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Histamine modulates NMDA-dependent swelling in the neostriatum

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Abstract

In the present study, infrared differential interference contrast videomicroscopy was used to examine the effect of histamine on *N*-methyl-D-aspartate-induced swelling in neostriatal neurons in a brain slice preparation. Histamine caused a concentration-dependent increase in swelling evoked by *N*-methyl-D-aspartate. By itself, histamine did not cause swelling. Electrical stimulation also caused *N*-methyl-D-aspartate-dependent swelling which was enhanced by histamine. In addition, histamine was found to enhance *N*-methyl-D-aspartate-induced swelling from postnatal day 7 to 28 but not at postnatal day 3. Finally, this histamine-induced enhancement was prevented by treatment with either the H_2 receptor antagonist cimetidine or with the potassium channel blocker tetraethylammonium chloride. Overall, these findings suggest that histamine modulates *N*-methyl-D-aspartate receptor function in the neostriatum through a H_2 receptor-mediated regulation of potassium channels. © 1997 Elsevier Science B.V.

Keywords: Excitotoxicity; Histamine; Infrared differential interference contrast videomicroscopy; Neostriatum; NMDA; Swelling

1. Introduction

Neostriatal cells are innervated by a major glutamate-containing projection from the cortex [15,27,28]. This projection forms the main excitatory drive into the basal ganglia. Like many glutamatergic synaptic connections, both *N*-methyl-D-aspartate (NMDA) and non-NMDA ionotropic glutamate receptors (GluRs) contribute to excitatory postsynaptic potentials recorded in neostriatal neurons [7,20,21]. Excessive activation of these GluRs can be lethal to neurons [8,26] and this excitotoxic response of neurons to GluR activation has been proposed to play a role in the pathology of a number of diseases affecting the neostriatum, including obsessive compulsive disorder, schizophrenia, Tourette's syndrome, Huntington's disease and Parkinson's and Alzheimer's diseases [3,4,12,42,43]. Thus, understanding the modulation and regulation of NMDA receptors in the neostriatum could be clinically meaningful.

Immunocytochemical studies have demonstrated that histaminergic fibers, originating from the hypothalamus, project to much of the nervous system including the neostriatum [14,47]. Within the neostriatum, histamine release can be shown via microdialysis [1] and autoradiographic studies have documented the presence of histamine receptors, particularly the H_2 and H_3 subtypes [24,32,35,36]. One consequence of the activation of these receptors in neostriatal neurons is an increase in electrical excitability due to the regulation of a potassium conductance [29]. In hippocampal neurons, histamine also increased excitability due to an H_2 receptor mediated decrease in a calcium-activated potassium conductance [17,18]. In addition, in hippocampal neurons, histamine potentiated NMDA receptor mediated responses [5,45,50] although this effect has not been previously reported in neostriatal neurons.

The aim of the present study was to investigate the action of histamine on NMDA receptor-evoked responses in neostriatal neurons. In order to investigate this issue, infrared differential interference contrast (IR DIC) videomicroscopy [13] was utilized to examine the excitotoxic response of neostriatal neurons to GluR stimulation. This technique takes advantage of the finding that GluR activation induces cell swelling, an early event in an excitotoxic cascade that can produce cell death [8,34]. We have previously shown that NMDA-induced swelling is associated with cell death measured by the dye trypan blue [9] and have used this technique to follow the dynamics of GluR-evoked responses in single cells in neostriatal brain slices [9,11].

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In order to investigate the possibility that histamine acts to modulate NMDA receptor function in the neostriatum, the present study was designed to: (1) characterize the effects of histamine on NMDA-induced swelling of cells in the neostriatal brain slice; (2) characterize the effects of histamine on swelling induced by electrical stimulation of neostriatal cells; (3) describe the postnatal development of this modulatory response; (4) determine the receptor pharmacology of the response; (5) explore the possibility that potassium (K^+) channels mediate this modulatory response.

2. Materials and methods

2.1. Preparation of neostriatal slices

Male Sprague–Dawley rats (Harlan/Sprague–Dawley, Indianapolis, IN) 3–21 days old were used. After animals were killed by decapitation, brains were dissected and placed in cold oxygenated (95% O_2, 5% CO_2) artificial cerebral spinal fluid (ACSF) containing (in mM) NaCl 130, $NaHCO_3$ 26, KCl 3, $MgCl_2$ 2, NaH_2PO_4 1.25, $CaCl_2$ 1.0, glucose 10 (pH 7.2–7.4). After cutting, transverse sections (350 μm) were placed in ACSF at 25–27°C for at least 1 h (in this solution $CaCl_2$ was increased to 2 mM, and 4 mM lactate was added). Individual tissue sections were then transferred to the perfusion chamber in which the slice was held down with thin nylon threads. The slice was submerged in continuously flowing oxygenated ACSF (25°C) at a rate of 4 ml/min.

2.2. IR DIC videomicroscopy

The brain slice was viewed with an upright compound microscope (Zeiss Axioskop) using a 40× water immersion lens (Zeiss, achroplan, numerical aperture 0.75) and DIC optics. Slices were illuminated with near infrared light by placing an infrared bandpass filter (790 nm, Ealing Optics, Hollston, MA) in the light path. This filter allowed passage of light between 750 and 1050 nm and thus cut off much of the longer wavelength infrared radiation which would heat the tissue. The image was detected with an infrared-sensitive CCD camera (Hamamatsu C2400, Tokyo, Japan) and displayed on a video monitor. Analog contrast enhancement and gain control were provided by the camera controller. Digital images were stored on a computer/optical disk for subsequent analysis and additional digital contrast adjustment when necessary. Cells could be visualized to a depth of about 100 μm below the surface of the slice.

In order to quantify changes in response to activation of GluRs, image analysis software (Optimas, BioScan, Edmonds, WA) was used to measure cross-sectional somatic area (the perimeter, maximal length and width were also measured in some cells) prior to, during and after experimental treatments. Each measurement was made twice and the average value recorded. Measurements were only taken from cells which exhibited clear borders, convex shapes, and phase brightness (Fig. 1).

2.3. Electrical stimulation

In these studies, the stimulating electrode used to evoke synaptic response consisted of a pair of 0.2 mm diameter Teflon-coated silver wires exposed at the tips. It was placed approx. 1–3 mm from the visualized cell. Typically, one tip was placed in the cortex while the other was placed in the dorsal neostriatum. A Grass stimulator (500 μsec square wave pulses of 10 V) connected to a stimulus-isolation unit was used to evoke responses.

2.4. Solutions and materials

For all solutions, osmotic pressure was measured and ranged between 290 and 300 mOsm. Pharmacological agents purchased from Research Biochemicals, Natick, MA) include DL-2-amino-5-phosphonopentanoic acid (AP5), cimetidine (SKF 92334), chlorpheniramine maleate, clobenpropit dihydrobromide (VUF9153), 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), NMDA, spermidine, spermine, and tetraethylammonium chloride (TEA). The AMPA/KA GluR antagonist CNQX and the H_3 receptor antagonist clobenpropit were dissolved in dimethyl sulfoxide. The final DMSO concentration was never higher than 0.01%.

2.5. Statistical analyses

Differences between average values for experimental and control groups were evaluated using *t*-tests or Mann–Whitney rank sum tests when appropriate. Values were considered significantly different if $P < 0.05$. All tests were performed using Sigmastat (Jandel, San Rafael, CA). In the text, values are shown as mean ± S.E.M.

3. Results

A total of 810 neostriatal cells were visualized using IR DIC videomicroscopy and all groups contained data from at least four animals. An example of a field of neostriatal cells is shown in Fig. 1. Large interneurons were easily identified and were not included in the data set. The effects of experimental and control manipulations were determined by measuring cell area before and after treatments 10 min in duration. The results are presented in the text and figures as percent change in area. We have previously shown that measurements of cell area did not change under control conditions in which the cells were continuously perfused with ACSF and that NMDA-induced swelling is not reversible [11].

3.1. Histamine modulation of NMDA-induced swelling

Bath application of NMDA caused dose-dependent swelling of neostriatal cells (1 μM NMDA: $1 \pm 2\%$ swelling, $n = 41$; 10 μM NMDA: $7 \pm 2\%$ swelling, $n = 36$; 100 μM NMDA: $26 \pm 1\%$ swelling, $n = 150$). This NMDA-induced swelling was blocked by the NMDA receptor antagonist AP5 but not by the AMPA/KA antagonist CNQX [11]. By itself, histamine did not cause swelling ($2 \pm 1\%$ swelling, $n = 46$). When histamine (100 μM) was applied in combination with NMDA, histamine significantly enhanced swelling (Fig. 2; histamine plus 10 μM NMDA: $17 \pm 2\%$ swelling, $n = 32$, $P < 0.005$; histamine plus 100 μM NMDA: $38 \pm 3\%$ swelling, $n = 39$, $P < 0.001$). This enhancement was not seen when histamine was combined with a lower concentration of NMDA which did not induce swelling by itself (histamine plus 1 μM NMDA: $1 \pm 3\%$ swelling, $n = 9$). The modulatory effect was also not seen at histamine concentrations lower than 100 μM (1 μM histamine plus 100 μM NMDA: $19 \pm 4\%$ swelling, $n = 15$; 10 μM histamine plus 100 μM NMDA: $22 \pm 4\%$ swelling, $n = 14$). Thus, histamine enhanced NMDA-evoked responses in the neostriatum.

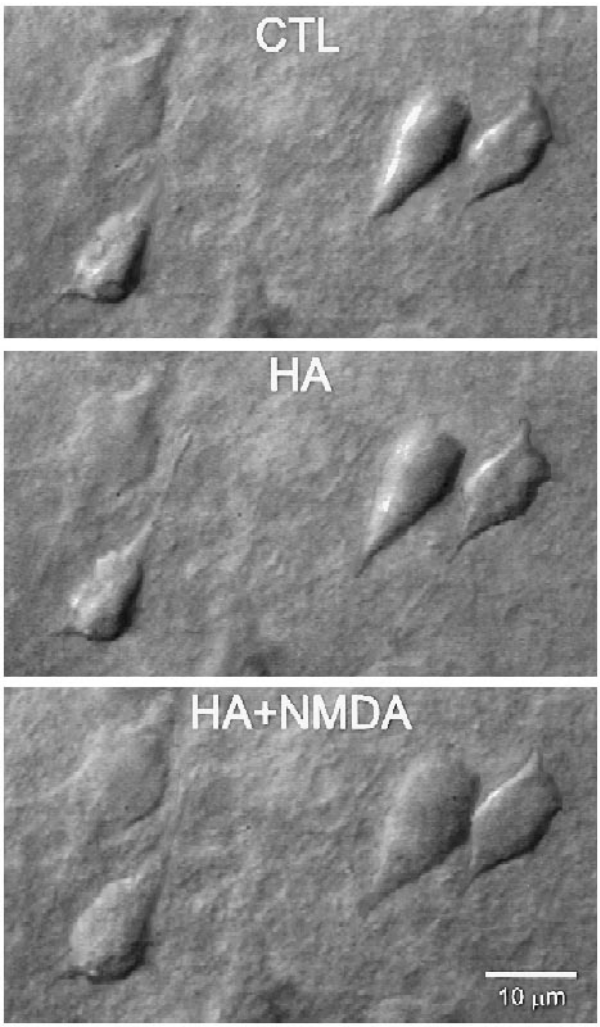

Fig. 1. Neurons in a neostriatal brain slice from a 14-day-old rat visualized by IR DIC videomicroscopy. Top panel: image of cells under control conditions. Middle panel: same cells after 5 min exposure to 100 μM histamine. Bottom panel: cells after 10 min exposure to histamine plus 100 μM NMDA.

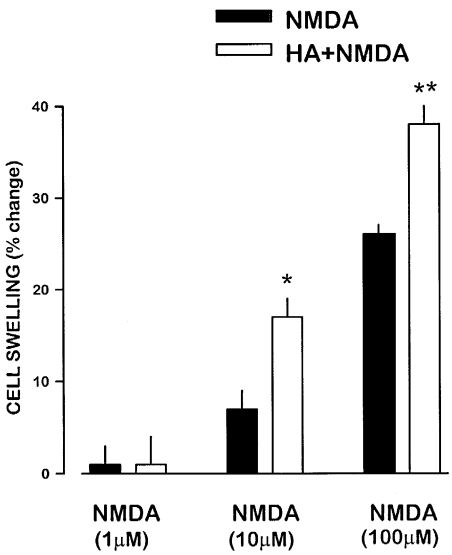

Fig. 2. Histamine enhanced NMDA-evoked swelling of neostriatal neurons. Swelling induced by NMDA (1–100 μM) alone was compared to swelling induced by histamine (100 μM) plus NMDA. Histamine significantly enhanced swelling caused by 10 and 100 μM NMDA. In this and subsequent figures, the cross-sectional area of cells was determined before and after 10 min treatment and expressed as % change. Error bars indicate S.E.M. and stars indicate groups in which swelling was significantly different (* $P < 0.005$; ** $P < 0.001$) from controls. Data were collected with tissue from PND 14 rats.

3.2. Histamine modulation of swelling induced by electrical stimulation

Strong electrical stimulation (100 Hz, 10 min) caused swelling of neostriatal neurons ($14 \pm 1\%$ swelling, $n = 72$). This swelling was blocked by the application of TTX ($2 \pm 3\%$ swelling, $n = 16$; $P < 0.001$) or AP5 ($2 \pm 2\%$ swelling, $n = 22$, $P < 0.001$) but not by CNQX ($14 \pm 4\%$ swelling, $n = 16$). The magnitude of electrically induced swelling varied with stimulus intensity and a weaker 10 Hz stimulation did not cause swelling by itself (4 ± 1 swelling, $n = 25$). When combined with 100 Hz stimulation, histamine produced a small but significant increase in this electrically induced swelling ($18 \pm 2\%$ swelling, $n = 27$, $P < 0.05$). Furthermore, when histamine was applied in combination with the weaker electrical stimulation, the swelling was strongly enhanced ($11 \pm 2\%$ swelling, $n = 29$, $P < 0.01$). Thus, histamine also enhanced swelling induced by electrical stimulation.

3.3. Development of histamine modulation

The effects of histamine (100 μM) on NMDA (100 μM) induced swelling was examined in neostriatal tissue

from different postnatal days (PND) (Fig. 3). At PND 3, there was no measurable response to NMDA ($1 \pm 1\%$ swelling, $n = 39$) or histamine plus NMDA ($0 \pm 4\%$ swelling, $n = 25$). At PND 7, histamine significantly enhanced NMDA-induced swelling (NMDA: $7 \pm 1\%$ swelling, $n = 94$; histamine plus NMDA: $20 \pm 2\%$ swelling, $n = 55$, $P < 0.001$). At PND 14, histamine also significantly enhanced NMDA-induced swelling (NMDA: $26 \pm 1\%$ swelling, $n = 150$; histamine plus NMDA: $38 \pm 3\%$ swelling, $n = 39$, $P < 0.001$). Likewise, at PND 21, histamine significantly enhanced NMDA-induced swelling (NMDA: $26 \pm 1\%$ swelling, $n = 37$; histamine plus NMDA: $34 \pm 6\%$ swelling, $n = 12$, $P < 0.05$). By itself, histamine did not cause swelling at any of the ages examined (data not shown). These findings suggest that histamine's modulation of NMDA responses occurs throughout postnatal development.

3.4. Effects of polyamines

Histamine has been reported to modulate responses mediated by NMDA receptors [5,45,48] through a mechanism which does not involve classical histamine receptors [45,50]. One possibility is that histamine acts at a polyamine site to modulate NMDA receptors [45]. In order to examine this possibility, the polyamine spermine (100 μM) was applied. By itself, spermine did not alter NMDA-evoked responses ($0 \pm 2\%$ swelling, $n = 16$) nor did it have any effect on NMDA-induced swelling ($25 \pm 4\%$ swelling, $n = 16$). Similar results were obtained with spermidine (100 μM). These findings suggest that histamine's actions are not due to interaction with the polyamine site of the NMDA receptor and that another mechanism must be involved.

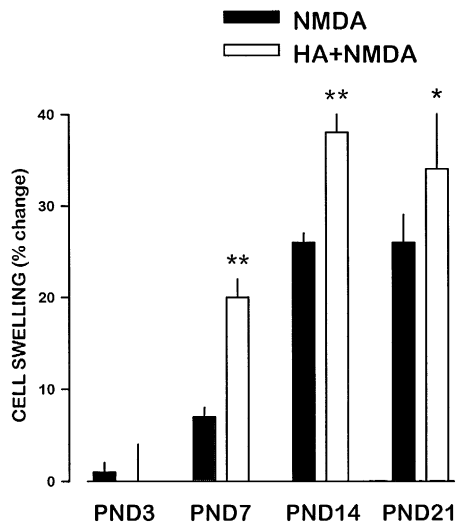

Fig. 3. Histamine modulation at different stages of postnatal development. Swelling induced by NMDA (100 μM) alone was compared to swelling induced by histamine (100 μM) plus NMDA (100 μM) in neostriatal tissue from animals at different ages (PND 3, 7, 14, 21). Histamine significantly enhanced swelling at all ages except for PND 3. Stars indicate groups in which swelling was significantly different (* $P < 0.01$; ** $P < 0.001$) from that caused by NMDA alone.

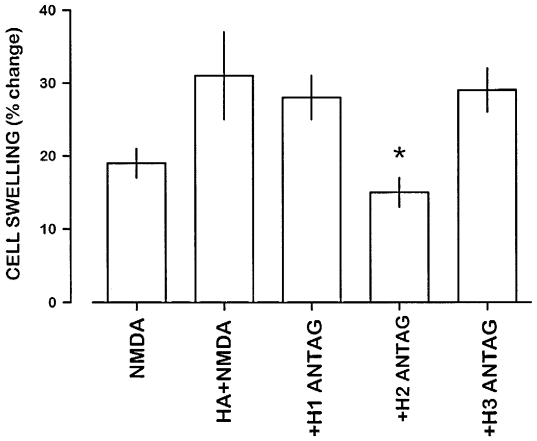

Fig. 4. The H_2 receptor antagonist cimetidine prevented histamine's modulatory effect. Swelling induced by histamine (100 μM) plus NMDA (100 μM) was examined in the presence of the following anti-histamines: H_1 antagonist chlorpheniramine (10 μM), H_2 antagonist cimetidine (50 μM), H_3 antagonist clobenpropit (10 μM). Only the H_2 antagonist cimetidine significantly reduced ($P < 0.001$) swelling caused by histamine and NMDA. By themselves, none of the receptor antagonists caused swelling. Data were collected with tissue from PND 14 rats.

3.5. Effects of histamine receptor antagonists

Next, the effects of histamine receptor antagonists were investigated (Fig. 4). In these studies, NMDA alone produced swelling ($19 \pm 2\%$ swelling, $n = 33$) which was enhanced by 100 μM histamine ($31 \pm 3\%$ swelling, $n = 20$, $P < 0.01$). Treatment with the H_2 antagonist cimetidine (50 μM) caused a significant reduction in the histamine enhancement of NMDA-induced swelling ($14 \pm 2\%$ swelling, $n = 39$). Cimetidine alone did not alter the NMDA-induced swelling ($17 \pm 4\%$ swelling, $n = 19$). Treatment with H_1 antagonist chlorpheniramine (10–50 μM) did not alter histamine-induced enhancement of NMDA-induced swelling ($28 \pm 3\%$ swelling, $n = 34$). Similarly, no inhibitory effects resulted from treatment with 10–50 μM of the H_3 antagonist clobenpropit ($29 \pm 3\%$ swelling, $n = 27$). By themselves, the histamine receptor antagonists did not cause cell swelling (data not shown). These findings suggest that histamine modulation of NMDA-evoked swelling is mediated by the H_2 receptor subtype.

3.6. Effect of histamine on NMDA response in the presence of the potassium (K^+) channel blocker TEA

H_2 receptors have been reported to regulate K^+ currents in neurons dissociated from the neostriatum [29]. If histamine was acting to enhance NMDA responses through this regulation of K^+ currents, then histamine should be ineffective in the presence of K^+ channel blockers. So

experiments were conducted in the presence of the broad spectrum K^+ blocker TEA (10 mM) which in our preparation blocks the majority of K^+ currents [2]. Under these conditions, NMDA caused swelling ($19 \pm 2\%$ swelling, $n = 28$) which was not enhanced by histamine ($17 \pm 2\%$ swelling, $n = 29$). In the presence of TEA, histamine alone did not cause swelling ($1 \pm 2\%$ swelling, $n = 23$). This finding adds support to the hypothesis that histamine enhances NMDA swelling through a regulation of K^+ currents.

4. Discussion

In the present study, IR DIC videomicroscopy was used to examine the effects of histamine on NMDA-induced swelling of neostriatal neurons in a brain slice preparation. Histamine caused a concentration-dependent increase in swelling evoked by NMDA. By itself, histamine was without effect on this measurement. Electrical stimulation also caused NMDA-dependent swelling which was enhanced by histamine. Next, the postnatal development of this modulation was determined. Finally, this histamine-induced enhancement was prevented by treatment with either a H_2 receptor antagonist or a K^+ channel blocker. Thus, in the neostriatum, histamine can function to modulate NMDA receptor function.

In this study, cell swelling was used primarily as an assay of receptor mediated responses. This is an unusual assay which has some unique advantages as well as disadvantages. Advantages include the ability to follow the temporal dynamics of functional responses in single cells and that different cell types within the neostriatum can be morphologically distinguished. In addition, this information can be simultaneously obtained from a field of cells allowing wide sampling of cell populations. The main disadvantages center on the slow time course of swelling (5–10 min) compared to electrophysiological assays which means that receptors may be 'desensitized' and that cell swelling is an indirect measure of receptor function. NMDA-induced swelling is presumably caused by the osmotic imbalance which results from an influx of sodium/chloride ions into the cell [11,24]. Thus, cell swelling is a reflection of more than just receptor activation but also of how the cell responds to the influx of current. For example, using this assay, it may not be possible to distinguish between an agent which enhanced receptor function and one which inhibited an ionic pump responsible for the maintenance of osmotic balance. Nevertheless, we feel that this technique has promise for following the dynamics of a single cell's response to receptor activation in a brain slice preparation.

4.1. Electrical stimulation

This study is the first to show that cell swelling can be induced by electrical stimulation. This swelling was blocked by the sodium channel blocker TTX and by a NMDA receptor antagonist suggesting that synaptic mechanisms are involved. These findings provide additional support for the idea that NMDA receptors somehow play a special role in inducing cell swelling and toxicity [8]. Previous electrophysiological studies in neostriatal cells have shown that the postsynaptic response evoked by single stimuli are mediated mostly by non-NMDA GluRs [20]. However, under conditions like those used in the present study, when a train of stimuli are used to evoke a response, a large component of the postsynaptic response is mediated by NMDA receptors [21]. Thus, histamine can apparently modulate synaptically stimulated NMDA receptors. The finding that synaptic stimulation can cause cells to swell raises the possibility that neuronal swelling may occur in vivo, at least under conditions of strong synaptic stimulation.

4.2. Development

Studies in the cerebellum and cortex suggest that NMDA receptors play a critical role in nervous system development [22,23,30]. Although not carefully studied, there is every reason to think that this receptor plays an equally important role in neostriatal development. This being the case, it is clearly important to understand how modulators alter NMDA receptor function in the developing nervous system. In rat brain, histamine concentration is high early in development and declines to adult levels by PND 16 [36,39]. However, this ontogeny is not necessarily a reflection of neuronal histaminergic development [39]. A better marker may be the activity of the synthetic enzyme L-histidine decarboxylase which is low at PND 5 and increases to adult levels from PND 16 to 23 [36]. H_1 receptor binding sites in neostriatum are present at low densities throughout development while H_3 receptor binding sites are not detectable until PND 9 and then increase until peak levels are reached at PND 23 [36]. Unfortunately, comparable information about the ontogeny of H_2 receptors in the rat neostriatum does not seem to be available. The present study examined the ontogeny of functional responses to histamine and showed that histamine can enhance NMDA receptor function as early as PND 7, but not at PND 3. Defining the ontogeny of NMDA-induced responses and this receptor's modulators represents an early step toward better understanding the role of these receptor systems in the developing neostriatum.

4.3. Mechanisms

In the present study, the H_2 receptor antagonist cimetidine prevented histamine's enhancement of the NMDA response. This receptor subtype appears to be abundant in the neostriatum [24,35,36,41]. Electrophysiologically, the antagonist cimetidine also blocked a histamine-induced

inward current in neostriatal neurons [29]. While these findings certainly suggest a functional role for H_2 receptors in the neostriatum, this regulation of inward current was found in cells which were likely interneurons [29]. In contrast, most of the data in the present study were likely collected from projection neurons, the 'medium spiny' neurons which make up as much as 95% of the neuronal population in the neostriatum [16]. Large interneurons could easily be identified in the brain slice preparation and were not included in the data set. When cells were filled with biocytin or Lucifer yellow, all cells of a similar size to those measured in the present experiments exhibited the morphology of medium-sized neurons [6]. Thus, the evidence suggests that H_2 receptors modulate NMDA receptor function in neostriatal medium spiny neurons.

Little information is available about the intracellular mechanisms by which histamine receptors influence neuronal function in the neostriatum. It is well established that H_2 receptors are positively coupled to adenylate cyclase and result in the accumulation of cAMP [19,33,38,40]. Interestingly, using intracellular recording techniques in a brain slice preparation, we have previously shown that treatment with forskolin, an activator of adenylate cyclase, enhanced NMDA-evoked responses in the neostriatum [10]. In addition, using the cell swelling assay, forskolin also enhanced NMDA-evoked swelling (unpublished data). Thus, it is appealing to speculate that H_2 receptors are acting through a cAMP-dependent mechanism to modulate NMDA responses.

Histamine regulation of K^+ currents has been previously reported in the neostriatum [29] as well as in other brain regions [18,25]. Accordingly, we examined whether histamine could still modulate NMDA-evoked responses in presence of the broad spectrum K^+ channel blocker, TEA. In the neostriatal brain slice preparation, bath application of TEA blocks the majority of K^+ currents [2]. TEA also prevented histamine's regulation of K^+ currents in hippocampal pyramidal cells [31]. Similar results were obtained in the present study as histamine did not enhance NMDA-induced swelling in the presence of TEA. This finding suggests that TEA-sensitive K^+ channels mediate histamine's enhancement of the NMDA-evoked response. There is one potential problem with this simple interpretation. TEA has been reported to block NMDA receptor channels in culture and expression systems [44,49]. This does not appear to be a factor in the present experiments as the magnitude of NMDA-induced swelling was virtually identical in the presence or absence of TEA. Still it is hard to completely rule out the possibility that TEA interferes with the histamine modulation through a non-specific pharmacological effect.

Histamine also enhanced NMDA mediated synaptic currents [5] and NMDA activated currents in acutely dissociated pyramidal neurons [45]. In hippocampal slices, histamine's modulation of synaptic currents is pH-dependent [37]. These actions of histamine are not mediated by known histamine receptors [45,50] and may occur at the polyamine regulatory site on the NMDA receptor [45]. However, the present data suggest that this mechanism of histaminergic regulation is not active in the neostriatum where the H_2 receptor, not the polyamine site, is implicated.

4.4. Function

The neostriatum receives a prominent histaminergic innervation from the hypothalamus, although the functional significance of this regulation is unknown. Based on anatomical considerations, the histaminergic transmitter system has been suggested to represent a regulatory center capable of altering arousal throughout the nervous system [46]. Similarly, electrophysiological analysis of histamine's effects on hippocampal pyramidal cells has led to the suggestion that activation of H_2 receptors regulates excitability by potentiating the cell's response to all excitatory input [17]. In the neostriatum, the finding that histamine, acting through H_2 receptors, inhibited a potassium conductance [29] as well as enhanced the response to treatment with NMDA (present study) is consistent with these functional suggestions. Some of the behavioral consequences of the intracerebroventricular administration of histamine include alterations in locomotor activity which are perhaps mediated by neostriatal histamine receptors [38,46]. Understanding how this combination of histamine regulated events alters the activity of motor control circuits based in the basal ganglia will be important in eventually explaining the functional roles of the histaminergic system.

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