. Main synaptic input to both cranial and spinal motoneurons comes from premotor and interneurons located close to the brain stem and spinal motoneuron pools; the few notable exceptions include direct corticospinal and rubrospinal inputs to motoneurons controlling the distal musculature, especially the digits, vestibulospinal projections to postural muscles, and bulbospinal projections transmitting inspiratory drive to phrenic motoneurons. Several cranial and spinal central pattern generators (CPG) are embedded in these premotor systems. The local premotor and interneurons also form the main gateway for relaying and integrating multisensorial afferent input from muscle, joints, skin, and descending synaptic information from forebrain, cerebellum, some brain stem nuclei, and the raphe, locus coeruleus, and other pontine/brain stem regions. Long projections from brain stem and pontine nuclei, both from diffusely projecting premotor groups, e.g., raphe and locus coeruleus, and from premotor groups involved in specialized motor tasks, e.g., respiration, equilibrium, posture, project directly to motoneurons, and to the local premotor and interneurons. Glutamate, GABA, and glycine are the principal transmitters of local premotor and interneurons but are also used in certain brain stem/pontine projections. 5-Hydroxytryptamine (5-HT), norepinephrine (NE), thyrotropin-releasing hormone (TRH), substance P (SP), and a host of other peptides are the main transmitters in the projections originating in brain stem/pontine nuclei, subserving modulatory functions in control of motoneuronal excitability. Symbols (solid circle, small open circle, large open circle, and fork shape) indicate different anatomical projection systems. Mns, motoneurons.

transmitter (939). Propriospinal neurons provide the major synaptic input to spinal motoneurons (502). Labeling of spinal premotor neurons has been achieved by transneuronal transport of wheat germ agglutinin, virus, or retrograde labeling following discrete injection of tracers in motor columns. The pattern of premotor neuron labeling varies considerably depending on the motor group studied (21, 227, 513, 515, 566, 1012, 1264). Some spinal motoneurons receive synaptic input via recurrent axon collaterals from other motoneurons innervating the same or synergistic muscles (248, 249). Recurrent inhibition is mediated by Renshaw neurons that send inhibitory (GABAergic and glycinergic) projections to motoneurons innervating mainly proximal muscles (409, 1099, 1370). Interneurons and propriospinal neurons from most of the spinal cord laminae relay afferent signals from muscles, joints, and skin (49, 475, 563, 869, 1064), as well as segmental (22, 534, 1236) or supraspinal input to spinal motoneurons. They also generate coordinated, rhythmic patterns of activity such as locomotion and scratching that are ultimately transmitted to motoneurons (533, 1240, 1355); only a few studies have identified rhythmically active propriospinal interneurons with direct connections to spinal motoneurons (533, 1240).

Spinal motoneurons receive extensive projections from the brain stem. The raphe pallidus and obscurus contain premotor neurons that project directly to spinal motoneurons via the lateral and ventral funiculi (69, 508, 802). There are monosynaptic projections from the raphe pallidus to deltoid motoneurons (23) and medullary raphe nuclei to phrenic motoneurons (296). Raphe-spinal projections send off collaterals to the ventral horn of the spinal cord (529) and to the intermediolateral cell column (where the other class of nervous system efferents, preganglionic neurons, are located in the spinal cord), suggesting coordination of autonomic and somatic motor activity through common premotor neurons (20). Raphe premotor neurons are either serotonergic (265) or nonserotonergic (1161). Substance P (134, 209, 495), thyrotropin-releasing hormone (TRH) (134, 471), enkephalin-like peptides (134, 397, 497, 531, 723), cholecystokinin (792), neurokinin A (907), galanin (41), and glutamate or aspartate (908) colocalize with 5-HT (based on immunohistochemistry) in neuronal cell bodies in the caudal raphe and medial reticular formation, as well as in fibers and terminals in the ventral horn of the spinal cord (39, 41, 42, 133, 575, 576, 907, 908, 1034, 1237, 1297, 1348). Peptidergic immunoreactivity largely disappears from the inputs to motoneurons after destruction of serotonergic neurons with neurotoxins such as 5,6-dihydroxytryptamine (426, 576).

Noradrenergic premotor neurons projecting to spinal motoneurons are in the locus coeruleus, the subcoeruleus, the medial and lateral parabrachial nuclei, and the Kölliker-Fuse nuclei (222, 232, 503, 507, 585, 925, 1011, 1352, 1353). Met-enkephalin or glutamate is colocalized with NE in spinally projecting locus coeruleus neurons (395, 398, 749). Intraventricular injection of 6-hydroxydopamine reduces the ventral horn content of NE and the number of noradrenergic fibers by ~85%, suggesting that the brain stem premotor neurons are the main source of noradrenergic input to spinal motoneurons (715).

Spinal motoneurons also receive direct brain stem inputs from the retroambiguus nucleus (501, 1302), ventromedial medulla (GABAergic and glycinergic neurons; Refs. 504, 506), ventrolateral medulla (331, 354, 1047, 1248), and the nucleus tractus solitarius (NTS; Refs. 331, 874). On the basis of ultrastructural analysis of synapses in the ventral horn, a glutamatergic projection to spinal motoneurons originating in the ventromedial medulla may exist, but the location of the medullary glutamatergic premotor neurons is unknown (505). The vestibulospinal system, including neurons in the medial and lateral vestibular nuclei, projects to head and neck motoneurons and lumbosacral motoneurons (299, 448, 545, 1057, 1368).

Most corticospinal projections to motoneurons are indirect, typically via interneurons in the intermediate zone of the spinal cord. Direct corticospinal projections to some motoneuron groups innervating distal musculature and perhaps functionally involved in control of fine movement, are present in primates and to a limited extent in rats (125, 146, 252, 714, 741). Finally, the red nucleus projects monosynaptically to spinal motoneurons innervating distal muscles (391, 392, 500). Several other premotor neuron systems likely project to spinal motoneurons, since transmitter-like substances are found in fibers/boutons in spinal motor nuclei, and several transmitter receptors and physiological actions of transmitters have been demonstrated in motoneurons. The anatomical location of the premotor neurons using a particular transmitter remains unknown in most cases (Table 2).

B. Afferent Projections to Orofacial Motor Nuclei

Proprioceptive information from the muscles of mastication reaches the trigeminal and hypoglossal motor nuclei via the trigeminal mesencephalic nucleus (1015). Afferent information from other peripheral sensors enters the brain stem through vagal, glossopharyngeal, and accessory nerves and is conveyed to the trigeminal, facial, and hypoglossal nuclei via premotor neurons in the nucleus of the solitary tract (83, 122, 759, 1235, 1263). A third major sensory afferent input to orofacial nuclei is from the spinal trigeminal complex (122, 482, 544, 737, 1263). The largest concentration of premotor neurons to the orofacial motor nuclei is in the medullary and pontine reticular formation adjacent to the motor nuclei themselves. Thus hypoglossal premotor neurons are ventrolateral and dorsolateral in the medullary reticular formation (122, 297, 1263), and the majority of trigeminal and facial premotor neurons are in the pontomedullary and parvicellular reticular formations (482, 535, 850, 1263). Some of these premotor neurons are GABAergic, glycinergic, or glutamatergic (738, 739, 1210, 1277, 1278). In addition to these regions, a smaller number of premotor neurons to trigeminal, facial, and hypoglossal nuclei are located in *1*) pontine nuclei (Kölliker-Fuse; parabrachial nucleus; and trigeminal, facial, and hypoglossal nuclei); *2*) periaqueductal gray of the midbrain (facial and hypoglossal nuclei); *3*) periambigual region (hypoglossal and facial nuclei); *4*) vestibular nuclei (facial nucleus); *5*) gigantocellular reticular nucleus (all 3 nuclei); and *6*) paralemniscal zone in the lateral midbrain and external cuneate nucleus (facial nucleus) (175, 297, 474, 482, 544, 737–739, 935, 1209, 1263, 1404).

Noradrenergic input to the hypoglossal nucleus comes from neurons in three pontine regions, i.e., nucleus subcoeruleus, A7 and A5 cell groups (12, 14). The facial nucleus receives input from noradrenergic neurons in the A5 cell group (451) and trigeminal motor nucleus from the A7 cell group (451). This differential distribution of noradrenergic input to brain stem (and spinal cord) nuclei suggests that noradrenergic neurons can be divided into subgroups that differ in their connections and functional capacities (452).

The raphe pallidus, obscurus, and magnus are the main regions containing 5-HT-positive neurons projecting to the trigeminal, hypoglossal, and facial nucleus (376, 740, 789, 790). The raphe nuclei also contain premotor neurons positive for several neuropeptides. Substance P-like immunoreactive neurons in the caudal raphe project to the trigeminal, hypoglossal, and facial motor nucleus, and Met-enkephalin-like immunoreactive premotor neurons are in the caudal raphe and medial reticular formation (375, 376, 477).

Some premotor neuron groups projecting to the orofacial nuclei are involved in dedicated motor tasks and thus have more restricted projection patterns. The central subnucleus of the solitary tract contains the pattern generator for swallowing and conveys direct synaptic information to hypoglossal motoneurons and motoneurons forming the compact formation of the ambiguus nucleus (30, 67, 467). The Edinger-Westphal nucleus projects to the facial nucleus, forming part of the circuit mediating the corneal blink reflex (645).

The nucleus ambiguus contains esophageal, pharyngeal, and laryngeal motoneurons (106). Premotor neurons projecting to the ambiguus nucleus arise from the nucleus of the solitary tract (including the swallowing-related central subnucleus), zona intermedialis reticularis parvicellularis, pontine nuclei (Kölliker-Fuse, parabrachial nucleus), vestibular nuclei, periambigual regions, paraventricular hypothalamic nucleus, external cuneate nucleus, area postrema, and periaqueductal gray (67, 467, 591, 698, 924, 998, 1130, 1144, 1427, 1428).

Surprisingly, few projections have been demonstrated from the cortex to orofacial motor nuclei (1098), emphasizing the general scheme that voluntary motor commands to motoneurons likely pass through various groups of brain stem and/or spinal premotor neurons.

C. Afferent Projections to Oculomotor Nuclei

Eye muscles are innervated by motoneurons in the oculomotor, abducens, and trochlear motor nuclei. Several neuronal circuits in the brain stem and midbrain are dedicated to the coordination of these motor groups, and the organization of afferent input is consequently complex. Reticular formation premotor neurons projecting to the oculomotor nucleus are in the medial midbrain reticular formation (891), reticular formation of the mesodiencephalic junction (896, 1148), and the dorsal paragigantocellular reticular nucleus (191). Premotor neurons to the abducens and trochlear motor nuclei are also in the pontine reticular formation (699, 1115, 1344, 1420). All three motor nuclei receive input from the vestibular nuclei as part of the vestibulo-ocular reflex (225, 341, 434, 685, 699, 943, 1051, 1283). Some of these premotor neurons are GABAergic (superior vestibular nucleus) or cholinergic (the medial vestibular nucleus; Refs. 191, 685, 1346). Coordination between motoneurons in the oculomotor and abducens nuclei is partly mediated by GABAergic internuclear neurons projecting contralaterally between the nuclei (284, 817, 1346). The nucleus prepositus hypoglossi contains premotor neurons (possibly glycinergic) that project to all three oculomotor nuclei (341, 684, 699, 816, 1181, 1344). The oculomotor nucleus and the trochlear nucleus receive afferents from the rostral interstitial nucleus of the medial longitudinal fasciculus (GABAergic and glutamatergic; Refs. 1180, 1335) and interstitial nucleus of Cajal (654). A small number of neurons in the locus coeruleus, trigeminal sensory complex and olivary pretectal nucleus project to the oculomotor nucleus (191, 455, 646).

Several other premotor neuron systems likely project to cranial motor nuclei (see Table 2).

There are several common principles underlying the organization of synaptic input to spinal and cranial motoneurons (Fig. 4).

1) Multisensorial afferent input is conveyed via sensory nuclei in the brain stem and spinal gray.

2) Premotor neurons located close to the motoneuron groups in the reticular formation or spinal gray provide the major synaptic input to motoneurons. One notable exception is the phrenic motoneuron pool that receives inspiratory drive from premotor neurons in the medulla. These local premotor neurons form the main gateway for relaying and integrating multisensorial afferent input and descending synaptic information. Several spinal and brain stem central pattern generators (CPG) (locomotion, scratching, and others) are embedded in this premotor system.

3) Long projections from brain stem and pontine nuclei, both from diffusely projecting premotor groups (e.g., raphe, locus coeruleus) and from premotor groups involved in specialized motor tasks (e.g., respiration, eye movements, equilibrium), converge on brain stem and spinal premotor/interneurons as well as motoneurons.

4) Some motoneurons controlling distal limb muscles receive direct cortico- and rubrospinal synaptic input.

IV. TRANSMITTER MODULATION OF MOTONEURONAL EXCITABILITY

Motoneuronal inputs are affected by the presynaptic release of various transmitters (amino acids, amines, peptides) acting on postsynaptic receptors; several of these transmitters can also affect signaling by actions at presynaptic receptors. The integrative effect of these transmitters acting on their receptors, in concert with the intrinsic motoneuron properties, determine the generation of the efferent signals, action potentials propagated along peripheral motor nerve fibers and recurrent collaterals. The integration is complex. Actions at ionotropic receptors induce (or reduce) localized current flows that spread according to membrane properties and cellular morphology. Actions at metabotropic receptors initiate second messenger cascades that have myriad effects, including altering channel or receptor function. Many of these actions are convergent, that is, they ultimately act via the same signal transduction mechanisms, or affect the same target, such as a specific type of channel.

In this section, we review the principal neurotransmitter systems affecting motoneuronal excitability. In each section, we discuss the important ligands, the associated receptors, the effects on neuronal properties affecting excitability, the signal transduction pathways, and, where known, the function.

A. Glutamate: Ionotropic Actions

Glutamate is the principal fast excitatory neurotransmitter in the CNS (226, 854, 890). The potent excitatory action of glutamate on CNS neurons was first reported in 1960 for sensory and motoneurons of cat spinal cord (262). In this section we briefly review *1*) glutamate receptor ligands; *2*) the molecular biology of glutamate receptors; *3*) the distribution of glutamate receptor subtypes/subunits on different motoneuron pools; *4*) functional implications of the structural diversity of glutamate receptors as it relates to motoneuron excitability in adult, during development, and in disease; *5*) pre- and postsynaptic actions of glutamate; and *6*) role of glutamate receptors in synaptic integration, production of oscillatory behavior and synaptic transmission.

1. Ligands

A major difficulty with establishing a role for glutamate and associated excitatory amino acids (EAA; L-as-

partate, L-homocysteate; Ref. 342) in synaptic signaling is that they are also involved in metabolic processes. Thus determining whether their presence, synthesis, release, and transport underlies a metabolic or signaling function is difficult (469). The relative roles of the different EAA remain unclear. Limitations of the various techniques applied to the problem are reviewed elsewhere (469). Data are most consistent with L-glutamate as the main EAA at motoneuron synapses. Circumstantial evidence includes presence of high-affinity uptake mechanisms and high glutamine levels (456, 1151) in neurons and terminals that synapse on motoneurons (144, 808); detection of increased glutamate levels in perfusate from in vitro preparations following synaptic activation or glutamate uptake inhibition in rat and frog spinal cord (443, 614, 1223); potentiation of endogenous activity by EAA uptake inhibitors (142, 442, 818); and immunohistochemical detection of glutamate in boutons synapsing on motoneurons (878, 937, 1207). Furthermore, group Ia primary afferent boutons synapsing on retrogradely labeled motoneurons are enriched in glutamate-like immunoreactivity (939).

2. Receptors

Three ionotropic glutamate receptor subtypes, each assembled from an unknown combination of receptor subunits (most likely 5, but see Ref. 1059), are classified on the basis of pharmacological and functional properties as follows: *1*) α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) [comprising glutamate receptor (GluR) 1–4 subunits]; *2*) kainate (KA: high affinity; comprising GluR5–7 and KA1, KA2 subunits); and *3*) *N*-methyl-D-aspartate (NMDA) receptors (comprising NMDAR1, NMDAR2A-D and NMDAR3A subunits). Two orphan subunits, δ_1 and δ_2, have also been identified (58, 100, 294, 499, 837, 853, 880, 1100, 1118, 1119).

The functional complexity of glutamate receptor-mediated synaptic signaling is conferred by variation in receptor subunit composition and further enhanced by posttranscriptional processing of gene transcripts through alternative splicing and RNA editing. All AMPA receptor subunits undergo alternative splicing of COOH-terminal sequences and flip and flop sequences near the M4 transmembrane domain. GluR2 subunit mRNA are edited at the Q/R site and GluR2, GluR3 and GluR4 subunit mRNA are edited at the R/G sites. Kainate subunit mRNA, GluR5 and GluR6, are edited at the Q/R site. GluR6 mRNA is also edited at I/V and Y/C sites. The NMDAR1 subunit exists as eight possible splice variants (NMDAR1a-4a and NMDAR1b-4b) generated through alternative splicing of one cassette in the NH_2-terminal region and the individual or combined deletion of two cassettes in the COOH-terminal region (711, 887, 1194).

3. Distribution of receptors on motoneurons

AMPA, NMDA, and kainate receptors have been identified on motoneurons via receptor autoradiography (RAR), immunohistochemistry (ICC), and in situ hybridization (ISH). However, as receptor subunit composition and posttranscriptional modification contribute to the pharmacological and physiological properties of the GluR subtypes, we will focus on ICC and ISH studies. These data are summarized in Tables 3–5 and provide specific information on receptor subunit/splice variant expression within different motor nuclei and therefore may reveal a structural/molecular basis for motoneuron pool-specific differences in physiological properties and susceptibility to excitotoxicity/motoneuron disease. The functional implications are further explored in section IV*A4*.

A) SPINAL MOTOR NUCLEI. Low levels of AMPA, kainate, and NMDA binding sites are seen in lamina IX of the spinal cord in rat (438, 558, 855), human (215, 565, 595,

TABLE 3. *Expression of AMPA receptor subunits in motoneurons*

	GluR1		GluR2		GluR3		GluR4		
Motoneuron Nuclei	I	ISH	I	ISH	I	ISH	I	ISH	Reference No.
Edinger-Westphal		1	+	2	+	1		1	Rat 801* 1082
Oculomotor (III)	2.5	nd	3	3	3	3	2.5	2	Rat 801* 978* 1082; human 1367
Trochlear (IV)		nd	+	3	+	3		2	Rat 801* 1082
Trigeminal (V)	2	nd	3	3	3	4	3	3	Rat 801 1279* 978* 1082
Abducens (VI)	2	nd	3	3	3	3	3	2	Rat 801* 978* 1082
Facial (VII)	3	2	3	3	3	3	3	3	Rat 801* 978* 1082
Vagal (X) (DMV)	1	1	2.5	2	2.5	1	2	1	Rat 801* 978* 1082 human 1367 cat 28*
Ambigual		1	+	3	+	2		2	Rat 801* 1082 cat 28*
Hypoglossal (XII)	1.5	2	3	3	3	2	2.5	3	Rat 801* 978* 1082 human 1367 cat 28*
Spinal	2	1	3.5	2	3.5	2.5	3.5	3	Rat 801 966* 975 1082 1257† 407* 1206* 559 1206* 558* 1206, 1257, 1258* 1206* 1145 human 1367

Labeling intensity is relative, with 1 being low, 2 moderate, 3 strong, and 4 very strong. Values represent an approximate average of studies that have graded labeling intensity. Where (+) is indicated, study did not quantify expression levels. nd, not detected; I, immunohistochemistry; ISH, in situ hybridization. * Antibodies in above studies do not distinguish between GluR2 and -3. † Antibody to 2/3/4.

TABLE 4. *Expression of kainate receptor subunits in motoneurons*

	GluR5		GluR6/7		GluR7		KA1		KA2		
Motoneuron Nuclei	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	Reference No.*
Edinger-Westphal			1						1		976
Oculomotor (III)			2						2		976
Trochlear (IV)											
Trigeminal (V)			2						2		976
Abducens (VI)			2						2		976
Facial (VII)			2						2		976
Vagal (X)			2						2		976
Ambigual			2						2		976
Hypoglossal (XII)			2						2		976
Spinal		1	2	nd		nd		1	2	nd	407, 976, 1257

I, immunohistochemistry; ISH, in situ hybridization; nd, not detected; KA, kainate. *All data are from the rat.

1132–1134, 1136), and cat (845). Binding is typically <50% of the strongest labeling observed in the substantia gelatinosa and does not vary between different spinal cord levels. Although there are some inconsistencies between ICC and ISH studies, a general pattern emerges. For AMPA receptor subunits, ICC studies from rat (407, 558, 801, 1206) and human (1367) suggest that GluR4 ≥ GluR3/2 > GluR1. Similarly, ISH studies, which distinguish between GluR subunits 2 and 3, suggest that GluR4 = GluR3 > GluR2 > GluR1 (407, 559, 966, 1082, 1145, 1257, 1258), whereas recent studies in human spinal cord suggest low levels of GluR2 subunits (1137) and the complete absence of GluR2 mRNA expression (1366). Low-level GluR2 expression in spinal cord motoneurons is further supported by low GluR2 ICC relative to GluR3 and GluR4 in rat spinal cord (975). Analysis of GluR splice variants is limited to spinal motoneurons where expression of GluR2-flip, GluR3-flip and flop, and GluR4-flip and low levels of GluR1-flop in rat (559, 1238, 1257, 1258) differs from human, where all splice variants are present but flop isoforms predominate (1259).

The distribution of spinal cord kainate receptors has been least studied. KA1 and GluR5 are present in lumbar motoneurons (1257) and GluR5 is present in cervical motoneurons in rat (407). Detection of GluR6/7 and KA2 ICC in cervical motoneurons (976) contrasts with absence of ISH labeling of GluR6, GluR7, and KA2 in lumbar motoneurons (1257) and may reflect differential expression of subunits between cervical and lumbar motoneuron pools, but more likely reflects the greater sensitivity of ICC. There is much speculation on the cellular distribution and function of KA receptor subunits, since, with the excep-

TABLE 5. *Expression of NMDA receptor subunits in motoneurons*

	NMDAR1		NMDAR2A		NMDAR2B		NMDAR2C		NMDAR2D		
Motoneuron Nuclei	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	Reference No.
Edinger-Westphal	2		2		2						Rat 977* 979
Oculomotor (III)	3	3	2	1	2	nd		nd		nd	Rat 977* 979; mice 1340
Trochlear (IV)	nd		nd		nd						Rat 977* 979
Trigeminal (V)	4	3	3	2	3	nd		nd		nd	Rat 977* 979; mice 1279, 1340
Abducens (VI)	3		2		2						Rat 977* 979
Facial (VII)	3	3	3	2	3	nd		nd		nd	Rat 977* 979; mice 1340
Vagal (X)	2	2	2	1	2	1		nd		nd	Rat 977* 979; mice 1340; cat 28
Ambigual	4	3	3	2	3	nd		nd		nd	Rat 977* 979; mice 1340; cat 28
Hypoglossal (XII)	3	3	3	3	3	1		nd		nd	Rat 977, 979; mice 1340; cat 28
Spinal	4	3	4	2	4	1		nd		0.5	Rat 407, 765, 977, 1257* 979; mouse 1341; human 1078, 1145

I, immunohistochemistry; ISH, in situ hybridization; NMDA, *N*-methyl-D-aspartate; nd, not detected. * Antibody does not distinguish b/w NMDAR2A/B.

tion of cultured hippocampal neurons (728, 729), dorsal root ganglia (528), and cerebellar granule cells (1170), presence of functional high affinity KA receptors in CNS neurons has not been confirmed. Recent developments of specific KA agonists and antagonists should facilitate functional characterization of KA receptors on motoneurons (217, 1201).

NMDAR1 and -2A subunits and transcripts are strongly expressed in cervical and lumbar motoneurons in rat (407, 765, 977, 979, 984, 1145) and mouse (1341), and NMDAR2A subunits are present in human (1078). The presence of NMDAR2B subunits remains uncertain as their localization with ICC in cervical spinal cord of rat is with an antibody that does not distinguish between NMDAR2A and -2B (977). In addition, ISH studies are inconsistent, showing low levels (765, 984) or absence of NMDAR2B transcript in rodent spinal cord (1257, 1341). Expression of NMDAR2D transcripts also varies from low levels (984, 1257) to none (765, 1145, 1341) in rodent spinal cord. NMDAR2C transcripts have not been detected (765, 1145, 1341). Thus the distribution of NMDA receptor subunits within the spinal cord appears to be NMDAR1 > NMDAR2A > NMDAR2B >> NMDAR2D > NMDAR2C with little variation along the rostrocaudal axis. NMDAR3A expression has yet to be examined. ISH analyses of the eight NMDAR1 splice variants (NMDAR1 1a,b to 4a,b) in the ventral horn of the cervical (765) and lumbar spinal cord (1255) are not entirely consistent. NMDAR1 type a and b splice variants are present within the ventral horn, as are NMDAR1–2 and NMDAR1–4 subunits. NMDAR1–3 expression is low in ventral horn cells. Furthermore, detection of multiple splice variants in single motoneurons supports heteromeric receptor assembly. Comparison of ISH images with functional analyses of heteromeric recombinant receptors and a more complete analysis of the properties of motoneurons will be required to determine whether splice variants of the NMDAR1 subunit contribute to heterogeneity of spinal motoneurons relevant to physiological and pathophysiological functions.

Assessment of the relative abundance of AMPA, KA, and NMDA receptors within spinal motoneuron pools is difficult, since most ICC and ISH studies do not simultaneously examine expression of all three receptor classes, nor do they assess labeling based on the summed expression of all receptor subunits. However, available data in rat indicate that AMPA ~ NMDA > KA (407, 1257), whereas data in rabbit suggest that AMPA ~ KA > NMDA (120).

B) CRANIAL MOTOR NUCLEI. As seen for spinal motoneurons, NMDA and non-NMDA receptor binding sites are low in brain stem motor nuclei relative to cortical regions (215, 795, 855, 856, 1135). NMDA receptor binding in motor nuclei subserving eye movements (III, IV, and VI nuclei) appears reduced relative to visceromotor nuclei [V, VII, and X (NA) nuclei] (1135) and the XII nucleus (855, 1135). In contrast, non-NMDA binding appears elevated in somatic motoneurons relative to visceromotor nuclei (215; see also Refs. 288, 865, 932, 1398).

With the exception of GluR1 subunits in the IV nucleus, GluR1–4 AMPA subunits and transcripts are present in all cranial motoneuron pools; GluR1 subunit expression is lowest, whereas levels of GluR2, -3, and -4 appear similar (28, 801, 978, 1082, 1367). Expression across functional groupings of cranial motoneurons is also similar, with the possible exception of a general reduction in expression of all subunits in general visceromotor nuclei (Edinger-Westfall, EW; dorsal motor nucleus of the vagus, DMV).

NMDA receptor subunit expression in spinal cord and brain stem motoneuron pools (EW, III, V, VII, X, NA and XII nuclei) are similar. In general, NMDAR1 > NMDAR2A > NMDAR2B (977, 979, 1340), with NMDAR2B identified in DMV and XII nucleus of mice only (1340). NMDAR2C and -D expression has only been examined in mice using ISH (1340), whereas NMDAR3A has not been examined. Again, differences in subunit expression across functional groups of cranial motoneurons are not obvious, aside from reduced signal in DMV and EW pools. Of note is that the IV nucleus fails to show immunoreactivity for NMDAR1 or NMDAR2A/B subunits.

Comparison of KA receptor subunit expression in spinal cord versus cranial motoneuron pools is premature. Expression of KA1 and GluR5 has not been examined, whereas moderate immunolabeling for GluR6/7 and KA2 has been observed in rat in all motoneuron pools examined (III, V, VI, VII, X, nucleus ambiguus, and XII nuclei). As seen for AMPA and NMDA subunit expression, ICC is reduced in EW relative to other motoneuron pools (976).

4. Physiological significance of glutamate receptor diversity

Molecular cloning and expression studies indicate that motoneuron responses to glutamatergic transmission, and to allosteric modulators, are determined by the type of subunits/splice variants that combine to form the glutamate receptor. Glutamate receptor expression is also dynamically regulated. Subunit expression can change during development (710, 711, 857), in response to afferent inputs and after ischemia (880). The physiological significance to motoneuron excitability of this potential diversity of glutamate receptors, however, is unclear. Continued development of subunit-/splice variant-specific agents such as Joro spider toxin (112), agriotoxin (478), Evans blue (616), and ifenprodil (1364, 1365; reviewed in Refs. 370, 427), combined with molecular physiological approaches similar to those used recently to introduce cDNA for the GluR1 subunit into motoneurons in vivo and in vitro (906), promise further insight into the role of specific glutamate subunits in controlling motoneuron

excitability (906). Moreover, the implication that differential susceptibility of motoneurons to degeneration in motoneuron diseases may in part be attributable to molecular diversity of glutamate receptors (193, 559, 1082, 1134, 1135, 1258, 1366) should accelerate discovery in this area.

At present, the significance of specific subunits/splice variants to motoneuron excitability must be inferred by comparing the expression patterns in motoneurons with properties of *1*) recombinant receptors studied in expression systems (e.g., Refs. 499, 752, 868) or *2*) native receptors studied using a combination of whole cell recording and single-cell RT-PCR (e.g., Refs. 416, 584). This section examines key structural features of glutamate receptors most likely to be relevant to motoneuron excitability by focussing on patterns of glutamate subunit expression in motoneurons (see sect. IV*A3*) and the influence of these subunit/splice variants on channel kinetics (deactivation and desensitization), ionic permeability, and glutamate receptor modulation through phosphorylation. A complete discussion of the functional properties imparted to recombinant receptors by each of the 15 glutamate receptor subunits and their modified transcripts is available elsewhere (294).

A) AMPA RECEPTORS. *I) Channel gating.* Non-NMDA receptors activate and desensitize rapidly and are primarily responsible for fast excitatory synaptic transmission (294). Thus modulation of AMPA receptor properties can profoundly alter motoneuronal excitability. Subunit composition, alternative splicing of the flip/flop module, and RNA editing at the R/G site affect gating of AMPA receptors. The relative abundance of GluR2 (especially GluR2-flip) and GluR4 (especially the flop variant) subunits appears to be a major factor determining gating kinetics of native AMPA receptors (294, 416, 868). GluR2 flip subunits give rise to slowly gated channels, whereas GluR4 subunits determine rapidly gated AMPA channels. Thus high levels of GluR4 in spinal and cranial motoneurons in conjunction with reduced levels of GluR2 in spinal motoneurons may predict AMPA receptor complexes with rapid deactivation and desensitization kinetics (416, 868) as well as slow recovery rates from desensitization (752). For example, lumbar motoneurons in chicks have rapidly gated receptors with rapid desensitization kinetics (1166) and glutamatergic inspiratory drive to hypoglossal motoneurons is potentiated by cyclothiazide (which blocks AMPA receptor desensitization) (406). Not only are the rapid desensitization kinetics of AMPA receptors likely to play a role in shaping synaptic currents (50, 406, 1166), but rates of desensitization threefold faster than rates of resensitization can produce rapid frequency-dependent modulation of excitability, since synapses rich in this type of receptor should become much less excitable during high-frequency activation. Furthermore, if desensitization kinetics are subject to endogenous modulation similar to that produced by exogenous drugs (50, 406, 1126), allosteric modulation of desensitization kinetics can provide a powerful mechanism for modulating motoneuron excitability to glutamatergic inputs.

Posttranscriptional modification of motoneuron AMPA receptors may also be important in channel gating. For example, AMPA receptors assembled from flop variants generally have faster desensitization kinetics and slower recovery from desensitization than flip counterparts (416, 868, 1120). Thus developmental increases in expression of flop isoforms of GluR receptor subunits in rat (559) and preponderance of GluR flop variants in spinal motoneurons of human (1259) may increase the inability of motoneurons to reliably follow fast trains of stimuli, thereby decreasing excitability to glutamatergic inputs.

In contrast, RNA editing at the R/G site of GluR2, -3, and -4 subunits in brain increases developmentally and is associated with slower desensitization rates and faster recovery from desensitization (752). Thus, if R/G editing in motoneurons follows a similar pattern, it may enhance the excitability of motoneurons to glutamatergic inputs and increase their ability to follow high-frequency inputs. Thus interactions between receptor subunit, alternative splicing, and RNA editing may interact to control motoneuron responsiveness to glutamatergic inputs. Cells with rapidly desensitizing, slowly recovering AMPA receptors should respond only to the beginning of a sequence of fast inputs, whereas rapidly recovering, slowly desensitizing receptors should integrate incoming signals as they will transmit with greater reliability during trains of high-frequency stimuli.

II) Ionic permeability. Most AMPA receptors are permeable to Na^+ and K^+ but impermeable to Ca^{2+}. Ca^{2+} impermeability is conferred by the presence of Q/R site-edited GluR2 subunits (167, 168, 498). Because virtually all (99%) GluR2 mRNA in the brain is edited at the Q/R site at all developmental stages, variation in Ca^{2+} permeability of AMPA receptors is determined by the presence or absence of the GluR2 subunit (167, 1120).

The relevance of Ca^{2+}-permeable AMPA receptors to motoneuron physiology remains speculative. Potential consequences include modulation of repetitive firing behavior through effects on Ca^{2+}-dependent K^+ channels. Developmental increases in the amount of GluR2 relative to other subunits have important implications for activity-dependent development of motor circuits (559), whereas low-level expression of GluR2 subunits may contribute to the selective vulnerability of different motoneuron pools to neurodegeneration in conditions such as amytrophic lateral sclerosis (193, 559, 1082, 1137, 1258, 1318, 1366, but see Ref. 866).

III) Modulation of AMPA receptors by phosphorylation. Little is known of the importance of AMPA receptor phosphorylation in modulating motoneuron activity. However, given the prominent role of AMPA receptors in

mediating synaptic drive to motoneurons, and that in many regions of the brain AMPA receptor function is regulated by phosphorylation of amino acid residues (serine, threonine, or tyrosine) of AMPA receptor subunits or associated proteins (68, 111, 363, 439, 655, 787, 821, 1052, 1229, 1331, 1396; for recent reviews, see Refs. 771, 871, 1053, 1173, 1174, 1256, 1395), phosphorylation may represent an important mechanism for modulating motor outflow from the CNS (e.g., Ref. 414).

Phosphorylation sites are not uniformly distributed on the different AMPA receptor subunits (583). Thus, in addition to physiological analyses of the effects of kinases and phosphatase inhibitors on AMPA-mediated synaptic inputs to motoneurons, determination of the receptor subunits that comprise AMPA receptors in motoneurons and identification of the phosphorylation sites in the AMPA receptor subunits are necessary steps to understanding the functional importance of phosphorylation, as well as subunit composition, in controlling motoneuron excitability. For example, although identification of multiple phosphorylation sites on the GluR1 subunit emphasize its importance in AMPA receptor regulation, its relevance to motoneuron control is questioned by the low-level expression of GluR1 in motoneurons. Potential phosphorylation sites on the remaining subunits (GluR2, -3, and -4, Ref. 895; GluR3, Ref. 617) may therefore be more relevant to control of motoneuron excitability.

B) NMDA RECEPTORS. NMDA receptors on motoneurons contribute to glutamatergic transmission, modulate repetitive firing behavior (through activation of $I_{K\,Ca}$), contribute to nonlinear behavior (152, 314, 486), and reduce the voltage dependence of glutamatergic synaptic inputs (486, 745, but see Ref. 201). In addition, their long-duration excitatory postsynaptic currents (EPSC), Ca^{2+} permeability, and voltage dependence are important in the detection and reinforcement of weakly correlated synaptic inputs that is thought to contribute to use-dependent synaptic plasticity during development, as well in the adult (279, 837, 1094).

Given the involvement of NMDA receptors in control of motoneuron excitability, it is clear that modulation of NMDA channel properties through alterations in subunit composition, alternative splicing, and RNA editing will have significant impact on motoneuron behavior. The strength and sensitivity of the voltage-dependent Mg^{2+} block, channel kinetics, and glycine sensitivity vary, depending primarily on expression profiles of NMDAR2 subunits (2A-2D) (542, 683, 853, 857, 858, 1349).

For example, the voltage sensitivity of the Mg^{2+} block of heteromeric NMDA receptors (NMDAR1 to NMDAR2), as well as the magnitude of the block, is much stronger for receptors containing NMDAR2A or -2B relative to NMDAR2C or -2D subunits (857). Predominant expression of NMDAR2A and 2B subunits in cranial and spinal motoneurons (Table 5) should reduce the potential impact of NMDA-mediated Ca^{2+} influx on repetitive firing (through activation of $I_{K\,Ca}$). The presence of significant levels of NMDAR2D subunits in lumbar motoneurons (1257), but not other motoneurons, may predict a greater susceptibility of spinal motoneurons to modulation by $I_{K\,Ca}$.

Gating kinetics are also affected by subunit composition. The decay time constant of NMDA currents, which has significant implications for synaptic integration as well as use-dependent synaptic plasticity, varies 3- to 40-fold depending on subunit combination with the decay time constants of NMDAR1–2A recombinant receptors $<$ NMDAR1–2B $<$ NMDAR1–2C $<<$ NMDAR1–2D (857, 858). Cranial and spinal motoneurons, which predominantly express NMDAR2A and -2B subunits (Table 5), may experience shorter duration EPSC relative to NMDAR2D containing lumbar motoneurons (984, 1257). Longer duration postsynaptic potentials and weaker Mg^{2+} block of receptors composed of NMDAR1–2B, -2C, and -2D subunits would facilitate detection and reinforcement of weakly correlated inputs.

Phosphorylation of NMDA receptors by a variety of transduction pathways is also dependent on the presence of subunit-specific phosphorylation sites differentially distributed over NMDAR1 and -2 subunits (312, 542, 658, 871, 1076, 1249, 1250).

5. *Pre- and postsynaptic actions of glutamate*

A) PRESYNAPTIC ACTIONS. The initial observations of kainate-mediated depolarization of afferent terminals in the spinal cord (8), in conjunction with localization of presynaptic ionotropic glutamate receptors and their enhancement of transmitter release in hippocampus (218, 994), raised the intriguing possibility that synaptic transmission may be modulated by presynaptic ionotropic glutamate receptors. Evidence, however, is sparse (819) and currently does not support a role for such receptors at the level of motoneurons. In contrast, there is considerable evidence that metabotropic glutamate receptors modulate presynaptic transmission (see sect. IV*B*).

B) POSTSYNAPTIC ACTIONS. Generation of an inward current or depolarization of motoneurons by exogenously applied glutamate or its agonists is clearly established for all motoneurons examined and probably should be considered dogma. Currents induced by exogenous glutamate in neurons cultured from ventral spinal cord (810, 811, 1350) reverse near 0 mV, are relatively linear between -20 mV and more depolarized potentials, but show a little change in slope conductance at more hyperpolarized potentials. This rectification is due to the action of glutamate at AMPA and NMDA receptors. In general, AMPA-induced currents are nonrectifying, reverse near 0 mV, desensitize rapidly, and are mediated by Na^+ and K^+. AMPA receptors lacking GluR2 subunits, however, also pass Ca^{2+} and

show doubly rectifying current-voltage (*I-V*) relationships. NMDA-induced currents, in contrast, exhibit a negative slope conductance in their *I–V* relationship between approximately −40 and −20 mV (due to a voltage-dependent Mg^{2+} block, Ref. 811), reverse near 0 mV, have slower kinetics of activation and longer decay than AMPA currents, and are mediated by Na^+, K^+, and Ca^{2+} (499, 1118, 1121).

Exogenous application of glutamate substantially increases motoneuronal conductance (up to 6-fold) (201, 745, 950, 1433). However, changes in conductance during synaptic activation of glutamate receptors are variable (201, 1139). During fictive locomotion in cat, motoneuron conductance can increase by ~20% relative to control. However, a conductance increase during the depolarized, relative to hyperpolarized, phase of the locomotor cycle occurs in only 8% of motoneurons (1139). Lack of phasic oscillation in input conductance in association with glutamatergic-mediated depolarization may reflect arrival of locomotor inputs on distal synapses where conductance changes are not detected with somatic intracellular recording (1162). Also, inhibitory inputs during the hyperpolarized phase of the cycle may produce increases in conductance similar to those produced during the depolarized phase by the excitatory inputs.

Despite the well-characterized nature of glutamate-induced currents, many potential sources of variability make description of a typical glutamatergic EPSP/C difficult. EPSP/C in motoneurons vary widely in shape, size, duration, onset and decay kinetics, voltage dependence, as well as antagonist sensitivity (86, 364, 412, 841, 926, 1158, 1433). The postsynaptic response to activation of a single glutamatergic synapse has been characterized in detail at few motoneuron synapses (412, 841, 1035). Stimulation of afferent pathways can lead to a distorted picture of individual synaptic inputs due to temporal dispersion in the arrival times of afferent impulses and difficulty in establishing an effective voltage clamp at distal synapses. Careful selection of somatic synapses for analysis is therefore required to obtain an accurate picture of evoked, spontaneous, or miniature EPSC. Differences between spinal and cranial motoneurons are not apparent. Activation of single group Ia afferent axons in vivo, primarily an AMPA receptor-mediated input (1327), produces an EPSC at somatic synapses with a peak amplitude of 330 pA (at resting membrane potential), a 10–90% rise time of 0.2 ms, and τ ~0.3–0.4 ms. The associated EPSP have a peak of ~100 V and, like the EPSC, reverse near 0 mV (364). AMPA-mediated EPSC evoked in spinal cord-spinal cord synapses in culture vary linearly in amplitude with membrane potential, have decay time constants between 0.6 ms (somal synapses) and 1–2 ms (proximal dendrites), and reverse near 0 mV (902). Combined AMPA/NMDA-mediated EPSC at similar spinal cord-spinal cord neuron synapses have decay time constants of 3.9 and 86 ms for the fast (AMPA) and slow (NMDA) components of the response, respectively (374). The slow component reverses near 0 mV, is blocked by NMDA antagonists, and is voltage dependent. Glutamate-mediated miniature EPSC (mEPSC) in lumbar motoneurons have a peak amplitude of 7.7 pA, a 1.2-ms rise time, and a 4-ms decay time constant (412). AMPA-mediated quantal EPSC in phrenic motoneurons have peak amplitudes of ~4 pA, whereas spontaneous EPSC have peak amplitudes of 5–50 pA, a mean rise time (10–90%) of 0.25–0.7 ms, and a decay time constant of 1.2–1.9 ms (746). In hypoglossal motoneurons, NMDA-mediated mEPSC average 16 pA in amplitude (range: ~5–60 pA), 10–90% rise time of 8 ms, and a decay time constant of >50 ms (at −50 mV). AMPA components of the mEPSC are markedly shorter, with decay time constants averaging ~10 ms (926).

Developmental changes in kinetic properties of mEPSC are also likely. Between embryonic *day 17* and postnatal *days 1–3*, although mEPSC rise time does not change (412), mEPSC amplitude increases ~40% and the decay time constant almost doubles. Later changes in mEPSC properties have not been examined in detail. However, the time course of mEPSC in postnatal motoneurons (413) is within the range reported for afferent-evoked EPSP in spinal cord of adult cats (1036).

6. Synaptic integration

The spatiotemporal integration of glutamatergic synaptic inputs and production of action potentials as output by motoneurons, i.e., their transfer function, is poorly understood. Most models of motoneuron input-output have focused on steady-state conditions and are predicated on the (relatively) linear summation of synaptic (and injected) inputs (107, 108). Although linear summation at the soma is likely, experimental (163, 165, 1025) and simulation data (733, 1124) suggest that glutamatergic EPSP (1380) add in a nonlinear fashion. Active dendritic conductances and motoneuron bistability are present in many motoneurons (see sect. II*C*) and, in conjunction with the voltage dependence of NMDA-mediated synaptic inputs (152, 374, 1433), will contribute to the nonlinearity (see below). Moreover, when glutamatergic inputs do add linearly, their combined effects on firing probability do not always sum in a linear fashion (359). In this light, the observation that unitary EPSP, or EPSP evoked from the same single fiber, vary up to eightfold in their rise times (reflecting dispersion of terminals over the dendritic tree, Refs. 33, 166, 1327) yet have similar amplitudes (33, 549) is also of interest. Motoneurons may therefore resemble hippocampal pyramidal neurons (197, 198) in having mechanisms for boosting the synaptic current at distal synapses to ensure equivalence in actions of synapses regardless of their location on the dendritic tree. Indeed,

motoneurons may be geometrically arranged for optimal current transfer from dendrites to soma (859, 862).

The pattern of excitatory input may prove to be a very important factor in determining motoneuronal excitability (359, 1005). For example, transient glutamatergic synaptic inputs, such as the excitatory input from Ia afferents, appear to have a relatively greater effect on output than steady-state inputs (1004). Recent work where glutamatergic inspiratory drive currents to phrenic motoneurons were first recorded under voltage clamp and then reinjected under current clamp before and after removal of synchronous 20- to 40-Hz components, suggests that synchronized presynaptic activity that produces large, high-frequency components on rhythmic drive currents may play an important role in maximizing output for a given current input (960).

7. Role of glutamate receptors on motoneurons in production of rhythmic activity

NMDA receptor-mediated currents, by virtue of their voltage dependence, not only introduce nonlinearities into the synaptic integration process, but can contribute to oscillatory behavior. NMDA-induced currents underlie TTX-resistant bursting in abducens motoneurons (313, 314), mastication-related motoneurons (636), lamprey spinal locomotor motoneurons (449, 450), and neonatal rat spinal motoneurons (486). Depolarization is proposed to bring motoneurons into a voltage region where the Mg^{2+} block is removed, giving rise to a regenerative depolarization (328, 449, 450). As seen for 5-HT in motoneurons from embryonic amphibians (1155), modulation of NMDA channel function, as well as Ca^{2+}-dependent K^+ channels or voltage-dependent Ca^{2+} channels, can alter the balance of membrane properties to induce, or continuously regulate, oscillatory activity according to behavioral circumstances (326, 632). Thus, provided that NMDA receptors are endogenously activated during these behaviors (as seen for lamprey), motoneurons can actively shape motor output.

8. Role of glutamate in synaptic transmission

Unequivocal evidence that EAA act as transmitters at any motoneuron synapses is sparse (469). However, involvement of glutamate/glutamate receptors in synaptic transmission to motoneurons is strongly supported by electron microscopic analysis of synaptic inputs (878, 937), the inhibition by glutamate antagonists of excitatory synaptic activity in virtually all motoneurons examined, and the potentiation of endogenous activity by EAA uptake inhibitors (142, 442, 818).

Molecular physiological analysis of motoneuronal AMPA and NMDA receptors and the functional role of glutamate receptor diversity in mediating/modulating synaptic transmission is relatively unexplored. Ongoing development of agonists/antagonists specific for receptors containing certain receptor subunits/splice variants should foster new insight.

Current understanding of glutamatergic pharmacology at motoneuron synapses was advanced most significantly through development and application of specific NMDA and non-NMDA receptor antagonists (most recently the quinoxalinediones; Refs. 370, 514) to in vitro preparations of CNS tissue (ranging from thin slices of spinal cord/brain stem to rhythmically active brain stem-spinal cord preparations in a variety of species; Refs. 94, 619–621, 813, 927, 944). Although it is important to remember that all receptors localized to a given synapse will act in concert to produce the postsynaptic response, considerable effort has been devoted to distinguish the relative roles of NMDA and non-NMDA receptors in mono- and polysynaptic transmission. This section considers some experimental difficulties of assessing the roles of these two receptor subtypes and then describes their contribution to the synaptic activation of motoneurons.

a) COMPLEXITIES OF ASSESSING NMDA AND NON-NMDA RECEPTOR CONTRIBUTIONS. *I) Voltage-dependent Mg^{2+} block of the NMDA receptor.* Experimental detection of the NMDA receptor contribution to monosynaptic inputs is complicated by the voltage-dependent Mg^{2+} block of the NMDA channel (811). Inclusion of high concentrations of the divalent cation Mg^{2+} in in vitro baths to isolate Ia monosynaptic inputs (557, 568) may obscure NMDA receptor contributions. Removal of Mg^{2+} in solutions bathing the neonatal rat spinal cord has inconsistent effects, revealing an NMDA component of the monosynaptic EPSP to motoneurons in one case (570) but not others (557, 568). More recent data, under conditions of normal Mg^{2+} levels, support a contribution of NMDA receptors to monosynaptic transmission (333, 335, 347, 368, 637, 991). The inability to observe a non-NMDA antagonist resistant component in monosynaptic reflexes (333, 347, 1190) does not rule out NMDA-receptor involvement. It may simply reflect the voltage-dependent block of NMDA receptors at resting membrane potentials (see below), i.e., the NMDA component does not show up in the absence of non-NMDA mediated, or experimental, depolarization (333, 347, 570, 637, 661, 991).

II) Developmental changes in NMDA receptors. Inconsistencies between studies may also result from a developmental decrease in the contribution of NMDA receptors to synaptic transmission. NMDA receptors are transiently expressed in high densities in the ventral horn during early postnatal development (432, 601). The magnitude of NMDA-induced depolarizations of spinal motoneurons decreases during development in neonatal rat between postnatal *days 0–15* (516). In isolated spinal cord of embryonic rat, NMDA receptors contribute up to 50% of the short-latency dorsal root-activated EPSP, a

contribution that decreases with age (1433). Complete loss of NMDA receptor involvement in monosynaptic transmission in mature mammals, however, is unlikely. Genes for NMDA receptor subunits are expressed in the ventral horn of adult rat cord, and a NMDA contribution has been observed in adult (335). Extension of experiments performed on adult rat cord in vitro (755–758) to include intracellular analysis of monosynaptic afferent inputs to motoneurons similar to that performed in neonates (661, 991) should help resolve this question.

III) Definition of mono- versus polysynaptic inputs. Establishing the relative roles of non-NMDA and NMDA receptors in mono- versus polysynaptic transmission is difficult, especially with stimulation of mixed afferent fibers. Stimulation of single, presynaptic axons can also be problematic because it produces postsynaptic effects with multiple (fast and slow) time courses. If the slow component is misinterpreted as polysynaptic, its depression by NMDA antagonists will not be seen to support involvement of NMDA receptors in monosynaptic transmission. Use of neonatal preparations in vitro advanced the pharmacological distinction of NMDA and non-NDMA receptors but perhaps clouded discrimination between mono- and polysynaptic inputs. Because of incomplete myelination, the conduction velocity of low-threshold fibers is ~10-fold slower in neonates than adults (1073). Differences in the threshold of activation for the different fiber types are also reduced. Although adult in vitro preparations address some of these issues, in vitro reductions in temperature to preserve spinal circuits may also affect response latency (109). Thus reference to mono- and polysynaptic transmission may be misleading and perhaps best reserved for paradigms where unequivocal distinction is possible; referring to early and late components of the afferent response (347) may be more appropriate.

B) ROLE OF GLUTAMATE IN TRANSMISSION OF PRIMARY AFFERENT FEEDBACK. *I) Spinal reflex transmission.* Primary afferent fibers have both mono- and polysynaptic projections to motoneurons, including those from Ia spindle afferents, Golgi tendon organs (Ib), and flexor reflex afferents (group II and III afferents from skin, joints, muscle, and group II spindle afferents), that mediate various reflexes. The general insensitivity of short-latency (presumptive monosynaptic) inputs and sensitivity of polysynaptic inputs to NMDA antagonists underlies the general consensus that non-NMDA receptors are primarily responsible for monosynaptic excitatory transmission while NMDA receptors underlie polysynaptic transmission (153, 277, 343, 346, 411, 470, 557, 568, 755–758, 996, 1160, 1246, 1381, 1382). Development of specific non-NMDA antagonists (514) confirmed the non-NMDA receptor involvement in monosynaptic (335, 347, 570, 637, 661, 758, 991, 1280) as well as polysynaptic afferent transmission (333, 347, 570, 637, 991).

The role of NMDA receptors in monosynaptic afferent transmission remains controversial. However, the existence of non-NMDA receptor antagonist-resistant components of monosynaptic inputs supports a NMDA receptor contribution (335, 570, 637, 991) (Fig. 5). For example, the Ia EPSP induced through muscle nerve stimulation in cats in vivo exhibits a GYKI 52466-insensitive component (335) that is weakly depressed by DL-2-amino-5-phosphonovaleric acid (APV) (368). In addition, the ventral root potential in adult rats in vivo (347), the monosynaptic EPSP in rat cord in vitro (637), and the fast EPSP associated with activation of ventrolateral spinal tracts (333) are depressed by NMDA antagonists. Similarly, a detailed intracellular analysis in isolated spinal cord of neonatal rat where polysynaptic inputs to motoneurons were reduced with mephenesin, reveals a significant NMDA component (991) (Fig. 5). Postsynaptic colocalization of NMDA and non-NMDA receptors at single afferent release sites mediating monosynaptic EPSP is further supported by similar sensitivity of NMDA and non-NMDA components of dorsal root or spinally evoked EPSC/EPSP to frequency-dependent changes in amplitude (661, 991, 1433).

While equivocal, taken as a whole the above data suggest that non-NMDA receptors underlie the majority of the short latency and perhaps even the longer latency reflex components, with a significant contribution from NMDA receptors to both components. The relative con-

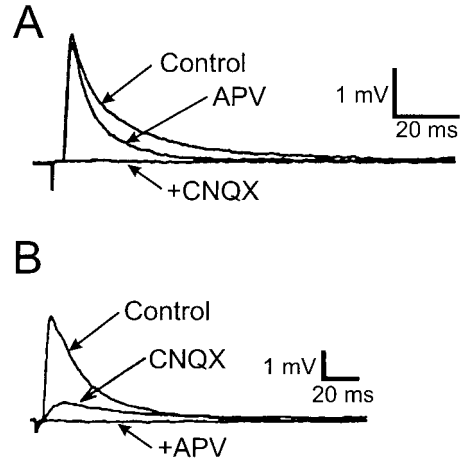

FIG. 5. DL-α-Amino-3-hydroxy-5-methylisoxazole-propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor components of monosynaptic EPSP, elicited by stimulation of dorsal root filaments, in a L_5 motoneuron in a hemisected spinal cord from neonatal rat. *A*: EPSP are shortened by bath application of 20 μM DL-2-amino-5-phosphonovaleric acid (APV; an NMDA antagonist). The remaining fast rising EPSP is blocked by addition of 10 μM 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; a non-NMDA antagonist) to the bath. *B*: addition of CNQX (10 μM) to the bathing medium eliminates a predominant non-NMDA receptor-mediated component of the monosynaptic EPSP, revealing a slow-rising EPSP, which is blocked by 20 mM APV. Bathing media contained 1 mM mephenesin (to reduce polysynaptic transmission), 5 μM strychnine, and 10 μM bicuculline. [Adapted from Pinco and Lev-Tov (991).]

tributions of the two components may be dynamically regulated. NMDA receptor subunit composition and densities appear to decrease developmentally. In addition, rapid desensitization of AMPA receptors and their slow recovery relative to NMDA receptors (294) may dictate greater involvement of NMDA receptors in mediating high-frequency afferent inputs. Although NMDA receptors have traditionally been envisioned as important mediators of low-frequency activity (especially during development) because of the increased probability of summation associated with their prolonged EPSP (1094), further examination of frequency-dependent changes in the relative roles of NMDA and non-NMDA receptors is warranted.

II) Cranial reflex transmission. Data concerning the role of glutamate receptors in mediating primary afferent inputs to cranial motoneurons are sparse. In addition to the complexities discussed above, activation of primary afferent nerves is more difficult for cranial than spinal motoneurons because they are generally less accessible. Activation of specific functional classes of afferents through stimulation of nuclei or fiber tracts within supraspinal structures is a poor alternative, since stimulation of a common site of origin or defined fiber tract guarantees less functional identity than similar procedures in the spinal cord (164). Thus many of the glutamatergic afferent synapses on cranial motoneurons that have been studied cannot be functionally classified. Because afferent-evoked EPSP in cranial motoneurons are rarely induced from first-order primary afferent fibers, the relative roles of NMDA versus non-NMDA receptors in transmitting mono- versus polysynaptic primary afferent inputs has received limited attention. Recent development of in vitro preparations with intact bulbar reflex circuits should facilitate progress (55, 648, 829).

The relative contribution of non-NMDA and NMDA receptors varies among synapses to cranial motoneurons, but both are involved in transmitting afferent signals. Trigeminal-induced EPSP in rat abducens motoneurons are mediated by non-NMDA receptors (950). In contrast, monosynaptic EPSP to jaw-closer motoneurons elicited from spindle or periodontal receptor fibers in mesencephalic nucleus of V, when examined intracellularly (1273) rather than extracellularly (206, 656), show a small but significant NMDA component. The greater sensitivity to NMDA antagonists of extracellular potentials induced in trigeminal motoneurons through stimulation of tooth pulp versus oral mucosa further supports the differential involvement of NMDA and non-NMDA receptors (609). Similarly, the NMDA contribution to dual component EPSP elicited from the NTS fiber tract onto ambigual motoneurons in medullary slices, believed to be the efferent limb of the swallowing reflex, is larger than seen at most other cranial motoneuron synapses (1336).

C) ROLE OF GLUTAMATE IN TRANSMISSION OF DESCENDING AND PROPRIOSPINAL/PROPRIOBULBAR INPUTS. *I) Spinal motoneurons.* Many excitatory supraspinal and propriospinal motoneuron inputs are mediated by glutamate or a related EAA (31, 143, 156–158, 266, 267, 450, 928, see also Ref. 449). Presumptive monosynaptic EPSP/C evoked by stimulation of reticulospinal or propriospinal neurons/axons in the medial longitudinal fasciculus (MLF) (371), ventrolateral funiculus (VLF), and ventral horn (333, 992) are sensitive to NMDA and non-NMDA antagonists. Although pathway-specific variation in the relative contributions of non-NMDA and NMDA receptors is evident, non-NMDA antagonists primarily reduce EPSP amplitude while NMDA antagonists shorten EPSP duration. Parallel frequency-dependent changes in the amplitude of NMDA and non-NMDA components of EPSP/C evoked through VLF, MLF, and spinal cord (as well as dorsal root) stimulation, further supports the conclusion that NMDA and non-NMDA receptors are colocalized on the postsynaptic membrane (371, 661, 991, 992).

II) Cranial motoneurons. Postsynaptic colocalization of non-NMDA and NMDA receptors and their concurrent mediation of synaptic inputs are also apparent at synapses between propriobulbar neurons and cranial motoneurons. EPSP induced in ambigual motoneurons from presumptive NTS axons in vivo (1336) and mEPSC in hypoglossal motoneurons from unidentified sources (926) are sensitive to NMDA and non-NMDA antagonists (1336). That some mEPSP have kinetics and pharmacology consistent with exclusive involvement of NMDA receptors, however, again points to considerable diversity in the subtypes of glutamate receptors at different motoneuron synapses.

In summary, although the majority of data indicate involvement/colocalization of NMDA and non-NMDA receptors at motoneuron afferent synapses, the relative roles of the two major subtypes do not appear to be uniform. There is considerable diversity in the glutamate receptor complement of different motoneuron synapses. Although such diversity is undoubtedly important, its functional significance remains to be determined.

D) ROLE OF GLUTAMATE IN TRANSMISSION OF RHYTHMIC MOTOR DRIVE. Glutamate receptors play multiple essential roles in generation of rhythmic motor behaviors (356, 590). They mediate many of the afferent or descending signals that initiate these behaviors, which include locomotion (43, 590), chewing (608), and deglutition (105). Furthermore, exogenous glutamate can activate a variety of episodic rhythmic behaviors. Local application of glutamate into the NTS in vivo elicits deglutition (466, 627, 628), into the pontine micturition center elicits micturition (785, 963), and intrathecal glutamate activates locomotion (304). Bath application of glutamate agonists to various in vitro preparations is a common method of activating rhythmic motor networks underlying locomotion (202, 469, 486, 1168) as well as chewing (648).

Glutamate receptors are also essential for generation

of rhythmic motor output from networks including those underlying locomotion (486, 1168), respiration (355, 357, 401, 405, 442, 1042, 1167), deglutition (105) and chewing (538, 648, 764). Distinguishing the role of glutamatergic receptors in rhythm generation from their role in transmission of the rhythmic drive to motoneurons, however, has been difficult due to the spatial proximity of many rhythm-generating networks to their output motoneurons. For example, application of EAA antagonists within the spinal cord to examine the pharmacology of rhythmic locomotor inputs to spinal motoneurons can interfere with rhythm generation itself.

I) Locomotion. Direct evidence for a role of glutamate receptors in signaling rhythmic locomotor drive potentials comes from experiments where the spatial proximity of locomotor rhythm-generating circuits and motoneurons has been overcome using muliticompartment perfusion chambers in vitro. Thus fictive locomotion is activated by local perfusion of discrete spinal cord segments with EAA agonists. Properties of rhythmic locomotor potentials in rat motoneurons outside the region of rhythm generation are consistent with NMDA and non-NMDA receptor involvement (201). Many motoneurons also receive tonic glutamatergic excitation during locomotion, which may serve to either increase motoneuron excitability, facilitate bistable behavior, or generate NMDA receptor-mediated pacemaker activity (see above).

II) Respiration. Spatial separation of cranial and especially spinal respiratory motoneurons from brain stem rhythm-generating networks has been exploited to establish the critical role of glutamate receptors in the transmission of excitatory inspiratory or expiratory drive (355, 401, 1026, 1042). The relative contribution of non-NMDA versus NMDA receptors is not firmly established. In vitro whole cell recording studies in rhythmic brain stem-spinal cord and transverse medullary slice preparations from neonatal rodents indicate that while phrenic (745) and hypoglossal motoneurons (405) possess NMDA receptors, inspiratory synaptic currents are unaffected by NMDA antagonists in the presence of normal Mg^{2+} concentrations (405, 745). In fact, inspiratory synaptic currents to hypoglossal motoneurons are similar in wild-type and transgenic neonatal mice lacking functional NMDA receptors (402). Furthermore, whole nerve (C4 or XII) inspiratory activity is not affected by NMDA antagonists (405, 442, 745) (in one case a minor decrease was observed, Ref. 818). Phrenic nerve output in adult rabbit and rat in vivo, however, is reduced by application of both non-NMDA and NMDA antagonists into the ventral horn (117, 216). Differences may reflect in vitro versus in vivo or neonate versus adult conditions. For example, in vitro, the concentration of glycine, an allosteric modulator of NMDA receptors, is reduced (96), and motoneurons may be relatively hyperpolarized due to deafferentation; consequently, NMDA channels may experience a greater Mg^{2+}-dependent block. In addition, there are also developmental changes in expression of NMDA receptors. Although many brain regions show reductions in NMDA receptor expression, NMDA receptor binding in NTS and the ventrolateral medulla, regions containing premotor neurons which provide rhythmic respiratory drive to phrenic motoneurons, increases from postnatal *day 0* and plateaus at approximately postnatal *day 9* (1031).

III) Other. Glutamate receptor activation underlies myoclonic twitches in lumbar motoneurons that characterize REM sleep (1178), putative swallowing-related information transfer between NTS and ambigual motoneurons (1336), cortically evoked rhythmical masticatory inputs to jaw opener motoneurons (608), micturition (593, 805, 963, 1188, 1193, 1411–1413), and emetic (190, 278, 724) reflexes. The precise pharmacology of motoneuronal glutamate receptors involved in these rhythmic behaviors remains to be established.

9. *Role of glutamate in activity-dependent development of motoneurons*

Synaptic transmission during critical periods in early postnatal life plays a central role in acquisition of mature electrophysiological, morphological, and molecular properties of neurons (487). The propensity for activity-dependent (re)organization of circuits in the neonatal, but not the adult, nervous system underlies the hypotheses that *1*) the molecular composition of neonatal circuits (including motor circuits) supports activity-dependent synaptic plasticity while maturational changes impede this process, and *2*) features of glutamatergic transmission factor importantly in activity-dependent development of motor circuits. Activity-dependent restructuring of neuronal circuits has primarily been examined for thalamic and cortical sensory maps, but evidence for its role in motoneuron development is growing (361, 487, 599, 750, 899, 900). Developmental alterations in motoneuronal glutamate receptor subunit expression (558, 559), binding profiles (432, 595, 601), changing contributions of receptor subtypes to synaptic transmission (719, 1433), and reductions in NMDA-induced currents (516, 876) underscore not only the potential for developmental change in motoneuron excitability but the possible contribution of glutamate receptors to activity-dependent development of motoneurons.

Attention has focused on the role of NMDA receptors. Their long-duration EPSC, Ca^{2+} permeability, and voltage dependence factor prominently in theories of activity-dependent phenomena (279, 837, 1094). In non-motoneuron systems, NMDA receptor composition appears to be regulated to produce longer lasting EPSC in young tissue and facilitate activity-dependent synaptic plasticity (187, 479, 857, 1028, 1141, 1364, 1365, 1429).

NMDA receptors also appear to be involved in activity-dependent development at the motoneuron level. *1*) Motoneuron somal growth and dendritic branching are inhibited by NMDA receptor antagonism in early postnatal life (594). *2*) Afferent expression of Cat-301 proteoglycan, a proposed marker for activity-dependent development (596), is dependent on NMDA receptor activation (597), motoneuron activity (600), and activity in large-diameter afferent fibers (598). *3*) Mouse dorsal root ganglion-ventral horn synapses undergo NMDA- and non-NMDA-mediated activity dependent modification in vitro (362, 901, 903). *4*) Establishment of active sensorimotor synapses is correlated with increased motoneuron sensitivity to NMDA and kainate, and decreased sensitivity to glutamate, suggesting that dorsal root afferents affect the number, location, or binding affinity of glutamate receptors, perhaps through an activity-dependent process (1433). *5*) NMDA antagonists extend the postnatal period where neonatal rats are able to recover from spinal cord injury (776). In fact, NMDA receptor properties and subunit composition may themselves be activity dependent. Early in development, when neurons receive few, weakly correlated inputs, long-duration NMDA-mediated events may be essential for synaptic organization. As development proceeds and synaptic inputs increase in strength and coherence, an activity-dependent change in NMDA receptor subunit expression/number favoring reduced NMDA currents may avoid excessive stimulation and excitotoxicity (1094). A developmental analysis of receptor subunit expression and properties is required to determine whether there is any transition in receptor properties to favor longer duration EPSP in motoneurons of younger animals.

Non-NMDA receptor properties may also be developmentally regulated to facilitate activity-dependent development of motoneurons. Higher levels of overall GluR subunit expression in neonates and a consistent bias of neonate motoneurons toward expression of flip GluR splice variants (559), which have higher gain than their flop counterparts, suggest greater excitability of neonatal motoneurons to glutamatergic inputs. The larger non-NMDA currents in neonates may lead to greater depolarization, greater activation of NMDA receptors, and greater Ca^{2+} influx. A greater Ca^{2+} permeability of neonatal AMPA receptors, suggested by the higher ratio of GluR1, -3, -4/GluR2 in neonatal motoneurons relative to adults (559), may also enhance plasticity in neonates.

In contrast to the postnatal period, disruption of glutamate/NMDA-mediated synaptic activity during fetal life appears to be without major effect on motoneuron properties or synaptogenesis. Developmental changes in excitability of embryonic rat spinal motoneurons grown in culture, although affected by changes in electrical activity, are unaffected by glutamate antagonists (1392). Monosynaptic afferents connect appropriately with fetal chick or frog spinal cord motoneurons when synaptic activity is blocked (380). In the absence of functional NMDA receptors (NMDAR1 knockout mice), rhythmic respiratory motor output is present at birth and in vitro is undistinguishable from that of normal mice (402). A role for glutamatergic activity in the programmed decrease in motoneuron cell number that occurs during fetal development (apoptosis) (176, 386, 387, 695) remains possible (176).

The relative role of activity and glutamate receptors in the development of spinal versus cranial motoneurons, somatotopic organization of motoneuron pools (297, 997, 1343) and the cellular mechanisms underlying activity-dependent changes are all areas requiring further investigation.

B. Glutamate: Metabotropic Actions

Glutamate, in addition to its role as the principal fast excitatory neurotransmitter, also modulates neuronal excitability by activating a large family of metabotropic receptors.

1. Receptors

Metabotropic glutamate receptors (mGluR) are coupled through GTP-binding proteins to intracellular second messenger cascades (196, 1101, 1164, 1195, 1369). There are at least eight subtypes of mGluR (mGluR1 to -8) (3, 517, 804, 885, 931, 1231, 1232) that can be divided into three groups (groups I, II, and III) on the basis of sequence homology and pharmacological profiles (234, 989). Group I mGluR (mGluR-1, 5) are coupled to phospholipase C (PLC) and increase the synthesis of inositol 1,4,5-trisphosphate (IP_3), and trigger intracellular Ca^{2+} release (3, 36, 804). Group II (mGluR2, -3) and group III mGluR (mGluR-4, 6–8) are negatively coupled to adenylyl cyclase and inhibit the formation of cAMP (315, 885, 931, 1085, 1231, 1232).

2. Cellular distribution of receptors

Metabotropic glutamate receptors are widely distributed in the CNS. There is a wide diversity and heterogeneous distribution of mGluR subtypes in different areas, with a unique differential cellular localization of receptor subtypes. Group I mGluR appear to be localized postsynaptically (71, 762, 800, 1146) where they act to increase neuronal excitability (905, 1105, 1108). Group II and III receptors are predominantly localized in presynaptic terminals (135, 638, 735, 1146, 1147) where they inhibit transmitter release (70, 373, 419, 773, 1075, 1107, 1272, 1314). This differential localization is by no means exclusive (419, 793, 1056). Nevertheless, the unique cellular localization of each mGluR subtype suggests that the precise

placement of receptors is a crucial factor contributing to the control of neuronal excitability.

3. Modulation of synaptic transmission to motoneurons

Activation of mGluR causes a profound inhibition of synaptic transmission to spinal and cranial motoneurons (301, 561). Both group II and group III mGluR reduce spinal segmental transmission to lumbar motoneurons (181, 541, 562, 618, 1243) and bulbospinal inspiratory synaptic inputs to phrenic motoneurons (301, 302). Only synaptic events are depressed. These two groups of mGluR have no effect on postsynaptic depolarization induced by exogenous EAA (302, 541) or postsynaptic membrane intrinsic properties (181, 301). Moreover, the frequency of mEPSC is significantly reduced by both group II and group III agonists, whereas the mEPSC amplitude is unaffected (301, 302). This suggests that activation of presynaptic group II and group III mGluR inhibits glutamate release to motoneurons. Activation of mGluR can also enhance synaptic transmission, as seen in frog (433) and lamprey (224) spinal motoneurons.

The precise mechanisms underlying the presynaptic action of mGluR are not known. Inhibition of transmitter release from presynaptic terminals may result from the reduction of presynaptic Ca^{2+} influx (915). Inhibition of voltage-dependent Ca^{2+} currents after mGluR activation occurs in neuronal soma (219, 428, 730, 1089, 1185, 1204, 1272, 1410); perhaps a similar mechanism underlies the presynaptic inhibitory action of mGluR agonists. Another possible mechanism is the direct modulation of the exocytotic machinery by influencing the availability of vesicles or their probability of release (468). The activation of mGluR is effective in reducing the frequency of spontaneous mEPSC when presynaptic action potentials are blocked in motoneurons (301, 302) and in other neurons, such as in hippocampus (419, 779, 1091) and striatum (1282). These spontaneous mEPSC seem independent of presynaptic Ca^{2+} influx since they persist in the presence of Ca^{2+} channel blockers (419, 1090, 1091, 1102). Thus the inhibition of presynaptic Ca^{2+} currents does not seem obligatory for the reduction of transmitter release by mGluR. mGluR may inhibit transmitter release by interfering with the secretion cascade subsequent to presynaptic Ca^{2+} influx (419, 468, 1091, 1105, 1282).

Group II and group III mGluR both appear to be present in terminals presynaptic to motoneurons. Because their actions appear similar, what purpose is served by having both types present? One possibility is that each group of receptors is located in different sets of terminals. Another possibility is spatial segregation of each group within presynaptic elements (1146). In hippocampal neurons, group III receptors are predominantly located in presynaptic active zones, whereas group II receptors are found at the preterminal axon at a site away from the release sites (1146). Thus group III mGluR would be preferentially activated, whereas group II mGluR would be activated only under higher release conditions. However, because the identification of mGluR subtypes relies largely on the selectivity of agonists, and because the two groups show high homology, the possibility that various agonists act through the same receptor cannot be excluded.

In addition to presynaptic actions, modulation of postsynaptic ligand-gated receptors can alter synaptic transmission. In lumbar (1285) and cranial trigeminal (287) motoneurons, depression of synaptic transmission is mediated by postsynaptic mGluR that decrease currents through ionotropic glutamate receptors. Group I mGluR appear to be involved in this process (1285).

4. Modulation of intrinsic membrane properties

Activation of mGluR, most likely of group I, causes membrane depolarization (287, 301, 302, 316, 540, 560, 561, 1242, 1244). This effect persists after block of synaptic transmission, suggesting mediation by postsynaptic receptors. In rat phrenic (301, 302) and trigeminal (287) motoneurons, depolarization is due to an inward current produced by activation of postsynaptic group I mGluR (301). This inward current consists of at least two components: a dominant component resulting from the blockade of a Ba^{2+}-sensitive resting K^+ current (287, 302) and an unidentified Ba^{2+}-resistant component (302). Inhibition of this tonic K^+ current results in membrane depolarization and increase in membrane resistance, both effects increasing motoneuronal excitability. Thus motoneurons show enhanced firing in response to either synaptic current or injected current after activation of mGluR (301, 302).

mGluR modulation of postsynaptic Ca^{2+} currents can also increase motoneuronal excitability (287, 285). In turtle spinal motoneurons, mGluR sensitive to (*R,S*)-α-methyl-4-carboxyphenylglycine (MCPG), a nonselective mGluR antagonist, facilitate plateau potentials by increasing an L-type Ca^{2+} current (285). Furthermore, the facilitation induced by mGluR activation can be compartmentalized to affect only part of the motoneuron membrane, i.e., a plateau potential in a medial dendrite can be facilitated, with no simultaneous effect in a lateral dendrite (286).

5. Endogenous activation of mGluR in motoneurons

Motoneuron activity changes significantly after administration of mGluR antagonists. Synaptic currents in rat spinal lumbar and cervical motoneurons are enhanced by antagonists for group II and for group III mGluR (182, 183, 301). This is presumably caused by the blockade of presynaptic receptors, suggesting that endogenous activa-

tion of these receptors attenuates synaptic transmission. In phrenic motoneurons, the group I mGluR antagonist (*R,S*)-1-aminoindan-1,5,dicarboxylic acid (AIDCA) significantly reduces EPSC amplitude, suggesting that postsynaptic group I mGluR, along with various ionotropic receptors (441, 745), are activated by endogenously released glutamate during inspiration.

In summary, three groups of mGluR are functionally expressed in motoneurons to mediate differential effects on intrinsic and synaptic properties via distinct mechanisms operating at pre- or postsynaptic sites. The diversity of actions mediated by various receptor subtypes provides a wide dynamic range for modulation of motoneuron excitability.

C. GABA and Glycine: Ionotropic Actions

GABA (920, 1016) and glycine (675, 700, 1023) are the principal fast inhibitory transmitters in the mammalian CNS. They are involved in all aspects of nervous system function, including control of motoneuron excitability (87, 101, 675, 700, 782, 847, 1306).

In this section we briefly review *1*) ligands responsible for endogenous activation of GABA and glycine receptors, *2*) the molecular biology of ionotropic GABA and glycine receptors, *3*) distribution of GABA and glycine receptors subunits amongst motoneuron pools, *4*) the physiological significance of GABA/glycine receptor diversity to the control of motoneuron excitability, *5*) post- and presynaptic actions of GABA and glycine, *6*) functional role of GABA and glycine in modulating motoneuron excitability, and *7*) development of ionotropic inhibitory systems.

1. Ligands

Compelling evidence indicates that GABA (920, 1016) and glycine (675, 700, 1023) are inhibitory transmitters in the mammalian CNS. β-Alanine is also a candidate ligand at GABA and glycine receptors (675, 1016); its effects are inhibited by GABA (SR-95531) and glycine antagonists (strychnine), and steroids potentiate the action of β-alanine at $GABA_A$ receptors (1384).

2. Receptors

A) GABA RECEPTORS. GABA produces its actions in the CNS by binding to two subclasses of ionotropic receptors, $GABA_A$ and $GABA_C$, and one class of metabotropic receptor, $GABA_B$ (see sect. IV*D*). Pre- and postsynaptic $GABA_A$ receptors play prominent roles in modulating motoneuron excitability. $GABA_A$ receptors form Cl^--selective channels; have allosteric sites for benzodiazepines, barbiturates, neuroactive steroids; and are phosphorylated by protein kinase C (PKC) and protein kinase A (PKA) (59, 579, 592, 606, 893, 1152, 1363). They are hetero-oligomeric, pentameric, protein assemblies of unknown subunit combination or stoichiometry. At least 15 genetically distinct subunit subtypes (α 1–6; β 1–4; γ 1–4; δ) as well as alternatively spliced variants and additional posttranscriptional modifications underlie the molecular diversity of $GABA_A$ receptors (60, 242, 282, 309, 682, 867, 893, 1016).

$GABA_C$ receptors are ligand-gated Cl^- channels that are insensitive to drugs that modulate $GABA_A$ and $GABA_B$ receptor function (123, 578, 580, 581). Compared with $GABA_A$ Cl^- channels, they are more sensitive to GABA, less prone to desensitization, and have longer open times. Their molecular biology has not been fully characterized. It appears that ρ_1-ρ_2 subunits, which are typically referred to as $GABA_A$ receptor subunits, may form $GABA_C$ receptors (242, 338, 581). The role of $GABA_C$ receptors in regulation of motoneuron excitability is not known. $GABA_C$ type responses have been characterized predominantly in the retina. Furthermore, although ρ_1 mRNA is exclusive to the retina, RT-PCR analysis of ρ_2 indicates its presence throughout the brain, including the spinal cord. Its expression in, or presynaptic to, motoneurons remains to be established (338).

B) GLYCINE RECEPTORS. Glycine modulates motoneuron excitability through activation of a group of postsynaptic receptors belonging to a superfamily of ligand-gated ion channels that share homology with $GABA_A$, nicotinic ACh, and 5-HT_3 channels. Glycine receptors have been the subject of several recent reviews (81, 101–104, 674, 675, 700, 1023, 1306). They form Cl^--selective channels, possess allosteric sites for Zn^{2+}, and are subject to positive (PKA, cAMP) and negative (PKC) modulation via receptor phosphorylation. The purified receptor contains two transmembrane subunits of 48 kDa (α) and 58 kDA (β) and a peripheral protein of 98 kDa (gephyrin). Glycine receptors form hetero-oligomeric, pentameric protein assemblies from α, which contain the glycine and strychnine binding sites, and β subunits. At least four genes code for separate α-subunits (α_1, α_2, α_3, and α_4), while diversity in β-subunits has not been found. Molecular diversity is further increased through alternate splicing. The α_1-, α_2-, and α_3-subunits undergo alternative splicing to produce $\alpha_{1\,ins}$, α_{2A} and α_{2B}, and α_{3K} and α_{3L} (917) splice variants, respectively, which modify pharmacological and electrophysiological properties of the receptor (82, 445, 676, 677). An additional subunit designated α_2* differs from the α_{2A}-subunit by only a single amino acid and likely represents an allelic variant of the α_2-gene (81, 101–104, 674, 675, 700, 1023, 1306).

Gephyrin, a 93-kDa peripheral membrane polypeptide, is associated with the β-subunit (835). At least five splice variants exist (1008). Gephyrin is of primary significance because of its pivotal role in the formation of

glycine receptor clusters, which most likely occurs through its anchoring of the receptor to the cytoskeleton (640, 641, 643, 1251, 1354). Although this protein may not be directly involved in signal transduction, its relevance to control of excitability is obvious due to the importance of synapse distribution over the somatodendritic tree in synaptic integration.

3. Distribution of inhibitory amino acid receptors on motoneurons

Understanding the types of receptors expressed by specific motoneuron pools and their spatial distribution on the surface of motoneuron in relation to functionally identified synapses (as well as the distribution of active dendritic conductances) is critical in understanding not only how motoneurons function as information processing units but how motoneurons target receptors to different synapse populations to effect various responses to input (831, 1162). This section *1*) examines expression patterns of inhibitory amino acid receptor subtypes/subunits within the different motoneuron pools and *2*) describes the spatial distribution of the amino acid receptors/synapses over the somatodendritic tree.

A) GABA$_A$ RECEPTOR LOCALIZATION. *I) Spinal motoneurons*. Consistent with GABA$_A$ receptor binding studies (54, 349, 827, 1414, 1415), GABA or glutamate decarboxylase (GAD) immunostaining is widespread throughout the spinal cord, and lower in the ventral relative to the dorsal horn. GABAergic terminals are consistently found surrounding and contacting motoneuron cell bodies and proximal dendrites (186, 510, 775, 827, 875). GABA or its receptors are present in synaptic densities of cervical and lumbar motoneurons (290, 878, 937, 941, 942, 1027, 1197), at a low percentage of presynaptic (axoaxonic) terminals (290, 1197), and at extrasynaptic sites (1197).

α_2- and α_3-subunit mRNA are the most abundantly expressed of the α-subunits in the spinal cord. The α_2-transcript (770, 971, 972, 1374) and protein (116) and the α_5-subunit (116) are present in spinal motoneurons, whereas the α_1-, α_3-, and α_6-transcripts (770, 971, 972) and α_1-protein (115) are either absent or very sparse. Binding studies are generally consistent with these findings. Most spinal neurons have only type II benzodiazepine receptors (136) which, in transfected cells, are associated with α_2- and α_3-receptors (1009). Benzodiazepine type I pharmacology, which is not apparent in spinal neurons, is typically associated with α_1-receptors.

β_3-mRNA, but not β_2 (971, 972, 1374), has been localized in spinal motoneurons. However, in contrast to dorsal horn cells and other regions of the spinal cord, the lack (116) or low level (25, 1045) of immunolabeling for β-subunit protein in spinal motoneurons questions a major role for β-subunits in native motoneuronal GABA$_A$ receptors.

Spinal motoneurons also express mRNA for the γ_2-subunit (770, 971, 972, 1374) and γ_2-immunolabeling (116, 1197). The γ_1- and δ-transcripts have not been localized to spinal motoneurons (972). Differences in expression along the length of the cord are not apparent (116). Thus the combinations of GABA$_A$ subunits most likely to form receptors on spinal motoneurons are $\alpha_2\gamma_2$ or $\alpha_2b_3\gamma_2$ in unknown stoichiometry. Continued development of subunit-specific antibodies (282) is required to confirm the presence of subunit protein.

II) Cranial motoneurons. GABA$_A$ receptors are also ubiquitous on cranial motoneurons (18, 875, 1177), but expression patterns of the various receptor subunits appear to differ between cranial and spinal motoneurons (Table 6). Facial and trigeminal motoneurons of adult rat express transcripts for α_1-, α_2-, β_{1-2}-, and γ_2-subunits but very low levels, or absence, of α_3-, α_5-, α_6-, β_1-, γ_1-, and δ-transcripts (972). α_1-mRNA is also strongly expressed in DMV, XII, facial, III, IV, VI, with only weak labeling in V (483). Immunohistochemical analyses with antibodies specific to α_{1-3}-, α_5-, $\beta_{2/3}$-, γ_2-, and δ-subunits indicate intense to moderate labeling for α_1-, α_2-, and γ_2-subunits and weak labeling for α_3 and α_5 in III, V, VII, ambigual, DMV, and XII motoneurons. The only exceptions to this general pattern are that V and DMV show minimal labeling for α_1 and that $\beta_{2/3}$ has only been detected in the VII nucleus (388). Thus the major feature distinguishing cranial from spinal motor pools is the presence of α_1- and α_3-subunits in cranial motoneurons. Of considerable interest as well is the apparent lack of $\beta_{2/3}$-subunits in all motoneuron pools (spinal and cranial), because β-subunits are widely expressed in many other neuron types. Differences between functional groups of cranial motoneurons are not yet apparent.

B) GLYCINE RECEPTOR LOCALIZATION. Localization of glycinergic neurons and terminals has been examined by exploiting high-affinity uptake of [^{3}H]glycine (494, 547) and glycine immunohistochemistry (180, 738, 739, 937, 941, 942, 1029, 1251, 1252, 1300, 1389). The postsynaptic localization of receptors on cranial and spinal motoneurons has been established through receptor autoradiography with [^{3}H]glycine and [^{3}H]strychnine (11, 140, 1010, 1061, 1419), immunohistochemistry (35, 115, 424, 1138, 1251–1253, 1270, 1271, 1300), and in situ hybridization (390, 642, 786, 1017, 1018, 1081, 1083, 1339). On cranial and spinal motoneurons, glycine receptors appear confined to the postsynaptic membrane, with few differences among the various motoneuron pools. One notable exception is the reduced labeling of visceromotor motoneurons (EW and DMV) relative to cranial motoneurons innervating striated muscle.

The differential expression of glycine receptor subunit proteins on motoneurons is poorly described. Specific antibodies are only available for α_1-subunits and gephyrin. Few motoneuron studies have used the α_1-an-

TABLE 6. *Expression of $GABA_A$ receptor subunits in motoneurons*

	α_1		α_2		α_3		α_5		α_6		β_1		β_2		β_3		γ_1		γ_2		δ		
Motoneuron Nuclei	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	I	ISH	Reference No.
Cranial motoneurons																							388, 483, 972
Oculomotor (III)	2–3	3	2–3		1		1						nd		nd				2	2–3	nd		
Trochlear (IV)		3																					
Trigeminal (V)	1	1	2–3	1	1	A/L	1	A/L		A/L		nd	1	1	1	1		A/L	2	2–3	nd	A/L	
Abducens (VI)		3																					
Facial (VII)	2–3	2–3	2–3	2	1	A/L	1	A/L		A/L		A/L	1	1	1	1		A/L	2	2–3	nd	A/L	
Vagal (X) (DMV)	1	3	2–3		1		1						nd		nd				2	2–3	nd		
Ambigual	2–3		2–3		1		1						nd		nd				2	2–3	nd		
Hypoglossal (XII)	2–3	3	2–3		1		1						nd		nd				2	2–3	nd		
Spinal motoneurons	A/L	A/L	2.5	3	A/L	A/L	1–2			A/L			A/L	nd	A/L	2		nd	2	2		nd	25, 115, 116, 770, 971, 972, 1045, 1197, 1374

Table 6 is based solely on data from immunohistochemical (I) and in situ hybridization (ISH) analyses. Subunits/transcripts for which data are not available have been excluded. Labeling intensity was reported as follows: nd, not detected; A/L, absent/low; 1, low; 2, moderate; 3, strong. Blank entry indicates data not available. Note: in general, antibodies to β_2-subunits do not distinguish between β_2 or β_3.

tibody (80, 1270, 1271). Most have used a nonspecific antibody or the antibody to gephyrin (35, 115, 424, 1138, 1251, 1252, 1300; for description of antibody specificity, see Refs. 80, 981, 1271). Evidence that gephyrin may also be expressed at nonglycinergic synapses indicates the need for caution in using gephyrin immunoreactivity on its own as a marker for glycinergic synapses (1251).

Distribution of glycine receptor subunit transcripts assessed with in situ hybridization indicates marked developmental changes in expression patterns but similar patterns between the different motoneuron pools of the adult. In general, transcripts for α_1- and β-subunits are highly expressed in adult cranial and spinal motoneurons (390, 786, 1081, 1083). α_2-Transcripts are reduced relative to α_1 (786, 1339) but show similar patterns of distribution (1017, 1018). Gephyrin transcripts are high in spinal motoneurons (642), whereas α_3-mRNA is barely detectable in spinal ventral horn and hypoglossal motoneurons (786, 1159). Details of the α_4-distribution are also unclear, but low levels are expressed in spinal cord of mouse. The only marked spatial difference in expression is that, relative to spinal and cranial motoneuron pools innervating striated muscle, α_1-transcripts appear reduced in motoneurons innervating the eye muscles (1083). Consistent with immunohistochemical data, α_1-, α_2-, and β-transcripts are also reduced in visceromotor nuclei (EW and DMV) relative to motoneurons innervating striated muscle (390, 1081, 1083).

Subcellular distribution of glycine receptor transcripts may, however, differ between spinal and cranial motoneuron pools. In the majority of spinal cord motoneurons, α_1- and α_2-transcripts are localized in the soma and dendrites, whereas β-subunit and gephyrin mRNA are restricted to the soma (1017, 1018). In contrast, in facial, hypoglossal, and ambiguual motoneurons, α-transcripts are restricted to the soma (1018). Association of α-subunit mRNA in the dendrites with postsynaptic differentiations could provide dynamic modulation of synaptic efficacy (in spinal motoneurons but not cranial motoneurons) by changing composition and density of receptors at glycinergic synapses (1017).

C) SPATIAL DISTRIBUTION OF AMINO ACID RECEPTORS OVER THE SOMATODENDRITIC TREE. Ultrastructural characteristics of excitatory and inhibitory synapses on motoneurons are well established. Analysis of the distribution of presumptive excitatory (glutamatergic; S- or M-type terminals) and inhibitory (GABA- or glycinergic; F-type terminals) boutons (97, 114, 238) (139, 691, 1058), combined with postembedding immunohistochemical studies of amino acid transmitters in boutons synapsing with motoneurons, have provided important insight into the spatial distribution of synapses on motoneurons. Although many of the original studies focused on the soma and proximal dendrites (290, 291, 510, 941, 1027), extension of these studies to include distal dendrites has been essential, since dendrites comprise >90% of the motoneuron receptive domain.

A number of general organizational features are emerging. *1*) Between 85 and 95% of boutons on spinal motoneurons (lumbar, phrenic, sacral) are immunoreactive for glutamate, GABA, and/or glycine (878, 937). *2*) There is extensive colocalization of GABA and glycine

with terminals that are exclusively glycinergic exceeding those that are exclusively GABAergic (582, 937, 941, 942, 1205). *3*) Close to 60% of boutons apposing dendrites of spinal and brain stem motor nuclei of cat and rat contain glycine and/or GABA (291, 937, 941, 942, 1027, 1071, 1150, 1205). *4*) Glutamate-enriched boutons appear to comprise just over one-third of boutons in lumbar and sacral motoneurons (937) and between ~48 and 58% of boutons in the phrenic nucleus (878, 1207). *5*) The proximal compartment (soma and stem dendrites) appears to be under powerful glycine/GABA inhibitory influence. The proximal compartment of lumbar motoneurons has a glycine/GABA-to-glutamate synaptic ratio of 3.5–4:1, and the distal compartment has a ratio of ~1.5:1 (937). The proportion of glutamate and inhibitory synapses does not appear to vary between proximal and distal dendritic compartments in phrenic motoneurons (878). However, exclusion of smaller distal dendrites from the sample raises the possibility that the proximal compartment of phrenic motoneurons is also under stronger inhibitory control. *6*) Inhibitory synapses are not limited to the soma and proximal dendrites. Distal compartments of lumbar motoneurons show a uniform balance between inhibitory and excitatory synapses, with glutamate accounting for 40% of synapses (937). The importance of inhibitory synapses in dendrites has long been recognized. Not only can inhibition gate action potential production at the soma, but it can control the weight of excitatory inputs from different dendritic regions (1162).

The spatial distribution of functionally identified synapses and the molecular composition of glutamate/GABA/glycine receptors underlying these inputs are not yet known. Postembedding immunohistochemical studies with antibodies specific to the different receptor subunits in conjunction with electron microscopic analyses, similar to that used for NMDA receptor subunits in hippocampal and cerebellar neurons (977, 979), will greatly increase understanding of the ultrastructural localization of receptor subunit protein on the cell soma and dendrites of motoneurons (for reviews on factors controlling glutamate receptor distribution, see Refs. 324, 662, 1349). Description of the receptor subtypes/subunits mediating specific physiological inputs will require controlled activation of synapses at specific sites on specific dendritic branches, refinement of techniques for precise application of agonists/antagonists, and continued development of subtype/subunit-selective agonists/antagonists (370).

4. *Physiological significance of GABA and glycine receptor diversity in modulation of motoneuron excitability*

Inhibitory control is elaborated by GABA and glycine receptor diversity, heterogeneous spatial distribution of receptors, and colocalization of GABA and glycine. As previously discussed for glutamatergic transmission, the physiological significance to motoneuron excitability of the potential diversity of GABA and glycine receptors conferred by multiple subtypes, subunits, and posttranscriptional modification remains one of the major unanswered questions of amino acid transmission. Relatively little is known of the structure-function relationships of native GABA receptors in any neuron. In motoneurons, attempts to identify the native GABA receptors have been limited to immunoprecipitation studies (971) and immunochemical and in situ hybridization analysis of subunit expression. Attempts to match properties of native receptors to those of recombinant receptors have not yet identified a single native $GABA_A$ receptor in any neuron; however, analysis of the contribution of subunits to functional properties of recombinant receptors is far from complete. Physiological properties of recombinant receptors affected by subunit composition include GABA potency, conductance state, gating properties, modulation by steroids and phosphorylation, and intensity of benzodiazepine amplification of Cl^- currents (150, 242, 772, 1016). The signal transduction mechanism, however, remains virtually unchanged in various receptor subtypes. The major functional implication of $GABA_A$ receptor diversity may be associated with changes in the channel-gating potency of GABA (242). The EC_{50} of 19 different subtypes of recombinant $GABA_A$ receptors varies from 0.3 to 15 μM (308). The importance of varied gating affinity of GABA receptors in control of motoneuron excitability is not clear, but in hippocampal and cortical pyramidal neurons, it is postulated to be critical for synchronizing the firing rate and coordinating neuronal interactions in columnary cortical activity (242).

The potential diversity of glycine receptors is less than that for $GABA_A$ receptors. However, variations in subunit composition affect gating properties and may account for the heterogeneity in the voltage dependence and desensitization properties of glycine responses (1023). The most obvious change in glycine receptor structure and function occurs during the first 2–3 postnatal weeks, when the fetal/neonatal receptor (most probably an homomeric α_2-receptor) matures to the adult heteromeric form that lacks significant α_2-subunit. The open time of recombinant α_2-receptors is much greater than for homomeric α_1- and native adult receptors (1159, 1219). These changes are consistent with developmental decreases in the decay time course of inhibitory postsynaptic currents (IPSC) in spinal neurons. In hypoglossal motoneurons, a postnatal switch from α_2- to α_1-glycine receptor subunit expression correlates with shorter channel open times and faster PSC/P decays, matching kinetic properties of glycinergic synaptic potentials to membrane properties of the motoneurons (1159). Thus changes in glycine receptor structure appear to significantly alter glycinergic transmission during development.

It is unlikely that any single approach will reveal the functional and molecular profiles of native GABA or glycine receptors in individual motoneurons (824, 1375); electrophysiology remains the best approach for assessing physiological, biophysical, and pharmacological properties of $GABA_A$/glycine receptors (1407), but without subunit specific agonists/antagonists, it does not provide information on subunit composition. Difficulties of examining multiple subunits in a single neuron must be overcome to identify native receptors.

For a more thorough treatment of physiological properties that may be conferred by the presence or absence of specific receptors subunits on motoneuron membrane, we refer readers to our summary of receptor subtypes/subunits expressed on specific motoneuron pools and recent reviews on analysis of recombinant $GABA_A$ (242, 761, 824, 852, 1016, 1309) and glycine receptors (1023, 1306).

5. *Post- and presynaptic actions of inhibitory amino acids*

A) POSTSYNAPTIC ACTIONS: $GABA_A$ AND GLYCINE RECEPTORS. Inhibitory postsynaptic potentials were first recorded in cat motoneurons (241) and subsequently attributed to activation of glycine and $GABA_A$ receptors (257, 668, 1347). Activation of glycine (213, 257, 649, 668, 1211, 1215, 1221) or $GABA_A$ receptors (257, 275, 668, 782, 1221) in adult spinal and cranial motoneurons by exogenous or synaptically released agonists elicits similar responses comprising an opening of Cl^--selective ion channels, inward movement of Cl^-, a decrease in membrane resistance, and membrane hyperpolarization. GABA and glycine receptors also have at least four similar conductance states, although the main conductance state differs (124, 462, 1169, 1218). The primary difference between the two receptors lies in their response kinetics; $GABA_A$ receptor-mediated responses decay more slowly and show greater desensitization.

Although predominantly hyperpolarizing, GABA and glycine responses can also be depolarizing if intracellular Cl^- concentration is elevated. Thus, in neonatal (or fetal) motoneurons, where intracellular Cl^- is elevated relative to adult, responses to $GABA_A$ (413, 1192, 1389) and glycine agonists, either exogenously applied (413, 1389) or synaptically released (412, 557, 582, 1159, 1211), are typically depolarizing (HCO_3^- flux does not contribute to the depolarizing response in motoneurons, Refs. 413, 967). Note that although these Cl^--dependent potentials are depolarizing, large decreases in input resistance are believed to underlie the fact that they remain inhibitory (412, 413, 1159, 1192, 1389).

The ontogeny of many aspects of GABA and glycinergic transmission has been examined in spinal motoneurons (412, 413, 1389); however, a clear description of the developmental stage where depolarizing GABA/glycine responses become hyperpolarizing is lacking. Whole cell recordings, while providing valuable information on kinetics of GABAergic and glycinergic IPSP/C of neonate and adult motoneurons (1215, 1218), are not well-suited for these measurements because of disruptions in internal Cl^- concentration. Perforated-patch recordings using the Cl^--impermeant ionophore gramicidin indicate a change in reversal potential of glycinergic IPSC in hypoglossal motoneurons from -37 to -73 mV between postnatal *days 0* and *18* (1159). A more complete developmental analysis using similar techniques in spinal as well as cranial motoneurons is required.

In summary, activation of $GABA_A$ and glycine receptors decreases motoneuron excitability, apparently regardless of whether the responses are depolarizing or hyperpolarizing. In adults, membrane hyperpolarization combines with a significant reduction in input resistance that shunts excitatory inputs to reduce excitability. In neonates, the reduction in input resistance and associated shunt has the dominant effect on excitability, reducing action potential output to injected and synaptic current despite the membrane depolarization (413, 668, 1192, 1389). Note, however, that a depolarizing versus hyperpolarizing shunt will have different effects on voltage-gated channels. The consequences of this differential activation of voltage-gated channels for motoneuron excitability remain to be studied.

B) COLOCALIZATION/CORELEASE OF GABA AND GLYCINE. A recurrent theme in studies of inhibitory transmission is the extensive degree of overlap between GABAergic and glycinergic systems. There is strong anatomical evidence for the colocalization of $GABA_A$ and glycine receptors at single postsynaptic densities (115, 1252, 1270) and for GABA and glycine colocalization in presynaptic terminals (937, 941, 942, 1150, 1205, 1252). Electrophysiological measurements are consistent with GABAergic and glycinergic contributions to IPSP/C in cranial motoneurons (656), as well as recurrent (1099), afferent, and descending inhibitory inputs to spinal motoneurons (412, 413, 991, 992, 1191, 1389). In fact, GABA and glycine can be coreleased from the same presynaptic vesicle (582) (see Fig. 6). The postsynaptic complement of receptors, however, is not constant between synapses. Analysis of evoked and mIPSC suggests three types of inhibitory synapses on spinal motoneurons: GABA only, glycine only, and mixed synapses comprising 15, 41, and 44% of the total input, respectively (582). These data raise a large number of important questions regarding how terminal type is determined, how transmitters are packaged, and how postsynaptic densities are constructed to match terminal type (914). The functional significance of this corelease to synaptic integration and motoneuron excitability is also uncertain. With the only major difference between the actions of GABA and glycine being the prolonged action

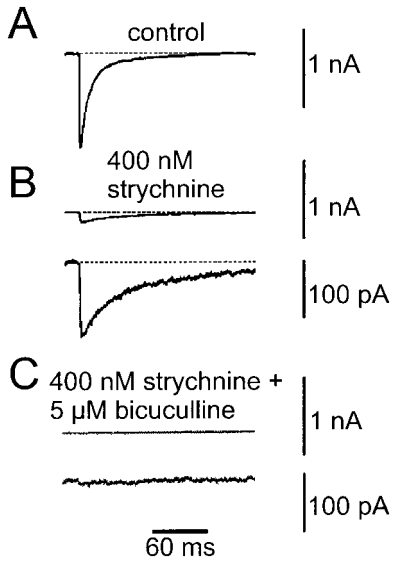

FIG. 6. Corelease of glycine and GABA. Simultaneous whole cell patch-clamp recordings from a spinal interneuron and a (putative) motoneuron in a spinal cord slice. *A*: unitary inhibitory postsynaptic currents (IPSC) in this neuron pair before antagonist application. *B*: IPSC is partially blocked by 400 nM strychnine (glycine antagonist). *C*: remaining inhibitory synaptic current is blocked by adding 5 μM bicuculline ($GABA_A$ antagonist), demonstrating corelease of glycine and GABA in this motoneuronal synapse. *Bottom traces* in *B* and *C* are shown at an expanded amplitude scale. [From Jonas et al. (582). Copyright 1998 American Association for the Advancement of Science.]

of GABA, e.g., time constants of decay for the $GABA_A$ and glycine component in spinal motoneurons are ~59 and ~16 ms, respectively (582, cf. Ref. 413), the control of the relative amount of GABA versus glycine may regulate the time course of the inhibitory input, which would be of critical importance for motor coordination.

c) PRESYNAPTIC ACTIONS OF $GABA_A$ RECEPTORS. Presynaptic inhibition by GABA receptors was first proposed to underlie the reduction in group Ia excitatory postsynaptic potentials in spinal motoneurons that could not be accounted for by postsynaptic mechanisms (381). The best anatomical evidence for $GABA_A$ receptor-mediated presynaptic inhibition of synaptic transmission to motoneurons is electron microscopic detection of GABA-like immunoreactivity in axoaxonic terminals presynaptic to afferent terminals in lamina VI and IX (280, 290, 809) and GABA receptor immunoreactivity on terminals presynaptic to motoneurons (1197; see also Refs. 824, 1187). Electrophysiological evidence for $GABA_A$-mediated presynaptic inhibition includes indirect measurement of changes in the inhibition of ventral root reflexes or dorsal root potentials after activation of a conditioning stimulus (253, 318) and direct intracellular measurement of presynaptic inhibition of afferent-motoneuron EPSP (1191).

$GABA_A$-mediated presynaptic inhibition appears to result from depolarization of primary afferent terminals in dorsal and ventral horns (256). Volleys of action potentials arriving in the spinal gray matter from segmental (afferent) or supraspinal (descending) sources initiate release of GABA from spinal interneurons. Subsequent activation of $GABA_A$ receptors on presynaptic terminals depolarizes the terminal and inhibits release of excitatory transmitter at the primary afferent-motoneuron synapses. $GABA_A$ receptor activation depolarizes primary afferent terminals because sensory neurons have reversal potentials for Cl^- that are more positive than resting membrane potential (see review in Ref. 26). However, the precise mechanism by which primary afferent depolarization (PAD) inhibits transmitter release is not known. The prevailing hypothesis is that PAD inactivates Na^+ channels sufficiently to block action potential invasion into the terminals (or reduce action potential amplitude), thereby suppressing transmitter release. Transmitter-induced membrane shunts (1326) and inactivation of Ca^{2+} currents may also contribute (254, 435, 697, 782, 819, 1123, 1328).

6. *Functional role of GABA and glycine in modulating motoneuron excitability*

a) POSTSYNAPTIC $GABA_A$ AND GLYCINE RECEPTORS. Activation of postsynaptic inhibitory receptors via local interneurons within or near cranial (199, 386, 387, 738, 739, 1029, 1277) and spinal (475, 1324, 1370) motoneuron pools, in conjunction with inhibitory projection neurons from the brain stem (504, 506) *1*) control motoneuron responses to mono- and polysynaptic afferent and descending inputs, *2*) help establish motoneuron recruitment order and gain, and *3*) shape temporal and spatial patterns of activity in different motoneuron pools during reflexive and rhythmic behaviors and changes in state.

The contribution of postsynaptic $GABA_A$ and glycine receptors to afferent reflex and descending inhibitory control of motoneuron activity has been demonstrated in spinal motoneurons through stimulation of dorsal roots (570, 571, 991, 1389), ventral funiculi (333, 992), single afferent fibers, and premoto/interneurons (582, 1215). Cranial motoneurons are subject to similar inhibitory control (429, 631, 656, 886, 1221, 1222, 1406). However, considerable heterogeneity is apparent in these control systems. The relative contribution of GABA and glycine varies regionally between motoneuron pools and input pathways.

GABA- and glycine-mediated postsynaptic inhibition of motoneuron activity also contributes significantly to production of rhythmic behaviors, including respiration (353, 834), locomotion (201, 486, 644, 968), chewing (207, 337, 538), and swallowing (105), where motoneuron activity is characterized by sequential phases of excitation and inhibition. Inhibitory synaptic control of excitability during the active phase will affect the timing of burst onset and offset (affecting onset of muscle contraction and relaxation), firing pattern, and recruitment order

(961, 969, 1049, 1377, 1379). Inhibitory inputs during the quiescent phase in a motoneuron, e.g., during the expiratory phase in an inspiratory neuron, will reduce the probability of spurious, and inappropriate, activation (1049). Inhibition seen at the end of each phase of activity is presumed to facilitate phase transitions but may not be obligatory to rhythm generation (355).

Inhibition may also provide phase-specific control of motoneuron gain, as suggested by the observation of a phasic inspiratory inhibition of phrenic motoneurons that matches the shape and time course of their inspiratory excitatory drive (961). Because phrenic motoneurons (444), like most motoneurons (292, 1084, 1143, 1221, 1394), participate in multiple behaviors, such a mechanism may contribute to the optimization of motoneuron excitability for different motor tasks.

Postsynaptic inhibition also modulates motoneuron excitability during behaviors such as micturition and over longer time scales associated with sleep state-dependent changes of muscle tone. In micturition, tonic activation of motoneurons innervating the external urethral sphincter during bladder filling (172, 351) is suppressed during voiding (350, 352), in part by a postsynaptic glycinergic mechanism (1138). Glycinergic inhibition of most spinal and some cranial motoneurons is also responsible for the atonia of rapid-eye-movement (REM) sleep (212, 485, 652, 1179). A perplexing aspect of this inhibition is its regional heterogeneity. Although most spinal motoneurons are inhibited, some inspiratory motoneurons are not, which is probably essential to avoid atonia of respiratory muscles. Among cranial motoneurons, the mechanism of inhibition varies during REM sleep. For example, in trigeminal motoneurons (649–651, 965, 1029), inhibition is glycinergic, whereas the inhibition of hypoglossal motoneuron activity results primarily from disfacilitation (669, 670, 672, 1378). The mechanisms underlying this differential control are incompletely understood but remain of considerable interest because of their potential involvement in conditions such as cataplexy, REM behavior disorder, and state-dependent respiratory disorders such as obstructive sleep apnea and perhaps sudden infant death syndrome.

B) PRESYNAPTIC $GABA_A$ RECEPTORS. Presynaptic inhibition mediated by $GABA_A$ (and $GABA_B$; see sect. IV*D3*) receptors is not ubiquitous within the spinal cord. It appears to be a specialized feature of specific pathways that is mediated through complex interneuronal circuits (see Fig. 4 in Ref. 753). For example, $GABA_A$ receptor activation depolarizes afferent terminals from muscle (Ia, Ib, and type II) and skin but does not depolarize terminals of neurons projecting from the lateral vestibular (263) or red (260, 261) nuclei. Moreover, PAD of various classes of afferents is differentially affected by segmental and descending inputs (1062, 1063). Activation of group I afferents and vestibulospinal pathways induces PAD in Ia afferents, whereas cutaneous, reticulospinal, rubrospinal, and corticospinal pathways inhibit PAD. In contrast, stimulation of group Ib afferents, reticulospinal, rubrospinal, vestibulospinal, and corticospinal pathways induces PAD in Ib afferent terminals. Cutaneous afferents induce PAD in some Ib terminals and inhibit it in others. Part of this differential control is due to mediation of PAD in Ia and Ib afferents by different pools of last order GABAergic interneurons, with descending activity targeting specific sets of these interneurons (753). The observation that presynaptic inhibition induced through intraspinal stimulation differentially affects separate axonal branches of the same group I fiber (322, 323), and that ascending and segmental collaterals of individual spindle afferents can be separately controlled (753), suggests a complex spatial organization of presynaptic inhibitory circuits.

The functional significance of pathway-specific expression and modulation of PAD is not known, but it may provide a substrate for gating of different functional classes of afferents. The pattern of coactivation of axoaxonic synapses could presynaptically control the flow of information through the axonal arbor (696). Thus presynaptic inhibition may play an important role in the selection of sensory signals required for the execution of specific motor tasks (221, 753, 819, 904, 1062, 1063, 1154).

7. Development of GABA and glycine receptor systems

A) GABA DEVELOPMENT. The GABAergic system undergoes substantial developmental regulation (709, 769, 770, 823, 1001, 1002, 1033, 1106, 1391). Transcripts for α_2, α_3, α_5, β_{2-3}, and γ_{2-3} are all present in presumptive motoneurons of the mantle zone by embryonic *day 13* in rat. Peak expression of subunits occurs between embryonic *day 17* and *20* when mRNA for α_{2-5}, β_{1-3}, and γ_{1-3} subunits are all present. α_{3-5}, β_{1-2}, γ_1, and γ_3 then decrease and are almost absent by the end of the second postnatal week (770). Developmental changes in transcript expression appear to result in changes in the amount of receptor protein subunit (389, 712).

The precise role of $GABA_A$ receptors in development of motoneuron circuits and modulation of motoneuron excitability is not known. GABA itself can alter $GABA_A$ (and $GABA_B$) receptor expression (748, 783, 784, 1106). In addition, the abundant expression of $GABA_A$ receptors in embryonic and neonatal spinal cord may serve a trophic role in regulation of neuronal differentiation and synaptogenesis (828). In early development, depolarization due to $GABA_A$ receptor activation could elevate intracellular Ca^{2+} levels, a potentially important signal in modulating early differentiation (1182). In addition, GABA- (and glycine-) mediated depolarization, in conjunction with the observation that in some systems glutamatergic synaptic transmission is strongly mediated by NMDA receptors early in development (1433), has led to the suggestion that in hippocampus GABA receptor activation may facilitate

activation of NMDA receptors (87). In such a scheme, GABA- (and glycine- see below) mediated depolarization would play the role in activity-dependent organization of neuronal circuits conferred on AMPA receptors later in development. The relevance of such a mechanism at the motoneuron level is not known.

B) GLYCINE DEVELOPMENT. Glycine receptors show marked developmental heterogeneity. Relative to the adult form, the neonatal receptor has low affinity for strychnine (1376) and contains an α-subunit with different molecular mass and antigenic epitopes (700, 1023, 1306). Developmental changes in subunit expression from a neonatal receptor composed primarily of α_2* are likely to underlie these differences, because α_1, α_3, and β subunits and transcripts are expressed at low levels in the fetus and neonate (786, 1339). Only α_2* receptors have the low strychnine sensitivity characteristic of neonatal receptors, whereas the prolonged time course of fetal/neonatal postsynaptic potentials/currents is consistent with recombinant α_2 receptors (1159, 1219). If the depolarizing actions of glycine (and GABA, see above) during development contribute to activity-dependent organization of motoneuronal circuits by removing the Mg^{2+} block of NMDA channels, the prolonged glycinergic postsynaptic potentials/currents in fetus and neonate (413, 1159) would facilitate this process.

D. GABA: Metabotropic Actions

GABA, in addition to its role as a fast inhibitory neurotransmitter, inhibits motoneuronal excitability by activating presynaptic metabotropic $GABA_B$ receptors.

1. *$GABA_B$* receptors

$GABA_B$ receptors are coupled through G proteins to produce increases in K^+ or decreases in Ca^{2+} currents and mediate slow synaptic inhibition. Two receptor genes have been identified by molecular cloning, $GABA_BR1$ and $GABA_BR2$. Interestingly, and unlike most G protein-coupled receptors which function as homomers, native $GABA_B$ receptors appear to be formed by heterodimerization of $GABA_BR1$ and $GABA_BR2$ (586, 613, 1356). Splice variants, $GABA_BR1a$ and $GABA_BR1b$, for the $GABA_BR1$ clone have also been identified. These forms have similar pharmacological profiles but clearly a major goal of future studies is to define possible receptor subtypes (99, 128, 446, 612). Analysis of native receptors suggests at least five receptor subtypes, but it is not yet clear whether individual genes exist for each (251, 417). The cloning of the receptor should precipitate a vast increase in our understanding of $GABA_B$ receptor physiology including further delineation of its mechanisms of action (99) as well as its pre- and postsynaptic distribution within the CNS (118, 129, 626, 843, 873, 893).

2. *$GABA_B$* receptor localization

$GABA_B$ receptor distribution has primarily been explored with receptor autoradiography (130, 132, 220, 415, 1006, 1007). Patterns of $GABA_A$ and $GABA_B$ receptor binding are not identical but do show considerable overlap. $GABA_B$ binding sites are distributed heterogeneously in the CNS. Within the spinal cord, the highest densities occur in the dorsal horn (11, 130, 783, 1006, 1007), but ventral horn binding is also present (11, 1006). Binding in the brain stem is highest in the spinal trigeminal nucleus.

A substantial presynaptic localization of $GABA_B$ receptors in the dorsal horn is suggested by 50% reductions in binding after capsaicin-induced degeneration of sensory afferents (1006, 1007). It is not known whether $GABA_B$ binding sites in the ventral horn are pre- or postsynaptic. Dorsal rhizotomy does not alter ventral horn binding, suggesting postsynaptic localization. $GABA_B$ agonists, however, have minimal effect on motoneuron properties (see below), leaving the possibility that ventral horn binding represents presynaptic sites on descending fibers (1006, 1007) or local interneurons.

3. *Post- and presynaptic actions*

A) POSTSYNAPTIC. In contrast to $GABA_A$ receptors, postsynaptic $GABA_B$ receptors appear to be of minimal importance in the regulation of motoneuron excitability. Application of the $GABA_B$ agonist baclofen at concentrations sufficient to depress excitatory and inhibitory synaptic activity is not associated with changes in motoneuron membrane potential, conductance, excitability, time constant, or EPSC decay (321, 572, 661, 731, 973, 985, 1317). Postsynaptic effects in mammalian motoneurons, including hyperpolarization, decreases in input resistance, and reductions in excitability and the afterhyperpolarization (276, 377, 1334; cf. Ref. 694), are only observed using high concentrations of baclofen.

Postsynaptic receptor involvement, however, cannot be completely excluded. $GABA_B$ agonists affect motoneurons of lower vertebrates (806). If the $GABA_B$-mediated postsynaptic action occurs at distal dendrites, as appears to be the case in other neurons (843, 873), a $GABA_B$ receptor-mediated change in membrane potential/conductance may not be detected at the cell soma (686) but could still affect the neuronal response to other distal dendritic inputs.

B) PRESYNAPTIC. $GABA_B$ receptor activation with exogenous agonists such as baclofen is associated with presynaptic inhibition of excitatory synaptic transmission to cranial (461, 930) and spinal motoneurons. Glutamatergic Ia, Ib afferent, and dorsal root evoked potentials in spinal motoneurons are inhibited by baclofen (27, 259, 276, 321, 377, 661, 731, 734, 973, 985, 991, 1191, 1317, 1334, 1390). $GABA_B$ receptor activation is also associated with reductions in presynaptic Ca^{2+} influx (255) and in release of

glutamate (604, 1239), substance P (780, 1239), and calcitonin gene-related peptide (CGRP) (781) from primary afferent terminals (127). A similar, although less potent, $GABA_B$-mediated inhibition of transmission occurs at excitatory synapses descending through ventrolateral (321, 992) and ventromedial funiculi or from the reticular formation and vestibular nuclei (572). The apparent absence of presynaptic $GABA_B$ modulation of some descending inputs (261, 611) again highlights the potential for pathway-specific presynaptic modulation of motoneuron excitability.

The action of baclofen on inhibitory synaptic transmission to motoneurons is less consistent. Positive and negative results have been reported (276, 377, 611, 985, 1013). Suppression of spontaneous and evoked IPSP in rat spinal motoneurons by baclofen (1334) suggests that inhibitory inputs to motoneurons are under presynaptic control. However, the possibility that the inhibitory actions of baclofen on IPSP in these polysynaptic pathways is secondary to blockade of release of excitatory transmitters acting on inhibitory interneurons cannot be excluded.

$GABA_B$ agonists also suppress $GABA_A$-mediated PAD (259, 1013). $GABA_B$ autoreceptors in terminals of last-order interneurons mediating PAD may function as a self-limiting mechanism controlling synaptic efficacy of these interneurons (843, 1013). Interestingly, the baclofen suppression of PAD is greater for Ib afferent-induced PAD than for PAD induced by descending reticular formation inputs. Thus last-order interneurons mediating PAD via segmental pathways may have a greater density of $GABA_B$ autoreceptors than those mediating PAD via descending pathways (1013). In spinal motoneurons of *Xenopus*, there is a $GABA_B$ receptor-mediated presynaptic inhibition of glycinergic inputs (1325); this has yet to be seen in mammalian motoneurons.

In addition to the effects on individual postsynaptic potential/currents, $GABA_B$ receptor activation is implicated in activity-dependent modulation of synaptic transmission. The efficacy of synaptic contacts can be modified by activity in the presynaptic neuron. For example, high-frequency activation of afferent inputs to spinal motoneurons can produce synaptic facilitation and depression and tetanic and posttetanic potentiation (973). For Ia afferent to motoneuron synapses, large-amplitude EPSP in motoneurons with large input resistance and small rheobase tend to show negative modulation (depression, a progressive decrease in EPSP amplitude during high-frequency stimulation). Small-amplitude EPSP in motoneurons with low input resistance and high rheobase undergo positive modulation (facilitation, Refs. 228, 229, 832, 1117). Both types of synapses are proposed to experience increased presynaptic Ca^{2+} and elevated probability of transmitter release. However, the greater susceptibility of synapses producing large EPSP to transmitter depletion is proposed to underlie their negative modulation. Reduced susceptibility of synapses producing small EPSP to transmitter depletion would show positive modulation. $GABA_B$ receptor activation with baclofen shifts negative modulation to positive (depression to facilitation) or increases the degree of positive modulation (facilitation) (731, 732, 973), presumably by decreasing Ca^{2+} entry into the terminal (255, 990, 1117), which decreases the probability of transmitter release and depletion.

The mechanism(s) by which baclofen reduces the release of transmitters from terminals presynaptic to motoneurons is not known. In dorsal root ganglion neurons, the presynaptic inhibitory action of $GABA_B$ receptors is proposed to result primarily from a G protein-mediated reduction of voltage-sensitive Ca^{2+} currents (255, 602, 731). An increase in K^+ currents (410, 843, 873), and a third mechanism that is independent of effects on leak or voltage-gated currents identified in hippocampus, may also contribute (843).

4. Endogenous role for $GABA_B$ receptors in modulating motoneuron excitability?

Despite the clear demonstration that baclofen inhibits motoneuron activity, establishing an endogenous role for $GABA_B$ receptors in modulating motoneuron excitability has been slower. Relatively few studies have been performed at the motoneuron level. In addition, $GABA_B$ antagonists have limited efficacy in potentiating synaptic transmission, questioning the endogenous role of $GABA_B$ in modulating inputs to motoneurons (154, 1191, 1317, 1390; see also Ref. 843). Part of the limited efficacy, however, may reflect use of weak $GABA_B$ antagonists, such as 2-OH saclofen, or that $GABA_B$ antagonists applied at the cell soma do not reach distal synapses (1191). Intravenous administration of recently developed selective antagonists (154, 687, 688, 783) suggests a marked involvement of $GABA_B$ receptors in the prolonged inhibition of monosynaptic reflexes (258). Results on spinal and cranial motoneurons in vitro range from indicating substantial $GABA_B$ involvement (33, 183, 686) to no effect (154) and levels in between (1317). Discrepancies may reflect varying degrees of endogenous activation of the relevant pathways in different experimental models.

Another possibility is that $GABA_B$ receptors on afferent terminals are located extrasynaptically (1191). Under such conditions, activation of extrasynaptic receptors is only likely to occur during periods of massive GABA release (or reduced uptake) due to highly effective GABA uptake mechanisms. Paracrine-like activation of extrasynaptic $GABA_B$ receptors is present in hippocampal CA1 cells (539). Thus modulation of GABA uptake systems may play an important role in presynaptic inhibition by $GABA_B$ receptors.

In conclusion, $GABA_B$ receptors enable GABA to

modulate excitability by inhibitory and disinhibitory effects. As a result of their coupling through second messenger systems and their differential effects on afferent and descending pathways, they have the potential to produce long-term changes in excitability in a pathway-specific manner, as suggested by the therapeutic value of baclofen and $GABA_B$-related compounds. Baclofen in particular is used as a muscle relaxant in the treatment of spasticity of spinal origin (131, 781, 782, 784). Recent cloning of the $GABA_B$ receptor subunits (612, 613) will define the basis for introducing and improving the clinical profile of $GABA_B$ receptor ligands (128).

E. Serotonin

1. *Ligands, receptors, and sources of 5-HT input to motoneurons*

Soon after its initial discovery in the periphery (serum, intestinal mucosa), 5-HT was shown to be present in the mammalian CNS (29). Using the Falck-Hillarp histochemical fluorescence technique, Dahlstom and Fuxe (264, 408) demonstrated that 5-HT-positive cells are located in the midline of the brain stem and project to most of the brain. 5-HT-immunoreactive boutons are found in the ventral horn of the spinal cord, in cranial motor nuclei, and apposed to the somatodendritic membrane of cranial and spinal motoneurons, suggesting that 5-HT-containing neurons project directly to motoneurons (19, 24, 38, 39, 569, 657, 908, 988, 1072, 1186, 1224, 1286). On average, ~1,500 5-HT-immunoreactive boutons contact the dendritic area of individual spinal lumbar motoneurons in adult cats, with the vast majority of 5-HT input on the dendrites (24). Compared with the estimated total number of synaptic boutons on spinal motoneurons (50,000–140,000; Ref. 937), this means that only 1–3% of synaptic boutons on spinal motoneurons are serotonergic. A large number of 5-HT-immunoreactive varicosities associated with spinal motoneurons also contain substance P, TRH, or other peptides (see sect. III; Refs. 39, 133, 245, 908, 1237, 1286, 1348, 1388). Similar observations of 5-HT and substance P coexistence have been made in axonal varicosities in cranial motor pools (1225).

Some 15 5-HT receptor subtypes, which can be divided into seven subfamilies, have been characterized. All 5-HT receptors belong to the superfamily of G protein-coupled receptors, except for the 5-HT_3 receptors, which are ligand-gated ion channels (420, 1296). The expression pattern of different 5-HT_{2A} receptors or their transcripts has been mapped in some spinal and cranial motoneurons by immunocytochemistry, in situ hybridization, and PCR reactions detecting mRNA encoding for 5-HT receptors. In the spinal cord, immunodetection of 5-HT receptor subtypes using an anti-ideotypic antibody recognizing 5-HT_{1B}, 5-HT_{2C}, and 5-HT_{2A} receptor subtypes reveals that one, two, or all of these receptors are present in the somatodendritic region of spinal motoneurons (1046).

Use of an antipeptide antibody (44, 629) reveals a striking distribution of 5-HT_{1A} receptors in cervical spinal motoneurons (44, 629). The axon hillock is densely, and the soma is diffusely, labeled, whereas dendritic labeling is absent, suggesting that 5-HT signaling via 5-HT_{1A} receptors is localized at the site of action potential generation (44, 629). Unassembled subunits of the 5-HT_3 receptor, which is a ligand-gated ion channel, are found in the soma of both spinal and cranial motoneurons, but the location of the assembled 5-HT_3 receptors is unclear (864). Cranial motor nuclei express transcripts for 5-HT_{1A} and 5-HT_{2A} receptors (1383); in the hypoglossal nucleus, transcripts encoding for 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_7, but not 5-HT_{1A} receptors, are expressed (929). However, 5-HT_{1A} receptors are expressed in motoneurons of neonatal animals (1228).

Pharmacological and electrophysiological studies have identified several 5-HT receptor subtypes in both spinal and cranial motoneurons, and in the following section we describe the pre- and postsynaptic actions of 5-HT on motoneurons and the receptors involved.

2. *Pre- and postsynaptic actions of 5-HT on motoneurons*

Application of 5-HT (by microiontophoresis) in the vicinity of spinal motoneurons in vivo or systemic injection of 5-HT precursors generally leads to the following: an increase in motoneuronal excitability (1362), tonic muscle electromyogram (EMG) activity increases (839, 1044), and some spinal motor reflexes are facilitated (223, 233, 1044, 1079, 1401). Locally applied 5-HT produces a small (2–6 mV) depolarization in spinal motoneurons in vivo, accompanied by an increase in membrane input resistance and a reduction in the spike AHP (1359).

The postsynaptic action of 5-HT in spinal motoneurons has been studied using in vitro preparations from neonatal or juvenile animals. Bath application of 5-HT depolarizes spinal motoneurons in spinal cord slices from the neonatal rat, an effect that persists after blockade of action potential-driven synaptic transmission (by adding TTX or replacing external Ca^{2+} with Mg^{2+}) (236, 332, 1216, 1332, 1434). The 5-HT-induced current is carried by both Na^+ and K^+ through activation of an inwardly rectifying current (likely I_h); 5-HT_{1A} receptors are involved in this action (1216). 5-HT also enhances LVA Ca^{2+} currents in neonatal rat spinal motoneurons (93). One study, however, reports depolarizations as well as hyperpolarizations induced by 5-HT in spinal motoneurons from neonatal rats, effects proposed to be mediated by decreasing and increasing a K^+ current via 5-HT_2 and 5-HT_{1A} receptors, respectively (1332). Thus some spinal motoneurons in neonatal mammals may be inhibited rather than excited

by 5-HT. Consistent with these observations, iontophoretic 5-HT applications to motoneurons in adult animals in vivo produce long-lasting hyperpolarizations following an initial short-lasting depolarization (1424). Neonatal rodent phrenic motoneurons are depolarized postsynaptically by 5-HT through activation of 5-HT_2 receptors (Fig. 7) (744). In addition to this effect, exogenous 5-HT reduces the amplitude of inspiratory-modulated synaptic drive to these motoneurons, probably through activation of presynaptic 5-HT_{1B} receptors, affecting synaptic release (295, 744).

5-HT induces plateau potentials in turtle spinal motoneurons under in vitro conditions (521, 1163). The plateau potential, which gives rise to long-lasting depolarizations and bistable firing behavior, is blocked by L-type Ca^{2+} channel antagonists. The underlying ionic mechanism may involve a reduction of outward K^+ currents (primarily $I_{K\,Ca}$), thereby uncovering a L-type Ca^{2+} current present both in the soma and dendrites of these motoneurons (522). However, a direct action on L-type Ca^{2+} channels is also possible (121, 522). Plateau potentials are found in spinal motoneurons in adult cats (see sect. II*D*), when descending brain stem-spinal cord systems are intact or after spinal transection when 5-HT or NE precursors are given intravenously (239, 244, 519, 632). A reevaluation of the functional consequences of plateau potentials in hindlimb motoneurons in cats led to the suggestion that plateau potentials under normal circumstances play a role in ensuring effective recruitment rather than in generating bistable behavior (88). Finally, 5-HT reduces the amplitude of dorsal root evoked EPSP and IPSP via presynaptic 5-HT_1 receptors (1387), a mode of action also found in several cranial motor pools.

The ionic mechanisms underlying 5-HT effects on cranial motoneurons have been worked out in greatest detail for facial, hypoglossal, and trigeminal motoneurons. In vivo or in vitro, facial motoneurons respond to exogenously applied 5-HT with a depolarization (5–8 mV) and an increase in membrane input resistance (705, 1303, 1304). The depolarization is unaffected by TTX, indicating a postsynaptic site of action (705). The receptor subtype mediating the depolarization is likely 5-HT_2, but not 5-HT_{1A}, receptors (1032). The underlying ionic mechanism is a 5-HT-induced enhancement of the hyperpolarization-activated I_h current (701, 702), concurrent with a decrease in a resting K^+ current $I_{K\,leak}$ (701, 703).

Hypoglossal motoneurons are also excited by 5-HT (91, 305, 671), but mechanisms change developmentally. Exogenous application of 5-HT to hypoglossal motoneurons from neonatal rodents gives rise to a spike-initiating depolarization, with no clear change in membrane input resistance (91, 1228). Compared with adults, there is marked reduction in the spike AHP in these motoneurons (73, 91, 1228). However, hypoglossal motoneurons from juvenile animals respond to 5-HT with a depolarization associated with an increase in input resistance and show no effect of 5-HT on the spike AHP (1228). The discrepancy with regard to the spike AHP is explained by a reduction in the expression of 5-HT_{1A} receptors in juvenile animals (79, 1228). In neonatal animals, activation of 5-HT_{1A} receptors leads to a reduction in N- and P-type Ca^{2+} currents, which in turn leads to reduced spike AHP (73). Interestingly, 5-HT also acts presynaptically in the hypoglosssal nucleus of neonatal rats, reducing glutamatergic and glycinergic synaptic transmission through activation of presynaptic 5-HT_{1B} receptors (1156, 1157, 1292).

Iontophoretic application of 5-HT to trigeminal motoneurons during cortically induced masticatory-like activity facilitates trigeminal discharge, suggesting an excitatory action of 5-HT (608). A detailed analysis of the underlying ionic mechanism in trigeminal motoneurons from juvenile guinea pigs under in vitro conditions shows that 5-HT reduces a resting K^+ current ($I_{K\,leak}$), enhances the hyperpolarization-activated cationic current (I_h, via activation of 5-HT_2 receptors), and induces a Na^+-dependent inward current (I_{inw}) (526). Furthermore, the medium-duration spike AHP is reduced by 5-HT (526), and, as found in spinal motoneurons, 5-HT can induce bistable membrane behavior (527). The bistable membrane behavior and plateau potentials are due to L-type Ca^{2+} channel activation with a contribution of the Na^+-dependent inward current, but it is unclear whether 5-HT acts directly on L-type Ca^{2+} and Na^+ channels, or indirectly by reducing opposing outward currents (527). In addition to these effects on the intrinsic properties of trigeminal motoneu-

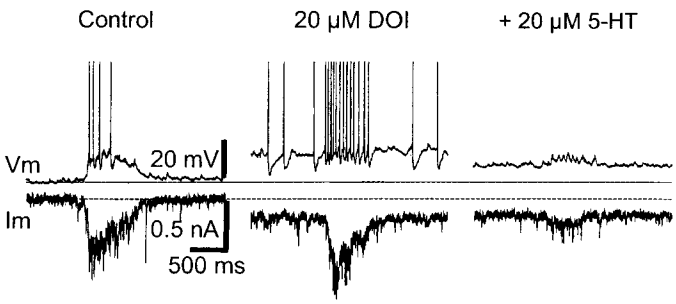

FIG. 7. 5-HT depolarizes neonatal rat phrenic motoneurons (postsynaptic effect) and reduces inspiratory synaptic drive (presynaptic effect). Current and voltage-clamp recording from a phrenic motoneuron in a brain stem-spinal cord in vitro preparation, which generates spontaneous respiratory-like motor activity. One burst of inspiratory synaptic drive is captured in each trace. Traces show the following, *left* to *right*: control condition, after exposure to 20 μM DOI (5-$HT_{2A,1C}$ agonist), and after addition of 20 μM 5-HT (25 min after DOI). Note that DOI depolarizes the membrane and induces an inward current, and addition of 5-HT reduces the amplitude of the inspiratory synaptic drive. Inspiratory drive is transmitted by glutamate. This dual action of 5-HT may play a role in ensuring transmission of inspiratory drive regardless of variations in 5-HT release as part of the sleep-wake cycle (355). V_m, membrane potential; I_m, membrane current. [Adapted from Lindsay and Feldman (744).]

rons, 5-HT enhances the response to EAA (endogenous or exogenous) via 5-HT_2 receptors (679, 1273). The facilitation could be a simple result of the increased input resistance, but may also involve direct actions of 5-HT on NMDA and AMPA channels (1273).

3. Signal transduction

Manipulations of intracellular signal transduction pathways suggest that 5-HT actions are mediated by receptors coupled to G proteins (except for the ionotropic 5-HT_3 receptors), and a phosphorylation-independent action of cAMP (6, 702, 704). Intracellularly applied cAMP or forskolin mimics the action of 5-HT on I_h in neonatal spinal motoneurons, and a broad range of protein kinase inhibitors fail to block the action of 5-HT (702, 704), suggesting that activation of 5-HT receptors stimulate cAMP production, which in turn induces an inward current, perhaps by a phosphorylation-independent direct action on I_h (702, 704). Mechanisms that account for inhibition of leak K^+ currents by 5-HT have not been determined but do not appear to involve PKC, at least in facial motoneurons (6).

4. Functional role of 5-HT in modulating motoneuronal excitability

Serotonergic neurons in the raphe nuclei are spontaneously active (1–5 spikes/s) during the normal waking state (552, 555). The discharge frequency changes during different motor behaviors, i.e., an increase in firing frequency is seen in raphe neurons in cats during treadmill locomotion compared with undisturbed waking and during oral activities such as chewing, biting, and licking (480, 1308). Conversely, a decrease in firing frequency is seen during REM sleep, when motor output is inhibited, and the release of 5-HT (measured by a microdialysis probe placed in the ventral horn) is reduced after exercise (421, 480, 556, 820). 5-HT exerts tonic facilitatory effects on spinal hindlimb motoneurons (635); after depletion of spinal monoamines in rats (using neurotoxins), there is a reduction in the total EMG activity of the soleus muscle and the duration and number of long-lasting gross-EMG episodes (635). Thus raphe neurons, projecting to spinal and cranial motoneurons, provide a tonic release of 5-HT during the normal waking state and increased cyclic release of 5-HT during gross repetitive types of motor behavior (552).

Local stimulation of the raphe nuclei with concurrent recordings from spinal motoneurons confirms the excitatory nature of the raphe-spinal 5-HT projection. Electrical stimulation of the nucleus raphe obscurus (for 1 min) induces a small depolarization in rat spinal lumbar motoneurons that is blocked by a systemic 5-$HT_{1,2}$ receptor antagonist (1048). Brief stimulation (0.1–0.7 ms) of the raphe pallidus induces subthreshold EPSP in cat spinal motoneurons (394). Stimulation of different raphe nuclei either facilitates or inhibits the activity of phrenic motoneurons (511, 512, 692, 693). The inhibitory effect is likely mediated by presynaptic 5-HT modulation of bulbospinal neurons transmitting inspiratory drive to these motoneurons, through activation of 5-HT_{1B} receptors (295, 744). Laryngeal motoneurons are excited by stimulation of the raphe pallidus, an effect blocked by pretreatment with a 5-HT_2 antagonist (37). Stimulation of the raphe pallidus-obscurus complex induces monosynaptic sub- or suprathreshold EPSP in trigeminal motoneurons (masseter and mylohyoid), and these potentials are reduced by a nonselective 5-HT antagonist (883).

In addition to these postsynaptic effects on spinal and cranial motoneurons, spinal and cranial reflex pathways are also affected by raphe stimulation. Stimulation of the raphe nuclei depress transmission from group II muscle afferents in the midlumbar spinal cord in cats (564), suggesting that release of 5-HT depresses transmission between spinal interneurons and motoneurons, or between the interneurons themselves (138). Crossed group II inhibitory reflex pathways (generating IPSP in contralateral extensor motoneurons) are under tonic control by descending serotonergic pathways, since the IPSP are abolished by lesions of descending pathways and restored by systemic administration of 5-HT_{1A} agonists (4). In spinalized rats, monosynaptic transmission is inhibited or facilitated by activation of 5-HT_{1A} and 5-$HT_{2A/2C}$ receptors, respectively (465). Under in vitro conditions, excitatory synaptic transmission induced by local electrical or dorsal root stimulation is facilitated via activation of 5-HT_{2A} and/or 5-HT_{2C} receptors (1400, 1434). Finally, 5-$HT_{2A/2C}$ agonists applied topically to the spinal cord of spinalized cats restore extensor reflex excitability, suggesting a facilitatory effect of 5-HT on the lumbar stretch reflex (839).

In conclusion, the dominant effect of the serotonergic raphe system is the enhancement of spinal and cranial motoneuron excitability. This action is mediated postsynaptically by activation of I_h, reduction of specific K^+ conductances, uncovering of L-type Ca^{2+} currents, reduction of spike AHP amplitudes, and an increase in membrane input resistance. Because raphe serotonergic neurons have a slow and regular firing pattern in the normal waking state, a constant release of 5-HT may set the overall level of excitability of motoneurons, in particular in motoneuron pools innervating axial and postural muscles (552, 555). Upon changes in motor activity, such as initiation of locomotion, mastication, and other rhythmic motor behaviors, the activity of the serotonergic raphe system is increased, and consequently, there is an increase in the responsiveness and ease of recruitment in motoneurons. In addition, the serotonergic raphe system may regulate or gate afferent inputs to motoneurons pools by modulating synaptic transmission in specific reflex

pathways and by direct actions on presynaptic terminals (355, 552). In this fashion, the raphe serotonergic system controls the excitability of motoneurons through direct actions on the motoneurons and through control of afferent input. These actions may be different in various motoneuron pools, especially those responsible for breathing movements (355).

F. Norepinephrine and Epinephrine

1. Ligands, receptors, and sources of NE input to motoneurons

Norepinephrine was initially established as a neurotransmitter in the periphery (490, 1320), and subsequently proposed to act centrally (1319). A large amount of work, neuroanatomical and neurophysiological, has since confirmed a prominent role for NE in controlling motoneuronal excitability.

All catecholamines, including dopamine, NE, and epinephrine, are synthesized in discrete populations of neurons by a series of enzymatic steps, beginning with the rate-limiting hydroxylation of the precursor amino acid tyrosine. The specific catecholaminergic neuronal phenotype is determined by the presence or absence of additional enzymes in the biosynthetic pathway: dopaminergic neurons express tyrosine hydroxylase (TH), but not dopamine β-hydroxylase (DBH); NE cells express TH and DBH, but not phenylethanolamine *N*-methyltransferase (PNMT); epinephrine-synthesizing neurons express all three (TH, DBH, and PNMT) (490). A brief discussion of dopamine and motoneuronal function will follow this section. Epinephrine and NE can both interact with adrenergic receptors at physiological concentrations. However, we limit our discussion to NE because neurons that make epinephrine have a more restricted brain distribution and provide little, if any, innervation of motoneurons (490).

The initial classification of adrenergic receptors into α- and β-subtypes (9) has expanded (173, 174, 909) to include three major classes of adrenoceptor (α_1, α_2, and β), each comprising at least three subtypes. These receptors are members of the rhodopsin family of G protein-coupled receptors. Members of each class of adrenoceptor share ~70–75% sequence homology, whereas sequence homology drops to ~40% between members of different classes (842). Pharmacological and molecular classifications of receptor subtypes do not, however, extend to clear functional differences among members of a given class, each of which utilizes similar transduction mechanisms (173, 174, 842).

Members of all three classes of adrenergic receptor are expressed in the CNS, with distinct and differential distributions for each receptor subtype. α_1-Adrenoceptors are highly expressed on cranial and spinal motoneurons, as assayed by ligand-binding autoradiography (587); in situ hybridization experiments indicate that this binding is probably somatodendritic and could reflect α_{1A}, α_{1B}, and/or α_{1D} expression, since transcripts for all three α_1-receptor subtypes are present in motoneurons at high levels (298, 986). Radioligand binding to α_1-receptors in motoneurons is detectable as early as postnatal *days 1–5*, and high levels of binding are maintained throughout development (588).

All three α_2-adrenoceptor subtypes are present in rat brain, with the α_{2B}-subtype expressed only in thalamic neurons (909, 910, 1095). Radioligand binding for α_2-receptors, both α_{2A} and α_{2C}, are found on motoneurons, albeit at low levels, and transcripts representing these α_2-subtypes are present in various motoneuronal populations (910, 1095, 1295). Immunohistochemical studies utilizing subtype-specific antibodies find somewhat different patterns of staining in motor nuclei; α_{2A}-immunoreactivity is diffuse, perhaps reflecting staining on terminals (1227), whereas α_{2C}-immunoreactivity is clearly somatic (1060). Furthermore, although α_{2A}- and α_{2C}-receptors are present at low levels in adult motoneurons, developmental studies suggest opposite developmental patterns of expression (1372, 1373). Thus α_{2A}-receptors are transiently expressed in rat motoneurons at high levels during embryonic and early postnatal periods, reaching sustained low levels by approximately postnatal *day 14* (1372); in contrast, α_{2C}-expression increases from undetectable levels in the embryo and neonate to reach somewhat higher levels in the adult (1373).

The β_1- and β_2- but not the β_3-adrenoceptors are expressed in brain (909, 911). However, there is little evidence for expression of β-adrenoceptors by motoneurons. Binding of β_1- and β_2-adrenoceptor ligands in motor nuclei is unremarkable (953, 1020), and neither β_1- nor β_2-adrenoceptor mRNA is found in motoneurons (909).

Motoneurons receive a relatively dense catecholaminergic input, the overwhelming majority of which represents NE (16, 863). NE fibers are present in spinal motor nuclei early in development (by embryonic *day 16* in rat), but they increase in density over the early postnatal period (1021, 1234). The NE input to motoneurons derives primarily from the A5-A7 cell groups in the dorsolateral pontine tegmentum, particularly from the nucleus coeruleus (A6) and subcoeruleus (A6v) (14, 451, 768, 925; see sect. III and Table 2). The relative inputs from these different NE-synthesizing cell groups to individual motor pools vary; trigeminal and spinal motoneurons receive most of their NE input from A5 and A7 cell groups, whereas the NE innervation of hypoglossal motoneurons emanates mostly from A6v cells (14, 451, 768). In addition, although NE fiber density is consistent in motor areas throughout most levels of the spinal cord and brain stem (863), a somatotopic distribution of innervation within individual motor nuclei is present. For example, fiber density is higher in the lateral part of the ventral horn at

cervical and lumbar enlargements, where motoneurons that innervate primarily distal limb musculature are located (863); it is also higher in the ventral aspects of the hypoglossal nucleus, where tongue protrusor motoneurons are located (15, 16, 297). Thus NE projections may be preferentially directed from different pontine nuclei to specific motor pools, suggesting the potential for a signaling specificity affecting motor control. It is important to point out, however, that the majority of NE-containing profiles in motor nuclei are nonsynaptic (17, 185, 1021, 1022), and therefore, extrasynaptic (i.e., volume) transmission may abrogate some of the specificity coded in the differential somatotopic distribution of fibers (1022). Nevertheless, some synaptic profiles, predominantly axodendritic, are observed between catecholaminergic terminals and motoneurons (17, 185, 1021, 1022).

2. *Pre- and postsynaptic actions of NE on motoneurons*

Early work investigating the postsynaptic effects of NE on cat spinal motoneurons reported depressed excitability and/or membrane hyperpolarization, associated with a decrease in a mixed cationic current (334, 798, 983). In contrast, all recent work indicates that the predominant postsynaptic effects of NE are excitatory, suggesting that the initial findings resulted from a methodological artifact (1362). Thus, in cranial and spinal motoneurons, NE causes a slow membrane depolarization associated with a decrease in input conductance (332, 701, 958, 1303, 1360) and enhances firing responses to glutamatergic inputs, whether applied exogenously or released endogenously (395, 608, 609, 1360–1362). These effects of NE are postsynaptic, since they are preserved in the presence of TTX or a high-Mg^{2+}, low-Ca^{2+} synaptic blockade medium.

The cellular mechanisms that mediate excitatory effects of NE have been investigated. An α_1-adrenoceptor is involved since effects of NE are *1*) blocked by α-adrenoceptor antagonists, prazosin and phentolamine, but not by the β-adrenoceptor antagonists propranolol or sotalol, and *2*) mimicked by the α_1-adrenoceptor agonist phenylephrine but not by either the α_2-adrenoceptor agonist UK-14,304 or the β-adrenoceptor agonist isoproterenol (332, 608, 609, 958, 1323). On the basis of relative agonist/antagonist potencies and insensitivity of the response to chloroethylclonidine, the facilitation of spinal motoneuronal activity by NE may be mediated primarily by the α_{1A}-adrenoceptor subtype (1323). If the excitatory effects of NE on motoneurons are indeed mediated by α_{1A}-adrenoceptors, what is the role of the other α_1-subtypes expressed by motoneurons? Perhaps individual subtypes are directed to different membrane locations, such as the motoneuronal terminals where α_1-adrenoceptors mediate facilitation of acetylcholine release by NE (1171).

As suggested by its association with an increased input resistance (332, 958, 1303, 1360), the ionic mechanism that underlies motoneuronal depolarization by NE includes a decrease in a K^+ current; the NE-modulated K^+ current is relatively voltage insensitive and blocked by Ba^{2+} (701, 958), not unlike the leak K^+ channel targeted by 5-HT, TRH, and substance P in motoneurons and by NE in other central neurons (e.g., Refs. 815, 1337). Furthermore, NE also activates a Ba^{2+}-insensitive current component in motoneurons that is carried, at least in part, by Na^+ (958) and that is also reminiscent of effects of 5-HT, TRH, and substance P in motoneurons (75, 91, 366, 367, 921). Indeed, the effects of TRH and NE occlude each other, suggesting a shared mechanism of action (958).

Two additional effects of NE influence firing responses (958): *1*) NE induces a decrease in AHP amplitude in a subset of adult hypoglossal motoneurons, which is associated with an enhanced firing response to current injection (958); *2*) NE causes an apparent enhancement of a transient K^+ current in hypoglossal motoneurons that delays the firing response to intracellular current injection (958). Interestingly, NE acting via α_1-adrenoceptors has the opposite effect on the transient K^+ current (I_A) in dorsal raphe neurons (5).

The possibility that NE mediates an endogenous excitatory effect on spinal motoneurons has been tested in rats and cats in vivo (204, 396). Electrical stimulation in the locus coeruleus increases excitability and generates a multicomponent postsynaptic potential in motoneurons (395). Similar to effects of exogenously applied NE on motoneurons, the increased excitability is associated with a lower current threshold to induce repetitive firing and a decreased spike AHP (393). Moreover, the motoneuronal excitation and the slow component of the electrically evoked EPSP are inhibited by α_1-adrenoceptor antagonists (395). These results suggest that increased activity in locus coeruleus neurons will excite motoneurons via mechanisms similar to those induced in vitro by α_1-adrenoceptor activation. The activity of locus coeruleus neurons in vivo is highly state dependent; these neurons also respond with increased activity to a variety of stress-inducing stimuli (553, 554). For example, firing of locus coeruleus neurons in cats increases dramatically in the presence of a dog (553, 554). This suggests that effects of noradrenergic systems may be important in facilitating motor activity during waking states, in general, and in providing additional support for motor activities that accompany physiological responses to stressors.

Although the predominant effect of NE on motoneurons is excitatory, resulting from activation of α_1-adrenoceptors, there is some evidence for inhibitory effects mediated by α_2-adrenoceptors. For example, muscle EMG activity and the flexor response to afferent nerve volleys in spinal rats are inhibited by the α_2-adrenoceptor agonist clonidine (1074, 1265); in a subpopulation of trigeminal motoneurons,

clonidine suppresses motoneuronal discharge induced by oral stimulation, an effect blocked by the α_2-antagonist yohimbine (609). This effect of α_2-adrenoceptor activation could be mediated by direct actions on premotor interneurons, or by pre- or postsynaptic actions at the level of the motoneurons. Certainly, presynaptic effects of α_2-adrenoceptors are well described in other systems (e.g., see Ref. 1066), although α_2-inhibition of synaptic inputs to motoneurons has not been directly demonstrated. On the other hand, clonidine causes a membrane hyperpolarization associated with a decreased conductance in rat spinal and hypoglossal motoneurons (237, 959). This direct inhibitory postsynaptic effect of clonidine in rat hypoglossal motoneurons is due to decreases in both the peak amplitude and activation kinetics of I_h attributed, in part, to α_2-adrenoceptor activation (959).

3. Signal transduction

The α_1-adrenoceptor signals primarily through pertussis toxin (PTX)-insensitive G proteins ($G\alpha_{q/11}$ family) to activate PLC and cognate downstream signaling cascades, e.g., production of IP_3, liberation of Ca^{2+} from intracellular stores, and activation of PKC (422, 423, 842, 1067). As with most other receptors, the signaling mechanisms are context dependent, and stimulation by α_1-receptors of various additional phospholipases (e.g., PLA_2, PLD) as well as adenylyl cyclase has also been reported (842). The relevance of any of these pathways to the direct α_1-mediated effects on motoneurons remains to be determined, although a similar effect of α_1-adrenoceptor activation on thalamic relay neurons (i.e., decreased leak K^+ current) involves PTX-insensitive G proteins (814).

Activation of α_2-adrenoceptors leads to PTX-sensitive inhibition of adenylyl cyclase and decreases in cAMP and PKA activity (1067), as well as direct activation of neuronal inwardly rectifying K^+ current by α_2-adrenoceptors (922). The latter mechanism is unlikely to account for the α_2-mediated hyperpolarization in hypoglossal motoneurons because that effect is associated with a decrease, rather than an increase, in conductance (959). Because I_h is activated by increases in cAMP (537, 702), the inhibition of I_h reported to underlie the clonidine-induced hyperpolarization could have resulted from decreased cAMP. However, this does not seem to be the case, at least inasmuch as the effects on I_h are unaffected by the adenylyl cyclase inhibitor SQ-22536 (959).

4. Functional role in synaptic integration and rate control

There have been no direct tests of NE effects on synaptic inputs to motoneurons. An increase in synaptic activity often accompanies the depolarizing effects of NE in vitro, which could be due to enhanced synaptic activity resulting from effects on presynaptic terminals or on local premotor neurons. Some α_2-adrenoceptors in motor nuclei, perhaps the diffusely staining α_{2A}-subtype (1227), may be on presynaptic terminals, where they could modulate fast transmitter release. The postsynaptic effect of NE to decrease input conductance would, by analogy with effects of TRH, be expected to enhance postsynaptic potential amplitude summation during repetitive synaptic stimulation (1039).

The effects of NE on the generation of action potentials have been studied in adult rat hypoglossal motoneurons (958). Without exception, NE decreases the current necessary to induce repetitive firing, even after compensating for the NE-induced depolarization; this is due to the decreased input conductance that follows from inhibition of a leak K^+ current. This effect is similar to that induced by TRH or 5-HT (75, 1228). In a subset of motoneurons, a decrease in the spike AHP is observed, and in these cells, there is also an increased slope of the firing frequency response to current inputs (958). These two mechanisms together predict more effective transduction of synaptic inputs into firing output. The superposition of an increased delay to firing suggests that spike patterning could be modified by NE (958); if this is due to enhanced I_A, then this altered patterning would be more pronounced after a period of membrane hyperpolarization. Thus, although generally excitatory, NE may induce complex and state-dependent changes in motoneuronal input-output properties.

The effects of NE have been examined in the context of complex behaviors. For example, NE enhances inspiratory-related hypoglossal nerve burst discharge in a brain stem slice preparation that maintains a respiratory rhythm. These effects of NE are developmentally regulated, since the potentiation of hypoglossal activity increases dramatically during the early postnatal period (400, 404). These postnatal changes are largely due to effects mediated by α_1-adrenoceptors, since phenylephrine mimics developmental changes observed with NE. Additional effects mediated by α_2- and β-adrenoceptors, perhaps indirect, cause inhibition and excitation of hypoglossal nerve discharge, respectively; the α_2-mediated effect decreases postnatally whereas the β-mediated effect increases (400, 1127). In cat spinal motoneurons, the α_1-agonist methoxamine enhances motoneuronal excitability and facilitates a bistable behavior reminiscent of that seen in other vertebrate motoneurons in the presence of monoamines (520, 722). A bistablelike behavior can also be generated in mouse nucleus ambiguus motoneurons in the absence of NE or other monoamines (1041).

G. Dopamine

In contrast to the situation in lower vertebrates and invertebrates, where dopamine effects on motoneurons have been studied extensively (447, 464), effects of dopa-

mine on mammalian motoneurons have received little attention. Traditionally, there has been little reason to suspect a major role for dopamine in the function of mammalian motoneurons, since they reportedly receive an extremely sparse dopaminergic innervation and show little, if any, dopamine receptor binding (110, 952). However, recent immunohistochemical work with new dopamine antibodies reveals a substantial dopaminergic innervation of spinal motoneurons (509, 1409). Motoneurons express D_1 and D_2 dopamine receptors (306, 1305, 1330, 1408), which are coupled, respectively, to activation and inhibition of adenylyl cyclase (844). Interestingly, the sexually dimorphic motor nuclei of the lumbar spinal cord (Onuf's nucleus) receive a more dense dopaminergic input and express higher levels of D_2 dopamine receptor than other motor pools (509, 1305); the physiological significance of this observation has not been determined.

Physiological investigations of dopamine effects on mammalian motoneurons have been limited. Dopamine enhances ventral horn field potentials during antidromic activation of motoneurons in rat lumbar spinal cord (53) but decreases the synaptic response to dorsal root stimulation in rat and cat motoneurons (189, 777). In addition, dopamine modulates Renshaw cell-mediated feedback inhibition of rat motoneurons via effects of both D_1- and D_2-type dopamine receptors (778, 1129). Intracellular studies on mammalian motoneurons are required to determine if mechanisms identified in lower vertebrates and invertebrates are retained in mammals. For example, dopamine inhibits Ca^{2+} currents and the spike AHP in lamprey motoneurons (447) and modulates I_A and I_h in lobster motoneurons (464); in chick motoneurons, D_1 receptor activation increases kainate-receptor currents via effects that involve increases in cAMP and PKA (1165). Clearly, much work will need to be done to clarify any role for dopamine in the control of motoneuronal excitability.

H. ACh

Motoneurons use ACh as their (primary) transmitter, but also receive cholinergic synaptic input, which in the spinal cord stems partly from axon collaterals from nearby homonymous motoneurons (248, 249), and in the brain stem from neurons in reticular formation and vestibular nuclei (191, 375, 1427). Cholinergic boutons on spinal and some cranial motoneurons are present (40, 532, 884, 1093); some are large varicosities forming en passant type contacts (884). Spinal and some cranial motoneurons have mRNA coding for the m2 subtype of muscarinic cholinergic receptors (1315), binding sites for muscarinic agonists (1092, 1316), and show labeling using m2-receptor antibodies (1345). Thus anatomical and molecular data suggest actions of ACh on both spinal and cranial motoneurons. However, studies demonstrating effects of cholinergic agonists on motoneurons are scarce. Spinal motoneurons in the adult cat and neonatal rat are depolarized by ACh or muscarinic agonists (680, 1431). Brain stem laryngeal motoneurons are depolarized by iontophoretically applied ACh (460), and motoneurons in the compact division of the nucleus ambiguus (swallowing motoneurons) are depolarized by cholinergic agonists acting at nicotinic receptors (1427). Finally, activation of presynaptic m2 receptors reduces the release of excitatory transmitters to hypoglossal motoneurons (86). Signal transduction pathways and effectors involved in these actions are presently unknown.

I. ATP

ATP has only recently been established as a transmitter within the CNS; its actions are mediated by two major types of P_2 receptor families (1, 2, 169–171, 320, 345, 384, 923, 1077, 1432). P_{2x} receptors, comprising seven receptor subtypes P_{2x1} to P_{2x7} and a variety of isoforms, are ligand-gated ion channels that mediate fast excitatory responses (344, 1198). P_{2y} receptors, comprising at least 11 major subtypes P_{2y1} to P_{2y11}, mediate slower responses via G proteins (61, 169, 170, 307). Purinergic synaptic signaling in the CNS is of growing interest because *1*) P_2 receptors are widely distributed (46, 113, 231, 605, 630, 1125, 1281, 1322), *2*) P_{2x} receptors mediate fast synaptic transmission and have a large Ca^{2+} conductance, and *3*) extracellular hydrolysis of ATP produces adenosine, which modulates synaptic transmission through activation of adenosine receptors, e.g., in phrenic motoneurons (303).

An important role for ATP in motor control is implicated by the ubiquitous presence of ATP binding sites (1281) and mRNA for several P_{2x} receptor subunits within cranial and spinal motor nuclei (231). Differential distribution of receptor subtypes between cranial and spinal motor nuclei is apparent from in situ hybridization data showing the following: P_{2x4} and P_{2x6} in EW, trochlear, motor trigeminal, and facial nuclei; P_{2x2}, P_{2x4}, and P_{2x6} in oculomotor, DMV, and hypoglossal nuclei; but $P_{2x2,4-6}$ in spinal motoneuron pools. Immunohistochemical analysis of brain stem P_{2x} receptor distribution using recently developed antibodies reveals even more extensive expression. Hypoglossal motoneurons, for example, express protein for P_{2x1-6} subunits (713). The functional significance of any differential distribution has not been established. P_2 receptor-mediated excitation has only been demonstrated for inspiratory-modulated hypoglossal motoneurons in neonatal mouse (in vitro), and adult rat (in vivo) (403), motoneurons of the dorsal motor nucleus of vagus (1284) and phrenic motoneurons in vitro (M. A. Parkis and G. D. Funk, unpublished observations).

With the consideration that ATP acts as the principal fast excitatory transmitter at some central synapses (320, 345), ATP may directly mediate specific behavioral inputs. Alternatively, ATP may modulate glutamatergic synaptic transmission (736, 872) to motoneurons (403). P_{2y} receptors are present in the CNS (61); however, their role in motor control remains to be established. Understanding the role that P_2 receptors play in modulation of neuronal (and motoneuronal) excitability will be greatly facilitated by development of agonists and especially antagonists with greater specificity for the P_{2x} and P_{2y} receptor subtypes. Suramin, the most commonly used general P_2 antagonist, and to a lesser degree pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonic acid (PPADS), the most selective P_{2x} receptor antagonist, also antagonize glutamatergic transmission and inhibit ecto-ATPase activity (45, 872, 894, 933; see also Ref. 530). Thus, although the actions of exogenous ATP on central neurons are under investigation, assessing the physiological significance of endogenously released ATP is more difficult. Pharmacological tools for selective manipulation of ecto-ATPases that rapidly degrade extracellular ATP will also be useful.

J. Adenosine

Adenosine, a constituent of brain extracellular fluid, is an important modulator of neuronal excitability, including motoneurons. Adenosine can be formed extracellularly following rapid hydrolysis of ATP released from axon terminals (250, 310) or formed intracellularly and released into extracellular space via specific transporters. Intracellular formation is believed to be the major source of adenosine (383). Four distinct subtypes of adenosine receptors, belonging to the superfamily of G protein-coupled receptors (384, 955), have been cloned and characterized: A_1, A_{2A}, A_{2B}, and A_3 (230, 269, 274, 358, 382, 384, 742, 743, 754, 934, 955, 1299, 1321). In brief, A_1 receptors are coupled to PTX-sensitive G proteins (385, 882, 1274, 1423), inhibition of adenylyl cyclase and decreased production of cAMP. A_1 receptors are the most abundant adenosine receptors and widely distributed in the brain. The effects of A_1 receptors are primarily inhibitory, including decreasing neuronal excitability by altering postsynaptic membrane properties (311, 418, 1097, 1122, 1153, 1245, 1430) and inhibiting release of a wide variety of neurotransmitters (137, 360, 550, 589, 851, 879, 1050, 1090, 1289, 1294, 1385). The two adenosine A_2 receptor subtypes (A_{2a} and A_{2b}) are both coupled to G_s proteins to stimulate adenylyl cyclase and consequently increase the formation of cAMP (268, 754). The physiological effects of A_2 receptors are less clear than those of the A_1 receptors. The function of A_{2b} receptors in the brain has not been thoroughly investigated, and their physiological roles remain unclear. On the other hand, considerable evidence favors an excitatory role of A_{2a} receptors in the CNS (149, 1116, 1422; cf. Ref. 708). Adenosine A_3 receptors have very low affinity to adenosine. A_3 receptors are coupled to $G\alpha_{i\text{-}2}$, $G\alpha_{i\text{-}3}$, and G_q-like proteins. Unlike other subtypes, A_3 receptors are linked to two second messenger systems: decreasing cAMP through inhibition of adenylyl cyclase or increasing intracellular Ca^{2+} through stimulation of IP_3 (see reviews in Refs. 155, 194, 1321). The physiological role of A_3 receptors is unclear at present.

Adenosine effects on motoneurons are mainly mediated by A_1 receptors. High levels of mRNA for A_1 receptors are present in rat cranial and spinal motoneuron pools (1043) and in the areas containing hypoglossal premotoneurons (297), such as the reticular formation lateral to the hypoglossal nuclei, and in the ventrolateral medulla (1043). A_1 receptors inhibit synaptic transmission to motoneurons via a presynaptic action. Activation of A_1 receptors by exogenous agonists decreases evoked EPSP in hypoglossal motoneurons (85) and endogenous inspiratory-modulated EPSC in phrenic motoneurons (300); there is appreciable endogenous activity of A_1 receptors, since A_1 antagonists increase EPSP (85) or EPSC (300) amplitudes. The agonist significantly decreases mEPSC frequency (300), an event dependent on transmitter release probability (348, 1035), but has no effect on mEPSC amplitude, an event associated with postsynaptic responsiveness to the endogenously released transmitter (348, 1035; see also Ref. 678). Thus a presynaptic mechanism is likely for the inhibitory effect of A_1 receptors on synaptic transmission to these motoneurons.

Activation of A_1 receptors decreases both spontaneous and evoked firing of vagal motoneurons (796, 1262). Although the mechanism for the inhibition of spontaneous firing is unclear, the increase in AHP amplitude by postsynaptic A_1 receptors, affecting $I_{K\,Ca}$, is likely responsible for the decrease in evoked firing (796). Adenosine is reported to cause hyperpolarization in hypoglossal motoneurons (987), which is not observed with an A_1 receptor agonist (85). However, the receptor subtype(s) mediating this hyperpolarization was not identified. In cultured motoneurons, activation of A_1 receptors inhibits HVA Ca^{2+} current (mainly N type) (882); the functional role of this effect remains unclear.

At present, our understanding of the physiological role of the other adenosine receptor subtypes in modulating motoneurons is poor, primarily due to the lack of selective ligands and the diffuse distribution of these receptors.

K. TRH

1. Ligands, receptors, and sources of TRH input to motoneurons

The tripeptide TRH (pyroGlu-His-Pro-NH_2) was the first hypophysiotropic hormone to be purified from hypo-

thalamic extracts and characterized (1037). TRH is the product of posttranslational processing of a TRH precursor (preproTRH) mRNA that contains five copies of the TRH progenitor sequences (718). A number of other peptides in addition to TRH are derived from the same preproTRH (717, 718, 1386). These other peptides are synthesized and released from some neurons in a depolarization- and Ca^{2+}-dependent manner and, in some systems, they affect target tissues with actions that are synergistic with TRH (160, 690). Effects of these additional preproTRH-derived peptides have not been reported on motoneurons.

Two mammalian TRH receptor genes, TRHR1 and TRHR2, have been identified (184, 423); they share ~50% sequence homology and are both members of the rhodopsin family of G protein-coupled receptors. The more recently identified TRHR2 has so far only been found in rat, where it is expressed in a pattern distinct from TRHR1; of particular relevance to this review, it appears that TRHR1, but not TRHR2, receptors are expressed in motoneurons (177, 184, 1416). TRHR1 receptors from rat, mouse, and human are nearly identical (~95% identity through residue 375) except for the COOH-terminal region where there is substantial variability (423). In the rat and mouse (but not human), two TRHR1 mRNA species have been identified. These arise by alternative mRNA splicing and differ in the COOH terminus, predicting a long and short isoform of the receptor. The significance of these TRHR1 receptor isoforms is unclear, since their expression in native tissue has not been demonstrated and the two isoforms appear functionally identical in heterologous expression systems (423).

Rat cranial and spinal motoneurons display dense TRH binding sites and express TRHR1 receptor mRNA at high levels (177, 1131, 1371, 1416). Expression of the TRH receptor is developmentally regulated, at least in some motoneuron pools. Thus TRH binding sites are at low levels in hypoglossal motoneurons of neonatal rat and increase in density over the early postnatal period to reach adult levels by approximately postnatal *day 14* (78).

There is a relatively dense TRH input to brain stem and spinal cord motoneurons (489), and TRH fibers make axodendritic and, to a lesser degree, axosomatic contacts with motoneurons (1000). The TRH innervation appears to arise primarily from medullary raphe neurons rather than from hypothalamic cells (see sect. III and Table 2). The medullary raphe nuclei and the hypothalamic paraventricular nuclei (PVN) are the two major areas in the brain in which TRH-containing somata are located (489, 576); these neurons send descending projections to regions of the brain stem and spinal cord that contain motoneurons (1202). However, combined histochemistry and retrograde tract tracing demonstrate that *1*) TRH-expressing medullary raphe neurons project to spinal cord and the dorsal medulla (484, 767, 1080), *2*) TRH-expressing PVN neurons are not retrogradely labeled from spinal cord or brain stem, and *3*) spinally projecting PVN neurons do not express TRH (72). Furthermore, cutting the projection path to the dorsal medulla decreases the number of TRH-immunoreactive fibers in the hypoglossal nucleus (954), and electrical or chemical lesion of medullary raphe nuclei (471, 576) decreases TRH concentrations and TRH-IR fibers in spinal cord. On the other hand, disruption of descending pathways from the hypothalamus (151, 551, 954) or electrolytic lesion of the PVN (716) does not decrease TRH concentrations in the brain stem or spinal cord. Some differences in the density of TRH-immunoreactive fibers are noted among motoneuron pools and throughout postnatal development. For example, a greater number of TRH-immunoreactive fibers form close appositions to respiratory-related motoneurons of the nucleus ambiguus than to either nonrespiratory ambigual motoneurons or to hypoglossal or facial motoneurons (1196). In addition, there are developmental increases in the density of TRH-immunoreactive fibers in brain stem and spinal cord motor pools (78, 999); in the hypoglossal nucleus, the increased TRH innervation coincides temporally with the increased expression of TRH receptors by hypoglossal motoneurons (78).

2. *Pre- and postsynaptic actions of TRH on motoneurons*

TRH has direct excitatory effects on spinal and cranial motoneurons (75, 76, 913, 1039, 1212, 1333, 1357). In mammalian motoneurons, TRH causes a depolarization associated with a decrease in membrane conductance. At least two ionic mechanisms contribute to the depolarization: TRH inhibits a relatively voltage-insensitive resting leak K^+ current and activates a mixed cationic current (75, 366, 921). This leak K^+ current is insensitive to TEA, Cs^+, 4-AP, or apamin and blocked by Ba^{2+} (75, 366, 921); the cationic current is partially inhibited by Cd^{2+}, Mn^{2+}, and Co^{2+}, suggesting that it may be Ca^{2+} dependent (366). This combination of effects is common to a number of transmitters that act directly on motoneurons, i.e., qualitatively similar effects are seen with NE, substance P, and 5-HT. The effects of TRH occlude those of NE and substance P (367, 958), further suggesting a common mechanism.

Associated with its postsynaptic actions, exogenous TRH application to in vitro preparations often induces an increase in synaptic potentials recorded from motoneurons (75, 1039, 1333). The mechanism of this effect of TRH remains to be determined; it could reflect excitation and increased activity-dependent transmitter release from local premotor neurons, or a presynaptic effect on terminals that impinge on motoneurons (689, 1333).

TRH acts directly on motoneurons to cause a slow membrane depolarization when applied in vitro, suggest-

ing that if it were released synaptically it might mediate a slow EPSP. In fact, electrical stimulation of the ventral funiculus in a neonatal spinal cord in vitro preparation to activate a descending TRH pathway evokes a slow EPSP in spinal motoneurons that is sensitive to TRH antibodies (1212). Identifying the role that such a TRH-mediated slow synaptic excitation plays in normal motor system function awaits the development of specific and selective TRH receptor antagonists (1358).

3. Signal transduction

The TRH receptor, like the α_1-adrenoceptor, signals primarily through PTX-insensitive G proteins ($G\alpha_{q/11}$ family) to activate PLC and cognate downstream signaling cascades, e.g., production of IP_3, liberation of Ca^{2+} from intracellular stores, and activation of PKC (422, 423, 842, 1067). However, under some circumstances and in some cells, the TRH receptor may also couple to a variety of other G proteins, including $G\alpha_i$, $G\alpha_o$, and a $G\alpha_s$-like protein to bring about additional effects (423). For example, antisense knockout studies indicate that Ca^{2+} channel activation by TRH in GH_3 pituitary cells is mediated by the PTX-sensitive G proteins, $G\alpha_{i\text{-}2}$ and $G\alpha_{i\text{-}3}$ (430, 431). Interestingly, this effect is blocked by $G\alpha_{q/11}$ antisense treatment and PKC inhibitors, suggesting that coordinate activation of both $G\alpha_q$ and $G\alpha_i$ signaling pathways may be necessary for Ca^{2+} channel activation by TRH (431). The intracellular mechanisms by which TRH modulates motoneuronal excitability have not been exhaustively studied but, insofar as they have been tested, there has been no evidence to support involvement of any of these pathways in mediating its direct postsynaptic effects. Thus, although TRH-induced depolarization of hypoglossal motoneurons involves G proteins, the TRH effect is independent of changes in intracellular Ca^{2+} or IP_3 and unaffected by activation of PKC or PKA (77). Indeed, it is noteworthy that despite its widespread presence in many other neurons, the mechanism by which transmitters that act via $G\alpha_q$-coupled receptors signal to cause inhibition of leak K^+ channels and/or activation of cationic channels remains enigmatic.

4. Functional role of TRH in modulating motoneuronal excitability

TRH increases the duration and amplitude of trains of electrically evoked postsynaptic potentials in guinea pig hypoglossal motoneurons, presumably via postsynaptic effects on membrane input conductance and time constant (1039). Although not directly tested, the altered membrane properties induced by TRH would also be expected to enhance inhibitory synaptic inputs; interestingly, TRH also potentiates NMDA-induced depolarization and NMDA-mediated EPSP (1040). This is not due to a direct effect of TRH on the NMDA channels, since under voltage-clamp the NMDA current is unchanged; rather, the combined action of TRH and NMDA on the motoneuronal membrane leads to a region of negative slope conductance, potentiating NMDA-induced depolarizations (1040).

The input-output relationship of motoneurons is also enhanced by TRH; the curve relating depolarizing current input and firing frequency output in rat hypoglossal motoneurons is shifted to the left in the presence of TRH, i.e., previously subthreshold current inputs induce repetitive firing with the frequency of discharge increased at each suprathreshold current input (75). This is due to the combined effects of TRH-induced depolarization and decreased conductance; membrane depolarization brings the neuron closer to action potential threshold while the decreased input conductance allows more effective transformation of current inputs to voltage responses. The shift in the input-output relationship caused by TRH is not associated with a change in slope (i.e., gain) (75). This is consistent with the finding that TRH has no effect on the spike AHP, which largely determines interspike interval, and distinctly different from effects of the presumptive cotransmitter, 5-HT, which decreases the spike AHP and increases input-output gain in neonatal hypoglossal motoneurons (75, 91).

A number of changes take place during the early postnatal period that influence TRH effects on motoneurons. Expression of the TRH precursor mRNA increases markedly in raphe neurons within the first 2 wk after birth (78), as does the density of TRH-immunoreactive fibers in motor nuclei receiving input from the raphe nuclei (78, 999). Concomitant with this elevated innervation, the levels of TRH binding sites also increase to reach sustained high levels in rat hypoglossal motoneurons by postnatal *day 14* (78). Thus both the presynaptic and postsynaptic elements of the raphe motoneuronal system mature over the first 2 wk via a process that is remarkably well matched in timing. Furthermore, the electrophysiological effects of TRH on motoneurons also change during this developmental period. An increasing fraction of TRH-responsive neurons are found through the early postnatal period, roughly paralleling the increase in receptor binding (78). However, a number of other changes also contribute to the functional maturation of hypoglossal motoneuron responses to TRH. Unlike adult hypoglossal motoneurons (75, 1039), in some responsive neonatal neurons TRH causes a depolarization that is not associated with decreased conductance, reminiscent of the TRH response after inhibition of the leak K^+ current by Ba^{2+}. The reason that TRH receptors do not appear to couple to K^+ channels in this population of neurons remains to be determined. It is noteworthy that 5-HT, which modulates Ba^{2+}-sensitive leak K^+ channels in adult motoneurons

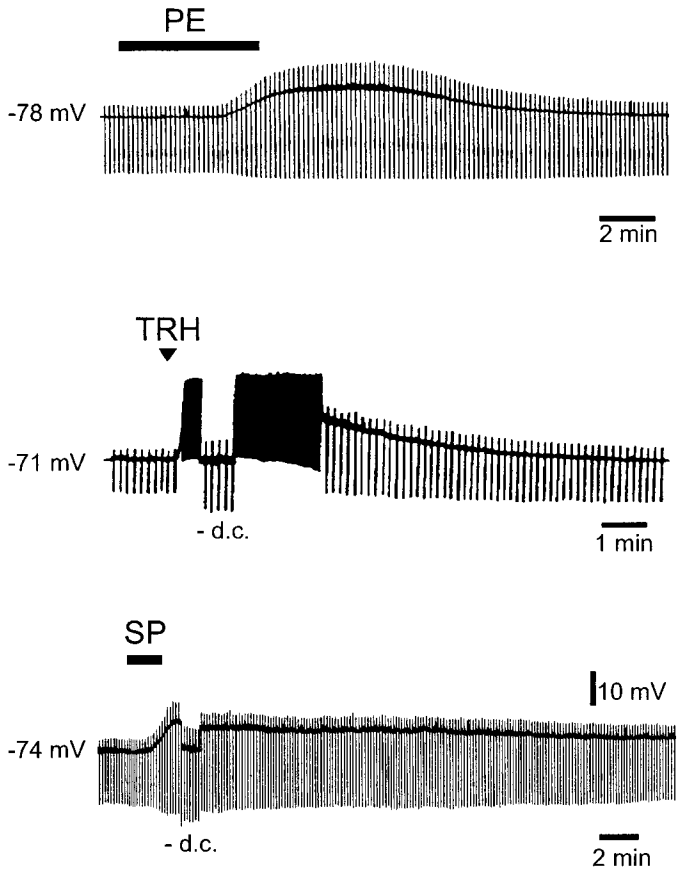

FIG. 8. Different neuromodulators can affect motoneuronal excitability via similar mechanisms. These records show the response of hypoglossal motoneurons to phenylephrine (PE), an α_1-adrenoceptor agonist [*top trace*; from Parkis et al. (958)]; thyrotropin-releasing hormone [TRH; *middle trace*, from Bayliss et al. (75)]; and substance P (SP; *bottom trace*). All 3 transmitters induce a membrane depolarization, which can reach threshold for repetitive firing, e.g., see *middle trace*, spikes at the peak of the TRH response are truncated. The negative deflections in the sample traces, which represent responses to constant-amplitude current pulses, are enhanced by the transmitters, reflecting the transmitter-induced decrease in a resting K^+ current. A second component, involving activation of a cationic current, also contributes to membrane depolarization by all 3 transmitters (data not shown). −d.c. indicates negative bias current used to bring the membrane potential back to control level.

(526, 1228), also fails to target those channels in neonatal hypoglossal motoneurons (91, 1228). Finally, there is a progressive increase in TRH current density that matches closely the increase in membrane conductance over the early postnatal period (78, 92, 1313). This latter effect ensures that the magnitude of the TRH-induced membrane depolarization will be comparable in adult and neonatal hypoglossal motoneurons, at least in the population of neonatal cells that are capable of responding (78) (see Fig. 8). Effects of TRH in the context of a more complex motor system are also enhanced with a similar postnatal time course; facilitatory effects of TRH on rhythmic inspiratory-related discharge measured on the hypoglossal nerve in vitro are greatly enhanced over the first 2 postnatal weeks (400).

L. Neurokinins

1. *Ligands, receptors, and sources of neurokinin input to motoneurons*

The neurokinins are the mammalian members of the tachykinin family of neuroactive peptides, which share a common structure that includes the COOH-terminal sequence Phe-Phe/Val-Gly Leu-Met-NH_2 (453, 472, 889, 948). The undecapeptide substance P was the first member of this family to be purified and characterized (208); other mammalian members were identified only after some years and include neurokinin A (NKA; also known as substance K, neurokinin α, and neuromedin L) and neurokinin B (NKB; also known as neurokinin β, neuromedin K), as well as the recently discovered NH_2-terminally extended versions of NKA, the so-called neuropeptide K (NPK) and neuropeptide γ (NPγ) (453, 472, 889, 948). In some tissues, fragments of NKA have been identified as well, e.g., NKA-(3—10) and NKA-(4—10), but it is unclear if these fragments are released or exist in these forms due to proteolytic degradation of NKA (1241).

All neurokinins identified to date derive from two closely related genes, preprotachykinin A (PPT-A) (615, 665, 897, 898) and preprotachykinin B (PPT-B) (119, 663), that may have arisen by duplication of a common ancestral gene (663, 888, 889). The PPT-A gene is differentially spliced, leading to three distinct mRNA isoforms: the α-form of PPT-A encodes only substance P, whereas the β- and γ-forms encode both substance P and NKA. The other neurokinin peptides, NPK and NPγ, are derived from β-PPT-A and γ-PPT-A mRNA, respectively (888). Although tissue-specific regulation of splicing has been suggested in other species, i.e., bovine (888, 898), in both rat and human CNS the preponderance of PPT-A mRNA exists in the γ- and/or the β-forms, with very little expressed as α-PPT-A mRNA in either species (195, 665). Thus preferential expression of the PPT-A mRNA isoforms that encode both substance P and NKA (as well as NPK or NPγ) suggests that individual neurons will usually coexpress multiple neurokinins. Indeed, with the use of specific antibodies, immunoreactivity for both substance P and NKA is seen in individual medullary raphe neurons that are known to project to motoneurons (907). In contrast to the complexity of PPT-A processing, with three splice variants and their multiple neurokinin products, the two (α and β) forms of the PPT-B mRNA give rise only to NKB among the currently known neurokinins (119, 663, 888).

As predicted from earlier autoradiographic studies (453), three neurokinin receptors that preferentially interact with each of the major tachykinins, the NK_1 receptor with substance P, the NK_2 receptor with NKA, and the

NK_3 receptor with NKB, have been identified by molecular cloning (889). All three cloned receptors are members of the rhodopsin family of G protein-coupled receptors. It is important to point out that the receptor-ligand associations described for the NK receptors are not absolute, since all known neurokinins can bind each of the NK receptor subtypes in nanomolar concentration ranges and activate each receptor with full potency (although EC_{50} values are ~1–2 orders higher) (536, 889). Moreover, a number of examples of mismatch between localization of NK receptors and preferred endogenous ligands have been noted (e.g., Refs. 293, 747, 892, 1149). Together, these observations suggest that there may be substantial cross-talk within the mammalian tachykininergic system.

The distribution of neurokinin receptors throughout the CNS, including motor nuclei, has been extensively investigated (90, 270–272, 293, 329, 774, 791, 892, 1014, 1149, 1405). The results of these studies are concordant with the conclusion that adult rat motoneurons predominantly express NK_1 receptors and display substance P binding sites. The expression of NK_1 receptors is not uniform among motoneuronal pools, however, implying that effects of substance P may vary depending on the particular motoneuronal pool. For example, some motoneuronal populations express very high levels, e.g., phrenic, pudendal motoneurons, whereas others express moderate, e.g., hypoglossal motoneurons, or only very low levels of NK_1 receptor, e.g., facial, trigeminal motoneurons (210, 791, 892, 1405). The NK_2 receptor is preferentially located in the periphery with only low levels of binding sites in the CNS, whereas the NK_3 receptor has a widespread CNS distribution; neither NK_2 or NK_3 receptors, however, are prominent in motor nuclei (272, 293, 1149, 1405). The generalization regarding the predominant expression in motoneurons of the NK_1 subtype among the NK receptors may not hold in all circumstances. For example, expression of each of the NK receptors is developmentally regulated (90, 211, 272, 1014) and, interestingly, high levels of NK_3 binding sites are present in the ventral horn of the spinal cord up to at least postnatal *day 10* (90). Whether these ventral horn NK_3 binding sites represent transient somatodendritic NK_3 expression by neonatal motoneurons or are associated with other neuronal elements remains to be determined.

The PPT-A and PPT-B genes are differentially expressed with overlapping but distinct patterns of expression (797, 1338). There is no significant NKB immunoreactivity in fibers innervating motoneurons (797, 833, 1260) and, consistent with this, no evidence for expression of its precursor PPT-B in cells that provide major projections to motoneurons, e.g., medullary raphe, sensory ganglia (797, 1338). Given that NK_3 receptors have only been found on neonatal motoneurons (see above), it is unlikely that the endogenous PPT-B/NKB system has a major role in regulating motoneuronal function, at least in the adult.

In contrast, there is a dense innervation of all motoneuronal pools by substance P-immunoreactive fibers that is potentially derived from at least three sources: brain stem raphe neurons, primary afferent neurons, or substance P-expressing cells intrinsic to the spinal cord (751, see sect. III and Table 2). Caudal raphe neurons, particularly in raphe obscurus and pallidus, express high levels of PPT-A mRNA, and individual spinally projecting raphe cells are immunoreactive for both substance P and NKA, the neurokinins encoded by PPT-A (576, 907, 1338). Descending inputs from medullary raphe neurons provide the most prominent neurokininergic innervation of motoneurons since the overwhelming majority of substance P and substance P-immunoreactive fibers in the ventral horn are lost after high spinal cord transection or chemical destruction of medullary raphe neurons (379, 473, 576, 603). Substance P is extensively colocalized with 5-HT and TRH in medullary raphe neurons and in fibers surrounding motoneurons (576, 951), and the density of substance P and 5-HT-immunoreactive fibers appears to increase during early postnatal development (951).

PPT-A is also expressed at high levels in many sensory ganglia neurons (1338), but dorsal rhizotomy causes only small decreases in substance P innervation of the ventral horn with much larger decreases in the density of dorsal horn substance P-immunoreactive fibers (492, 567, 1220). This is consistent with the preferential immunohistochemical localization of substance P to capsaicin-sensitive sensory neurons associated with small fibers in the C and Aδ range that carry nociceptive inputs and terminate primarily in the dorsal horn, and its absence in muscle afferents that project monosynaptically to spinal motoneurons (493, 812). A small amount of ventral horn substance P innervation may arise from spinal dorsal horn neurons that express PPT-A and substance P (751, 1338), and these may be important in conveying polysynaptic sensory inputs to the motoneurons (425).

2. Pre- and postsynaptic actions of neurokinins on motoneurons

Otsuka and colleagues (660, 945, 946, 1199, 1217) first demonstrated an excitatory effect of substance P on neonatal rat spinal cord motoneurons; they found that substance P causes a slow depolarization of the ventral root or the motoneuronal membrane potential. This is due to a direct postsynaptic effect on motoneurons because it persists, at least in part, after blockade of synaptic transmission in TTX or in a low-Ca^{2+}/high-Mg^{2+} synaptic blockade medium (947, 1199). The depolarization of neonatal rat spinal motoneurons by substance P is associated with an apparent decrease in membrane conductance (365, 367), involving two ionic mechanisms: inhibition of a relatively voltage-independent resting K^+ current and activation of a (presumably) mixed cationic current (367). The charac-

teristics of these effects of substance P are highly reminiscent of those of TRH (see above), and accordingly, the effects of the two transmitters mutually occlude each other (367). Moreover, this mechanism of action involving a decrease in a K^+ current combined with activation of a cationic current has also been described for substance P in locus coeruleus neurons, although in those cells the K^+ current is inwardly rectifying (1140).

The identity of the neurokinin receptor that mediates the direct depolarizing effects of substance P on motoneurons is not yet entirely clear, although the bulk of the pharmacological evidence supports the aforementioned histochemical data that predicts involvement of NK_1 receptors. Thus a number of selective NK_1 agonists mimic effects of substance P on motoneurons, e.g., substance P methyl ester and [$Sar^9Met(O_2)^{11}$]substance P, and those effects are blocked by some NK_1 receptor antagonists, i.e., SR-140,333 (52, 365, 726). However, a number of additional NK_1 antagonists are without effect on substance P responses, i.e., (±)-CP-96,345, RP-67580, and GR-82334, or display pharmacological profiles unlike that of the classical NK_1 receptor, i.e., spantide (51, 726, 1402). Motoneurons may express a distinct isoform of the NK_1 receptor that possesses atypical antagonist binding characteristics (1402). Alternatively, because most electrophysiological studies utilize preparations from neonatal rats in which more than one NK receptor may be expressed (especially both NK_1 and NK_3; see above), the atypical pharmacological results could simply reflect a mixed receptor population in those developing neurons.

The effects of the other neurokinins, NKA and NKB (and/or agonists selective for their cognate receptors), have also been studied on spinal motoneurons. In neonatal rat spinal motoneurons, NK_2 and NK_3 agonists cause a slow membrane depolarization that is reduced, although not completely, by TTX (365, 727, 807), suggesting these effects are mediated by premotor neurons. This is consistent with histochemical studies suggesting that ventral horn motoneurons do not express the NK_2 or NK_3 receptor subtypes, which are more prevalent in the dorsal horn. The small residual current occasionally seen in the presence of TTX may reflect effects mediated by NK_2 or NK_3 receptors expressed transiently on some neonatal motoneurons, or could be due to small crossover effects of the agonists onto NK_1 receptors. The nature of the transmitter released onto motoneurons from spinal presynaptic neurons following NKA or NKB stimulation has not been determined, but it is notable that it causes a depolarization associated with an apparent decrease in input conductance, not unlike that produced directly by NK_1 receptor activation (365). Of further interest, NK_3-selective agonists ($MePhe^7$)NKB and Senktide often induce a burst-firing behavior that is superimposed on the depolarization; the nature of this burst mechanism remains to be explored (365).

The effects of exogenously applied NK receptor agonists suggest that neurokinins, particularly substance P and other NK_1 agonists, cause a slow membrane depolarization by acting directly on the motoneuron. Therefore, synaptically released substance P might be expected to mediate a slow EPSP in motoneurons. Indeed, electrical stimulation of upper cervical segments designed to activate descending substance P pathways to lumbar motoneurons in an isolated neonatal rat spinal cord induces a slow EPSP that is blocked by NK_1 receptor antagonists and enhanced by a peptidase inhibitor (681). Moreover, a component of the slow EPSP is also sensitive to ketanserin, a 5-HT_2 antagonist and the SP-dependent EPSP is virtually absent after treatment of the spinal cord with a chemical neurotoxin for 5-HT, suggesting that the substance P is released from fibers that also contained 5-HT (681). Thus this descending pathway from medullary serotonergic neurons that contain substance P probably represents the principal direct mechanism for substance P modulation of motoneuronal function. The release of substance P is apparently frequency dependent so that it may only be released at times of increased activity in raphe neurons (378), e.g., during increased locomotor or respiratory activity (1308). It is important to point out that reflex activation of motoneurons after stimulation of dorsal roots at intensities sufficient to activate small fibers can also induce a slow NK_1-dependent EPSP in motoneurons (52, 457, 949). However, this effect is probably polysynaptic, since it is blocked by glutamate receptor antagonists and only the long-latency responses are sensitive to NK receptor antagonists (52).

3. Signal transduction

There is good evidence that all three NK receptors couple via PTX-insensitive G proteins to activation of PLC and production of IP_3 and diacylglycerol as the major, although not only, signaling pathway (889, 948). In this respect, the NK_1 receptor is similar to other receptors, e.g., 5-HT_2, α_1-adrenergic, TRH, that also mediate direct motoneuronal depolarization via inhibition of a resting K^+ current and activation of a cationic current (75, 77, 526, 958). However, as in those other cases, the involvement of PLC and/or its downstream mediators in these effects remains to be demonstrated.

4. Functional role of neurokinins in modulating motoneuronal excitability

The effects of substance P on synaptic inputs to motoneurons have not been directly studied. There is currently no information as to whether substance P can modulate fast excitatory or inhibitory inputs onto motoneurons at a presynaptic site. Substance P may act presynaptically to enhance 5-HT release (846), perhaps by blocking a 5-HT autoreceptor on its own terminals (491,

496). The postsynaptic mechanisms of action of substance P, which are similar to those of TRH, suggest some additional possibilities. For example, the substance P-induced decrease in membrane conductance would be expected to increase the amplitude and duration of postsynaptic potentials by altering membrane characteristics, i.e., length and time constants, as shown for TRH (1039). This would be the case for both inhibitory and excitatory synaptic inputs. Furthermore, the firing response to current inputs is shifted to the left in the presence of substance P, presumably by virtue of the combined effects of substance P to depolarize and decrease the motoneuronal input conductance (726).

M. Arginine Vasopressin and Oxytocin

1. Ligands, receptors, and sources of arginine vasopressin and oxytocin input to motoneurons

Arginine vasopressin (AVP; also called antidiuretic hormone) and oxytocin are nine-amino acid posterior pituitary peptide hormones arranged in a six-amino acid disulfide ring with a three-amino acid side chain; they differ by only two amino acids (1038). AVP and oxytocin are cleaved from precursor hormones encoded by separate but closely linked genes that are likely derived from a common ancestral gene (546). The discovery of an extrahypothalamic distribution of AVP and oxytocin suggested CNS functions in addition to their well-known roles in regulating plasma osmolarity and increasing intramamallary pressure leading to milk ejection (1175).

Three receptors for AVP are suggested based on its distinct actions and pharmacology in different tissues: in vascular smooth muscle, the V_{1a} (or V_1) receptor causes vasoconstriction; in the anterior pituitary, the V_{1b} (or V_3) receptor induces ACTH release; and in the kidney, the V_2 receptor enhances water reabsorption. To date, only a single oxytocin receptor has been identified. The existence of pharmacologically defined AVP receptor subtypes, as well as the oxytocin receptor, have now been verified by molecular cloning, and all are members of the rhodopsin family of G protein-coupled receptors (56, 57, 974).

The predominant AVP receptor in the CNS is the V_{1a} subtype, and it is this isoform that appears to be expressed transiently on cranial motoneurons as identified by ligand binding autoradiography with either [^{3}H]AVP or ^{125}I-VPA (a selective V_{1a} radioligand) (956, 1269). High levels of binding are detected in rat facial motoneurons from embryonic *day 20* through the second postnatal week, whereupon AVP binding sites progressively diminish in density to reach low levels by postnatal *day 19* and barely detectable levels in adulthood (1269). Likewise, V_{1a} receptor binding is very low in most spinal cord motor nuclei of adult rats, although there are some exceptions; dorsolateral ventral horn motoneurons at the cervicothalamic spinal cord junction and medially located motoneurons throughout the lumbar cord show higher levels of V_{1a} binding (1267). Most notable, however, are the sexually dimorphic pudendal motoneurons. In adult male rats, these motoneurons have much higher levels of V_{1a} binding than any other spinal motoneurons. Moreover, the elevated levels of binding in pudendal motoneurons are apparently dependent on sex steroid hormones since binding is reduced by castration and is not elevated in the same motoneurons of female rats (1267). Interestingly, after axotomy of brain stem (facial, hypoglossal) and spinal motoneurons in the adult rat, receptor expression increases markedly, suggesting that those motoneurons revert to an immature neonatal-like phenotype after axotomy (1266).

Oxytocin receptors have not been studied as extensively as V_{1a} receptors in the context of motoneurons. Nevertheless, oxytocin binding sites are not generally associated with adult motoneurons, although they are detected on hypoglossal motoneurons in the neonatal rat (956, 1268). Thus the expression of oxytocin receptors by motoneurons, at least by hypoglossal motoneurons, may be developmentally regulated in a manner somewhat analogous to V_{1a} receptors.

AVP and oxytocin are synthesized in hypothalamic neurons, primarily but not exclusively in the paraventricular and supraoptic nuclei (1038). Descending projections from AVP- and oxytocin-containing hypothalamic neurons to the brain stem and spinal cord arise from the lateral parvicellular division of PVN (203, 1086). However, AVP- and oxytocin-immunoreactive fibers are localized to the dorsal horn of the spinal cord and to regions involved in sympathetic and parasympathetic autonomic regulation, e.g., intermediolateral cell column and dorsal motor nucleus of the vagus nerve, and are actually only sparsely represented in somatic motor nuclei (1175, 1203). Thus, if AVP and oxytocin elaborated from these fibers activate motoneurons, they may have to act at some distance from their release site. To our knowledge, a study of the motoneuronal innervation by these peptides throughout early postnatal development has not been reported. Therefore, it remains to be determined if the AVP and/or oxytocin inputs are more substantial in neonates when the cognate receptors are expressed at higher levels by motoneurons.

2. Pre- and postsynaptic actions of AVP and oxytocin on motoneurons

A direct, largely TTX-resistant postsynaptic depolarization of motoneurons by AVP was first demonstrated in a neonatal rat spinal cord preparation (1199); a depolarization in response to oxytocin was also noted, although that effect was somewhat more sensitive to TTX (1199). Subsequently, excitatory effects of both AVP and oxyto-

cin have been documented in other neonatal motoneurons (956, 1019, 1269). Although the receptor and ionic mechanisms for effects of AVP have been studied most extensively, oxytocin and AVP each invokes inward currents that are similar in magnitude and time course in the same neonatal hypoglossal motoneurons, suggesting that they may share a common mechanism (956). Presynaptic effects of these peptides have not been demonstrated in motoneurons except insofar as showing that a component of their effects is inhibited by TTX or a low-Ca^{2+}, high-Mg^{2+} synaptic blockade medium (956, 1199).

In neonatal rat brain stem slice preparations, AVP increases the firing rate of facial motoneurons and induces the development of an inward current in both facial and hypoglossal motoneurons (956, 1019, 1269). These effects are blocked by an AVP receptor antagonist and mimicked by a V_1 but not a V_2 receptor agonist (956, 1019, 1269). Together with the receptor binding data presented above (956, 1269), these results indicate that AVP acts via a V_{1a} receptor to depolarize and increase the excitability of neonatal motoneurons. We are unaware of published reports of effects of either AVP or oxytocin on adult motoneurons, but effects on those older motoneurons are unlikely given the ephemeral nature of V_{1a} and oxytocin receptor expression on those cells (1268, 1269).

The mechanism by which AVP modulates neonatal cranial motoneurons has been studied in vitro under voltage-clamp conditions. The AVP-induced current is voltage dependent, TTX insensitive, and carried, in part, by Na^+ (10, 1019); the current in facial motoneurons is enhanced in low extracellular Ca^{2+}, suggesting that it is partially inhibited at normal Ca^{2+} concentrations, i.e., 2 mM (10). This AVP-induced cationic current shares some features with the current induced by 5-HT in neonatal rat hypoglossal motoneurons (91) as well as with a Ba^{2+}-resistant cationic current component induced by a number of transmitters in various adult motoneuronal preparations, e.g., 5-HT, TRH, and NE, although those other transmitter-induced currents are not noticeably voltage dependent, and their inhibition by extracellular Ca^{2+} has not been reported (526, 958). The voltage-dependent and kinetic characteristics of the AVP-sensitive current are distinctly different from those of I_h, a voltage-dependent cationic current that is modulated by 5-HT in some motoneurons (526, 701, 1216).

3. Signal transduction

The V_1 and oxytocin receptors interact via $G\alpha_{q/11}$ to activate PLC and downstream signaling cascades in vascular smooth muscle, corticotropes, and neurons (56, 57, 974); whether this signaling pathway contributes to effects of AVP and oxytocin on motoneurons remains to be determined. This same pathway is putatively activated by a host of other motoneuronal excitatory neurotransmitter receptors (e.g., see sect. IV, *E*, *F*, and *K*). Whereas these other transmitters inhibit resting K^+ channels in addition to activating a cationic current, V_1 receptors apparently target only the cationic channels (75, 526, 958). This may reflect the fact that effects of AVP and oxytocin were tested on neonatal motoneurons, since other transmitters that modulate both channels in adult motoneurons apparently activate only the cationic channel in neonatal motoneurons, e.g., 5-HT and TRH (78, 91, 1228). Thus it may be a general finding that ion channels modulated by $G\alpha_{q/11}$-coupled receptors, and/or the transduction pathway from the receptor to those channels, are developmentally regulated in motoneurons (79).

4. Functional role of AVP and oxytocin in modulating motoneuronal excitability

The effects of both AVP and oxytocin on motoneurons are excitatory, although their precise role in control of motoneuronal function remains speculative. The high levels of V_{1a} receptor binding in sexually dimorphic nuclei of adult male rats suggest a role for AVP in sexual reflexes (1267). The transient developmental pattern of AVP and oxytocin receptor expression in most other motoneuron pools suggests that effects of these neuropeptides may be important early in the motoneuronal maturation process (1269). Clearly, a number of important developmental changes occur in motoneurons and their targets during the early preweaning postnatal period when those receptors are strongly expressed (92, 95, 760, 1329). As mentioned, there does not appear to be a dense innervation of motor nuclei directly by either AVP or oxytocin (1175, 1203), and the source of endogenous peptides to interact with those transiently expressed motoneuronal receptors is unclear. In this regard, it would be interesting to know if a more dense plexus of AVP and oxytocin fibers surrounds motoneurons during this early period. Perhaps the early development of an excitatory AVP and/or oxytocin input to motoneurons serves to compensate for the delayed development of other excitatory neurotransmitter systems in the neonate (e.g., TRH, NE; Refs. 78, 400).

N. Other Neuropeptides

Numerous neuropeptides have been identified in fibers near motoneurons (330 and Table 2), but for the most part, their electrophysiological effects on motoneurons have not been systematically characterized. For example, an extensive enkephalin innervation of brain stem and spinal motoneurons suggests that they may be modulated by this peptide (13, 330, 477). Consistent with this, electrical stimulation in the region of enkephalin-synthesizing locus coeruleus neurons evokes a naloxone-sensitive IPSP (395). However, nothing is known of the mechanism by which enkephalin mediates this inhibition.

Likewise, there has been little, if any, information regarding pre- or postsynaptic effects of other peptides. Almost 20 years ago, Suzue et al. (1199) showed that a number of peptides caused membrane depolarization in neonatal rat spinal motoneurons (e.g., bombesin, cholecystokinin, angiotensin II, neurotensin), but the receptor and ionic basis for effects of many of those transmitters still have not been elucidated.

V. CONCLUSIONS AND PERSPECTIVES

Motoneurons are specialized neurons, genetically programmed to form specific motor pools, which have a clearly defined and important role in brain function and behavior, i.e., control of skeletal muscle contraction and relaxation that underlies all movements. As such, the principles and mechanisms that determine their performance, especially the transformation of their inputs into action potentials to innervated motor units, are of interest. Moreover, insofar as motoneurons process signals like all other neurons, insights into their function may illuminate basic processes of brain function.

We have reviewed the basic properties of motoneurons and their synaptic inputs. Their common biophysical properties, e.g., voltage-dependent ion channels, and synaptic properties, e.g., amino acid, amine and peptide transmitters and associated receptors, are sufficiently rich that the combinatorial possibilities for different states of excitability are legion. The majority of these properties have been measured in highly reduced or constrained conditions that are amenable to experimental manipulation. Although these conditions may be distinctly different from those occurring during natural behaviors in unrestrained, undrugged mammals, a few transcendent principles and mechanisms have been revealed that are worth emphasizing.

1) *The anatomical organization of inputs to cranial and spinal motoneurons follows several common features.* Afferent input is conveyed via sensory nuclei in the brain stem and spinal gray. Premotor neurons are mostly located close to the motoneuron groups in the reticular formation or spinal gray. Long projections from brain stem and pontine nuclei converge on brain stem and spinal premotor/interneurons as well as motoneurons. The distributed innervation of motoneuron pools by supraspinal modulatory systems and local premotor/interneurons may be part of a general scheme where the excitability of brain stem and spinal functional units (composed of CPG, sensory interneurons, and motoneurons) are changed in a coordinated fashion during particular motor acts.

2) *Inputs defining the precise timing of movement are mostly signaled by amino acids acting on ionotropic receptors.* For example, signals related to voluntary movement, originating in the cortex, and relayed through a host of intermediate, and occasionally direct, pathways, appear to excite motoneurons via the release of glutamate and inhibit motoneurons via the release of GABA and glycine, all acting via ionotropic receptors. Similarly, rhythmic movements such as respiration, locomotion, and mastication, as well as postural and oligosynaptic reflexes, ultimately drive the appropriate movements by signals mediated by amino acid neurotransmitters acting via ionotropic receptors. With respect to the signaling of inputs related to the precise timing of movement, these neurotransmitters affect receptors that have fast onset and relatively fast offset of action. However, under certain conditions, e.g., plateau potentials or long-term facilitation, they may also trigger long-lasting changes in neuronal excitability. Insofar as functional signals transmitting information related to precise timing can be identified in other neurons, we propose that these too would be conveyed by amino acids acting at ionotropic receptors.

3) *Inputs related to more generic aspects of movement, e.g., exercise, or state, such as related to or affected by the sleep-wake cycle, autonomic function, attention, or emotion (including fear), are conveyed to motoneurons by other neurotransmitters, such as the amines or peptides, mostly acting on metabotropic receptors.* Modulatory inputs alter the excitability of motoneurons over a variety of time scales, affecting their responses to those inputs signaling precise timing signals for movement, but do not themselves code signals for movement. They play a basic role in determining the motoneuronal input-output relationship, which would be reflected functionally in the size and shape of bursts of activity that produce muscle contraction with timing and magnitude appropriate for performance of any coordinated movement.

4) *Many modulators of motoneuronal excitability act through common effector mechanisms and may even share common second messenger pathways.* For example, *a*) glutamate (metabotropic)-, NE-, 5-HT-, TRH-, and substance P-mediated signaling converge on a resting leak K^+ current and/or a cationic inward current (Fig. 9). These effector mechanisms change motoneuronal excitability by altering two important electrophysiological parameters: membrane potential and input resistance. Activation of a steady inward current and reduction of leak outward K^+ currents lead to depolarization, and the associated increased input resistance results in an electrotonically more compact neuron. *b*) NE and 5-HT systems converge on the hyperpolarization-activated inward current I_h, also increasing the level of motoneuronal excitability. *c*) Glutamate (metabotropic), 5-HT, and adenosine modulate Ca^{2+} channels. Influx of Ca^{2+} is a main determinant of the spike afterhyperpolarization ($I_{K\,Ca}$), and the charge carried by Ca^{2+} can also lead to membrane depolarizations, e.g., plateau potentials, or changes in recruitment thresholds. Both of these effects can profoundly

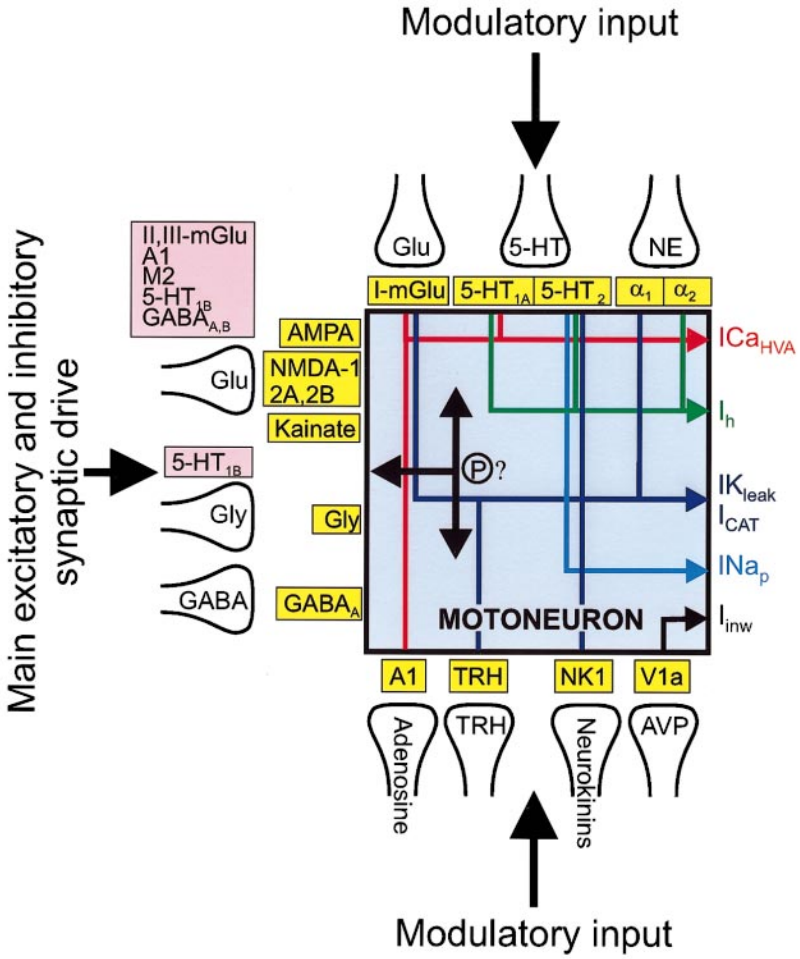

FIG. 9. Major transmitters (labeled in presynaptic terminals), presynaptic (red boxes) and postsynaptic (yellow boxes) receptors, and ion channel effectors involved in conveying main excitatory/inhibitory synaptic drive and modulatory input to motoneurons. Transmitter systems converge on 3 major effectors: $I_{Ca\ HVA}$, I_h, and $I_{K\ leak}$-I_{CAT}. Although graphically separated, several of the listed transmitters are colocalized in synaptic boutons. (P)?, possibility that phosphorylation of receptors or associated synaptic proteins play a role in regulating motoneuronal excitability; Glu, glutamate; Gly, glycine; AVP, arginine vasopressin.

alter the input-output function of motoneurons. *d*) Glutamate- (metabotropic), adenosine-, ACh-, 5-HT-, and GABA-mediated synaptic transmission can modulate presynaptic transmitter release. At present, only glutamatergic and glycinergic signaling are known to be presynaptically modulated, but other transmitter system may be under similar control. The change in motoneuronal excitability elicited by these convergent transmitter systems has mostly been studied using exogenous application of different receptors ligands (iontophoresis, bath application). This represents a significant limitation, since very little data exist on endogenous release of any particular modulatory transmitter. Thus the duration and amplitude of the change in motoneuronal excitability due to activation of these modulatory systems during normal motor behavior is unknown.

There are many important and interesting questions for future study. These might include the following:

1) *What is the particular role of the distributed inputs and conductances on the somatatodendritic membrane in ensuring proper signal processing in motoneurons for given movements?* In principle, motoneurons have complex geometry and many highly nonlinear properties, but under some conditions, they appear to behave like spheres receiving inputs that are summed (nearly) linearly. Under what conditions do motoneurons exploit or minimize nonlinearities?

2) *What are the actions of the multitude of peptide transmitter systems (Table 2) in ensuring the proper functioning of motoneurons?* Under what conditions are peptides released, and what are their effects? Their actions may go beyond short-term regulation of excitability and may be related to longer term adaptation associated with learning, or to changes in motor unit or muscles properties with development, exercise, aging, or disease.

3) *Are motoneuronal properties and/or synaptic processes modified on a short time scale during different motor behaviors?* Motor networks in the brain stem and spinal cord are likely reorganizing, and not dedicated, networks, i.e., they probably undergo functional reorganization to generate different motor tasks. For example, respiratory motoneurons involved in normal quiet breathing also take part in producing numerous other motor acts such as phonation, coughing, emesis, and sneezing. Rapid changes in channel properties and synaptic functions may be involved in these transient reorganizations.

4) *What are the cellular and molecular bases for intrinsic properties of motoneurons and their modulation by transmitters?* Intrinsic membrane properties of motoneurons influence the manner by which synaptic inputs are transformed into the production of action potentials that ultimately dictates behavior. Numerous voltage-dependent and -independent currents contribute to motoneuronal membrane and transduction properties, and these currents are subject to modulation by transmitters. To understand these processes, it will be critical to *1*) identify the molecular basis for intrinsic motoneuronal ionic currents, i.e., which of the myriad cloned channels underlie the measured currents, and *2*) determine the cellular and molecular mechanisms that contribute to ion channel modulation by transmitters, i.e., which specific receptors and ion channels are involved, and what transduction pathways are interposed between receptor and channel. Finally, motoneuronal membrane properties and their modulation are not static during postnatal development. Thus it will also be important to characterize molecular and cellular mechanisms underlying motoneuronal membrane properties and their modulation at different developmental stages.

5) *Do motoneurons exploit the molecular diversity of receptors to fine tune their phenotypic properties, especially because they may be useful in the control of particular muscles during particular (classes of) movements?* Although many different receptors can be assembled, we do not know the significance of the combinatorial possibilities and if motoneurons exploit this potential. Differences in expression of glutamate receptor subtypes among different motoneuron groups (and within motor pools), together with the possibility of molecular modulation, e.g., phosphorylation of these subunits, would permit motoneuronal excitability to be regulated by differential expression patterns and posttranscriptional modification of receptor subunits or associated synaptic proteins. These mechanisms could contribute to the regulation of motoneuronal properties during development, aging, or disease.

6) *Does phosphorylation of ionotropic amino acid receptors affect excitability to precisely control given movements or adapt motoneuronal function over longer time scales?* The precise timing signals for movement are mediated by amino acid receptors. Specific regulation of their properties by phosphorylation of the receptors or associated synaptic proteins would provide a mechanism for controlling the underlying currents specifically, without generic alteration in motoneuronal properties.

In summary, control of motoneuronal excitability is an essential feature of all behavior. We are beginning to understand the grammar that underlies motoneuronal properties, but ultimately we need to understand their language as they act during behavior. This will require intense efforts and probably novel approaches.

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