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Effects of hypomagnesia on histamine H_1 receptor-mediated facilitation of NMDA responses

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1 The ability of histamine to facilitate the N-methyl-D-aspartate (NMDA) induced depolarization of cortical projection neurones was examined by use of grease-gap recording.

2 Histamine (1 to 15 μM) reversibly facilitated the NMDA-induced depolarization yielding a bell-shaped concentration-response relationship. The peak enhancement was 167% above the control at 10 μM histamine. Desensitization was present in 4 out of 5 slices on second exposure 40 min following the first exposure.

3 Histamine did not alter the depolarization induced by 10 μM kainate.

4 The histamine-induced facilitation persisted in the presence of tetrodotoxin, but was reduced in a concentration-dependent manner by diphenhydramine ($IC_{50} = 7.6$ nM). Cyproheptadine (10 nM) also reduced the facilitation, whereas ranitidine (200 nM) and thioperamide (10 nM) were ineffective in this regard.

5 Histamine (10 μM) facilitated the NMDA (25 μM)-induced depolarization in nominally Mg^{2+}-free medium. The magnitude of the facilitation was smaller than that observed in Mg^{2+}-containing medium (17% above the control) and desensitization was not observed. This facilitation was not reduced by cyproheptadine (10 nM) or diphenhydramine (1 μM).

6 We conclude that histamine facilitates the NMDA depolarization at cortical neurones via two distinct mechanisms. One mechanism involves activation of the histamine H_1 receptor and is sensitive to Mg^{2+}. The second mechanism is independent of histamine cell surface receptor activation and may reflect a direct action of histamine at the NMDA receptor.

Keywords: Histamine; Mg^{2+}; N-methyl-D-aspartate; cerebral cortex

Introduction

Histamine selectively facilitates currents evoked by N-methyl-D-aspartate (NMDA) at neurones in hippocampal slices (Brown *et al*., 1995; Saybasili *et al*., 1995), hippocampal neurones in culture (Bekkers, 1993; Bekkers *et al*., 1996), acutely dissociated hippocampal neurones (Vorobjev *et al*., 1993), and at *Xenopus* oocytes expressing NMDA receptors (Williams, 1994). Three histamine cell surface receptor subtypes have been identified, H_1, H_2 and H_3 (see Hill, 1990 for review). Despite the presence of all three receptors in the hippocampus (Pollard & Bouthenet, 1992), the enhancement of NMDA receptor-mediated responses by histamine at hippocampal neurones is either insensitive or weakly sensitive to histamine receptor antagonists (Bekkers, 1993; Vorobjev *et al*., 1993; Brown *et al*., 1995). Moreover, histamine facilitates NMDA-induced responses at *Xenopus* oocytes expressing NMDA receptors and yet *Xenopus* oocytes do not normally express histamine cell surface receptors (Williams, 1994). This facilitation, as expected, is insensitive to histamine receptor antagonists (Williams, 1994). Spermine, a polyamine, facilitates NMDA induced currents and in the presence of spermine the histamine-induced facilitation is occluded (Vorobjev *et al*., 1993; Williams, 1994), although the reverse is not the case (Williams, 1994). It has been proposed that histamine acts at a unique site on the NMDA receptor complex and in this manner enhances NMDA responses (Bekkers, 1993; Vorobjev *et al*., 1993; Williams, 1994; Brown *et al*., 1995; Bekkers *et al*., 1996).

Histamine H_1 receptors are linked via G-proteins to phospholipase C (Daum *et al*., 1984; Donaldson & Hill, 1986; Carswell *et al*., 1987; Bristow *et al*., 1993; Hill & Donaldson, 1992). Other G-protein coupled receptors which activate phospholipase C, including 5-hydroxytryptamine$_{2A}$ (5-HT_{2A}) receptors, Group I metabotropic glutamate receptors, muscarinic acetylcholine receptors and α_1-adrenoceptors uniformly facilitate NMDA receptor mediated responses (Nedergaard *et al*., 1987; Reynolds *et al*., 1988; Markram & Segal, 1990; 1992; Mally *et al*., 1991; Kelso *et al*., 1992; Harvey & Collingridge, 1993; Kinny & Slater, 1993; Rahman & Neuman, 1993a; 1996a). Enhancement of NMDA responses following activation of these receptors has been variously attributed to activation of protein kinase C (Aniksztejn, 1992; Kelso *et al*., 1992) or to a rise in intracellular Ca^{2+} resulting from the production of inositol 1, 4, 5 trisphosphate (IP_3) (Markram & Segal, 1992; Kinny & Slater, 1993; Rahman & Neuman, 1993a, b; 1996a, b; Kong & Neuman, 1995). In either case the activation of phospholipase C is a central event. Thus, it is surprising that histamine fails to facilitate NMDA responses at hippocampal neurones, at least in part, through an action at the histamine H_1 receptor (Vorobjev *et al*., 1993; Brown *et al*., 1995).

The facilitation of NMDA responses mediated by 5-HT_{2A} receptors and α_1-adrenoceptors is eliminated in cortical slices perfused with Mg^{2+}-free medium (Rahman & Neuman, 1996b). The failure to observe facilitation of NMDA responses mediated by histamine H_1 receptors may therefore have resulted in part from the use of Mg^{2+}-free medium (Bekkers, 1993; Vorobjev *et al*., 1993). H_1 receptors are found on cortical neurones (Hill *et al*., 1978; Tran *et al*., 1978; Pollard & Bouthenet, 1992) and by use of a cortical slice preparation we examined the effects of histamine on the NMDA-induced depolarization and how this was influenced by hypomagnesia.

Methods

Coronal slices of cortex (500 μm) were prepared from male Sprague-Dawley rats (125–275 g) that had been anaesthetized with urethane (1.5 g kg^{-1} i.p.) and killed with a heavy blow.

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Slices were cut on a Vibroslicer (Camden Instruments) in modified artificial cerebrospinal fluid (ACSF) at 0 to 4°C and were allowed to recover for 30 min at room temperature (20–24°C) in modified ACSF before the medium was exchanged for regular ACSF. After an additional 60 min recovery, a wedge of sensorimotor cortex was cut from a slice and mounted in a grease-gap chamber (School of Pharmacy, University of London) as described by Harrison & Simmonds (1985). Only one wedge from approximately the same dorso-lateral position was prepared from each hemisphere. Each compartment of the grease-gap bath (~1.5 cc) was perfused at 2 ml min^{-1}. Ag/AgCl electrodes, embedded in saline with 3% agar, were employed to record agonist-induced depolarization of the dendrites and cell bodies with respect to the corpus callosum (Harrison & Simmonds, 1985). Experiments were conducted at room temperature. Drugs were dissolved in ACSF and applied by perfusion to the compartment which contained the cell bodies and dendrites. Regular ACSF consisted of (mM): NaCl 126, KCl 3.5, $CaCl_2$ 2, $MgCl_2$ 1.3, NaH_2PO_4 1.2, $NaHCO_3$ 25 and glucose 11. *Myo*-inositol (5 mM) was added to reduce homologous desensitization (Rahman & Neuman, 1993c). Aerated with O_2/CO_2 (95%/5%) the pH of the ACSF was 7.3. In modified ACSF the NaCl was replaced with isoosmotic sucrose (252 mM; Aghajanian & Rasmussen, 1989). NMDA at a concentration of 50 μM, an optimal concentration for demonstrating facilitation with 5-HT (Rahman & Neuman, 1993a), was perfused for 2 min every 20 min unless otherwise indicated. Ranitidine, cyproheptadine, diphenhydramine and thioperamide were perfused for 30 min before the addition of agonists.

Data analysis

Depolarization amplitude was converted to a percentage of control ([(Treatment/Control)] × 100) and log normal value computed (Gaddum, 1945). Repeated measures were analysed by paired *t* tests. Multiple comparisons were analysed by one-way analysis of variance followed by the Bonferroni test (Instat, GraphPad Software). Statistical significance was evaluated by two-tailed tests. Data are presented as the antilog of the geometric mean ± s.e.mean. TableCurve (Jandel Scientific) was used for nonlinear regression analysis.

Drugs

Kainate, N-methyl-D-aspartate (NMDA) and ranitidine HCl were obtained from Sigma. Cyproheptadine HCl, diphenhydramine HCl, histamine HCl, tetrodotoxin and thioperamide maleate were obtained from Research Biochemicals International. Drug concentrations were calculated as the salt. Stock solutions were kept frozen until use. Solutions of ranitidine were prepared fresh.

Results

Histamine facilitates the NMDA depolarization

Perfusion of histamine (10 μM) alone for 2 min did not alter the recorded potential ($n = 3$). However, the co-perfusion of histamine (10 μM) with NMDA (50 μM) for 2 min resulted in a depolarization that was significantly larger than the NMDA control response (Figure 1). Following 20 min of wash the NMDA depolarization returned to the control value (Figure 1). A second exposure to histamine plus NMDA 40 min after the first exposure resulted in a smaller depolarization than observed initially (Figure 1) in four out of five wedges, although this did not reach statistical significance (88 ± 12% of control, $P = 0.17$, $n = 5$). The depolarization of cortical neurones induced by NMDA is stable for hours when applied at 20 min intervals (Rahman & Neuman, 1993b). Thus, a reduction in the histamine-induced facilitation probably represents desensitization of the histamine component. As a consequence, each cortical wedge was exposed to histamine only once unless stated otherwise.

The concentration-response relationship for the histamine-induced facilitation is shown in Figure 2. Histamine was effective in facilitating the NMDA depolarization over a rather narrow concentration range. The peak facilitation was observed at 10 μM histamine and at 15 μM histamine the facilitation had nearly returned to the baseline. The rapid decline in the maximal facilitation with an increase in the concentration of histamine may represent a form of desensitization. The bell-shaped concentration-response relationship is reminiscent of the facilitation induced by activating 5-HT_{2A} receptors which undergo desensitization (Rahman & Neuman, 1993a, b, c).

The facilitation induced by activating receptors that positively couple to phospholipase C is selective in that the depolarization induced by other ionotropic glutamate receptors is not enhanced (Nedergaard *et al*., 1987; Reynolds *et al*., 1988; Markram & Segal, 1990; Aniksztejn *et al*., 1991; Harvey & Collingridge, 1993; Rahman & Neuman, 1993a, 1996a). The

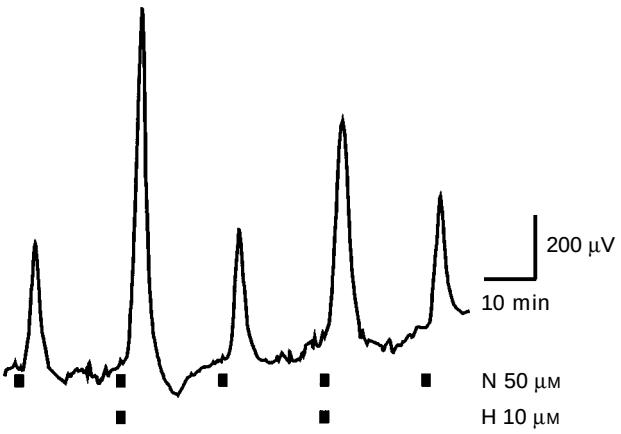

Figure 1 Histamine facilitated the depolarization of cortical neurones induced by NMDA. Co-application of 10 μM histamine with 50 μM NMDA for 2 min reversibly enhanced the amplitude of the NMDA-induced depolarization. Application of histamine (H) and NMDA (N) 40 min after the first exposure yielded a smaller enhancement. In this figure and subsequent figures traces were digitized with a scanner and the normal centre line of each trace determined with CorelTrace (Corel Corp.).

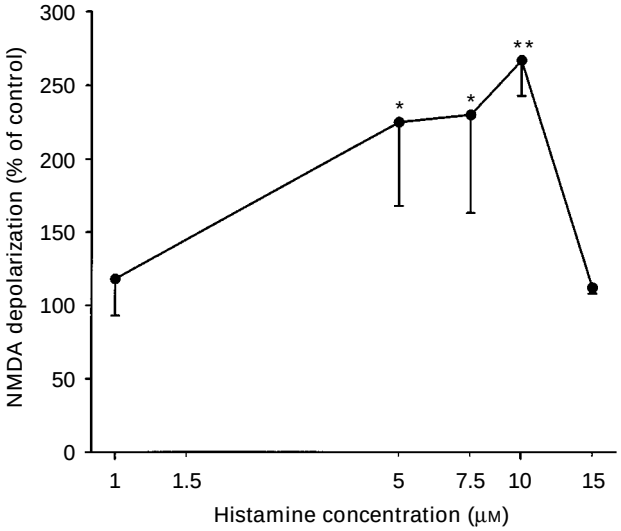

Figure 2 The concentration-response relationship for the histamine-induced facilitation. Three to seven wedges were used for each concentration of histamine. Each wedge was only exposed to one concentration of histamine. *$P < 0.05$, **$P < 0.001$.

histamine-induced facilitation was also found to be selective. Thus, co-perfusion of 10 μM histamine with 10 μM kainate failed to enhance the kainate-induced depolarization ($109 \pm 7\%$, $n=4$; $P=0.25$).

Histamine might indirectly alter the depolarization of projection neurones through an action on interneurones. However, perfusion of 0.3 μM tetrodotoxin for 30 min before testing with histamine plus NMDA only revealed a small, nonsignificant reduction in the extent of the facilitation (Table 1).

Histamine receptor antagonists

The histamine-induced facilitation observed in the present study differed from that reported previously (Bekkers, 1993; Vorobjev *et al*., 1993; Brown *et al*., 1995; Bekkers *et al*., 1996) in that the magnitude of the facilitation was larger at 10 μM histamine, the effective concentration range of histamine which produced a facilitation was smaller and the facilitation typically exhibited long lasting desensitization. Since histamine H_1 receptor-mediated responses exhibit desensitization (Dillon-Carter & Chuang, 1989; Bristow *et al*., 1993), possible histamine receptor involvement was investigated. Application of the histamine H_1 receptor antagonist diphenhydramine (Trottier & Malone, 1969), reduced the histamine (10 μM)-induced facilitation in a concentration-dependent manner (Figure 3) with an IC_{50} of 7.6 ± 1.1 nM and a Hill coefficient of 2 ± 0.5. Cyproheptadine (10 nM), a potent, but non-selective, histamine H_1 receptor antagonist (Stone *et al*., 1961; Trottier & Malone, 1969) also significantly reduced the histamine induced facilitation (Table 1). Neither diphenhydramine nor cyproheptadine significantly altered the NMDA-induced depolarization in the absence of exogenous histamine (Table 1). Ranitidine and thioperamide, histamine H_2 and H_3 receptor antagonists (Hill, 1990), respectively, did not alter the histamine-induced facilitation (Table 1).

The effect of hypomagnesia

The effectiveness of diphenhydramine and cyproheptadine suggests that the histamine-induced facilitation is mediated in large part by the histamine H_1 receptor. Other than the use of cortical rather than hippocampal slices, a methodological difference that might account for the apparent disparity between the present observations and previous data on the histamine-induced facilitation was our use of ACSF containing 1.3 mM Mg^{2+} rather than nominally Mg^{2+}-free medium. Hypomagnesia eliminates the facilitation induced by 5-HT and phenylephrine (Rahman & Neuman, 1996b). Therefore, the effects of histamine were re-examined in nominally Mg^{2+}-free ACSF. To compensate for the larger NMDA-induced depolarization expected in Mg^{2+}-free medium (Rahman & Neuman, 1996b), the concentration of NMDA was reduced to 25 μM. Following at least a 2 h wash in Mg^{2+}-free ACSF, histamine (10 μM) induced a facilitation of the NMDA depolarization (Figure 4). However, compared to the facilitation in Mg^{2+}-containing ACSF, the magnitude of the facilitation was smaller. Moreover, desensitization was not observed during a second exposure to histamine plus NMDA 20 min following the first exposure (Table 2). Cyproheptadine (10 nM) failed to reduce the histamine-induced facilitation (Table 2). Indeed, the magnitude of the facilitation was slightly increased. However, this small increase did not appear to result from antagonism of an H_1 receptor-mediated response, since a similar enhancement was not observed with 1 μM diphenhydramine (Table 2).

Table 1 Effects of various treatments on the histamine-induced facilitation of the NMDA-evoked depolarization and on the NMDA depolarization

Treatment	*NMDA depolarization* (% of control)
Histamine (10 μM)	$267 \pm 24\%$ ($n=7$)
+ TTX (300 nM)	$213 \pm 42\%$ ($n=3$)
+ cyproheptadine (10 nM)	$121 \pm 13\%$ ($n=3$)[A]
+ ranitidine (200 nM)	$215 \pm 42\%$ ($n=5$)
+ thioperamide (10 nM)	$243 \pm 36\%$ ($n=6$)
NMDA (50 μM)	
+ diphenhydramine (1 μM)	$111 \pm 16\%$ ($n=5$)
+ cyproheptadine (10 nM)	$105 \pm 3\%$ ($n=3$)

Data shown are means $\pm$ s.e.mean. [A] $P<0.0055$, treatment vs histamine control.

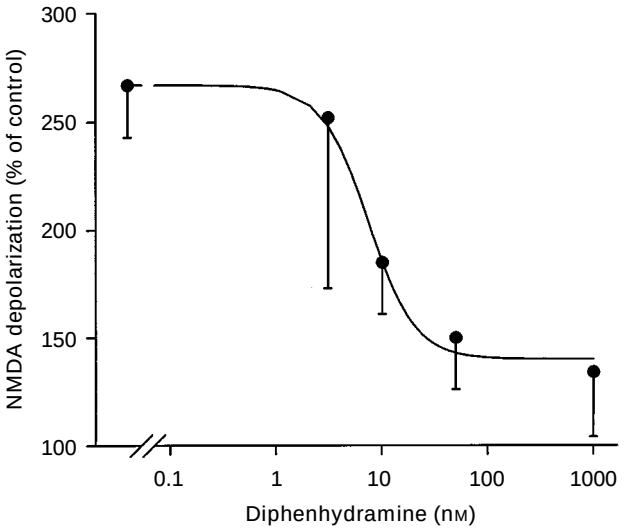

Figure 3 Diphenhydramine antagonized the histamine-induced facilitation. Each wedge (four to five per group) was exposed to one concentration of diphenhydramine along with 10 μM histamine plus NMDA and the response compared with the response induced by NMDA in the presence of diphenhydramine. The smooth curve through the data points was fitted with the Hill equation. Note that the asymptote of the nonlinear regression remains above the NMDA control.

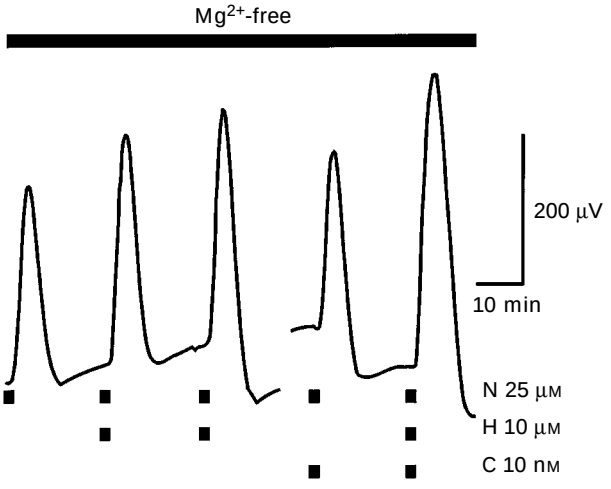

Figure 4 Histamine facilitated the NMDA induced depolarization in nominally Mg^{2+}-free medium. Co-application of histamine (H) with NMDA (N) resulted in a small facilitation which did not desensitize during a second exposure 20 min after the first exposure. A 30 min bath perfusion of cyproheptadine (C) did not reduce the histamine-induced facilitation.

Table 2 The facilitation induced by histamine in Mg^{2+}-free medium did not exhibit desensitization and was not reduced by histamine H_1 receptor antagonists

Treatment	*NMDA[A] depolarization* (% of control)	
Histamine (10 μM) first exposure	117±3%	($n=8$)[B]
Histamine (10 μM) second exposure	122±4%	($n=8$)[C]
Histamine (10 μM)		
+cyproheptadine (10 nM)	142±14%	($n=3$)[D]
+diphenhydramine (1 μM)	124±4%	($n=3$)[E]

Data shown are means±s.e.mean. [A]The concentration of NMDA was 25 μM; [B]$P<0.01$, treatment vs NMDA control; [C]$P<0.001$, treatment vs NMDA control; [D]$P<0.02$, treatment vs NMDA plus cyproheptadine, [E]$P<0.01$, treatment vs NMDA plus diphenhydramine.

Discussion

In keeping with previous data from studies on acutely isolated or cultured hippocampal neurones (Bekkers, 1993; Vorobjev *et al*., 1993; Bekkers *et al*., 1996), hippocampal slices (Brown *et al*., 1995; Saybasili *et al*., 1995; but see Bekkers *et al*., 1996) and *Xenopus* oocytes (Williams, 1994), histamine facilitates the NMDA-induced depolarization of cortical neurones. However, the histamine-induced facilitation observed in the present study differed in a number of respects from that described previously. Thus, in the present study the histamine induced facilitation: (1) was larger in magnitude; (2) was sensitive to histamine H_1 receptor antagonists; (3) typically exhibited long-lasting homologous desensitization; (4) demonstrated a narrow concentration-response relationship and (5) was readily induced in slices. We suggest that the histamine-induced facilitation consists of two additive components, one dependent on H_1 receptor activation and one independent of such activation. Differences between the present findings and previous results can be accounted for in large part by the Mg^{2+}-sensitivity of the histamine H_1 receptor-mediated facilitation and receptor desensitization.

The results of our experiments with histamine antagonists suggests that a large component of the histamine-induced facilitation is mediated through histamine H_1 receptor activation. Thus, ranitidine and thioperamide, relatively selective antagonists at H_2 and H_3 receptors, respectively, did not significantly decrease the histamine-induced facilitation when applied for 30 min at concentrations near their K_D values (see Hill, 1990). On the other hand, diphenhydramine, a histamine H_1 receptor antagonist (Trottier & Malone, 1969), produced a concentration-dependent reduction in the histamine-induced facilitation with an IC_{50} of 7.6 nM, a value close to its K_A of 3.2 nM at guinea-pig ileum (Trottier & Malone, 1969). Diphenhydramine also binds to muscarinic acetylcholine receptors (Burgen & Harbird, 1983). Moreover, the release of acetylcholine in cortical slices makes a small, but significant, contribution to the NMDA-induced depolarization (Rahman & Neuman, 1993a). However, at the highest diphenhydramine concentration employed, 1 μM, the amplitude of NMDA-induced depolarization was not reduced, from which we conclude that muscarinic acetylcholine receptors remained functional. The potent antagonism of the histamine-induced facilitation by cyproheptadine is consistent with the involvement of a histamine H_1 receptor (Stone *et al*., 1961; Trottier & Malone, 1969) and complements the more complete diphenhydramine data. Cyproheptadine is also an antagonist at L-type Ca^{2+} channels (Lowe *et al*., 1981; Bolger *et al*., 1983). However, the concentration employed in the present study is 10 fold lower than the minimum concentration necessary to reduce activity at L-type Ca^{2+} channels (Lowe *et al*., 1981).

Although diphenhydramine and cyproheptadine antagonized the facilitation, the response nevertheless remained larger than the control response. This is most easily seen by examining the diphenhydramine concentration-response curve. The data are well fit by the curve and yet the asymptote of the nonlinear regression is 40% above the NMDA control. This value is close to the magnitude of the facilitation induced by 10 μM histamine in Mg^{2+}-free ACSF with or without the presence of antagonists (Table 2). From these findings it may be concluded that histamine facilitates the NMDA-induced depolarization via two distinct mechanisms, only one of which is sensitive to histamine H_1 receptor antagonism. The antagonist data imply that both mechanisms are active in Mg^{2+}-containing medium. Additivity of the two mechanisms could account for the larger facilitation observed in the present study when compared to previous observations on the histamine-induced facilitation (Bekkers, 1993; Vorobjev *et al*., 1993; Brown *et al*., 1995).

The second application of histamine plus NMDA in regular ACSF typically resulted in a smaller facilitation than the initial response. Repeated application of NMDA at 20 min intervals does not result in a decline of the NMDA depolarization (Rahman & Neuman, 1993b). Moreover, 1**S**,3**R**-1-aminocyclopentane-1,3, dicarboxylic acid facilitates the NMDA-induced depolarization of cortical neurones to a greater extent than does histamine (Rahman & Neuman, 1996a) and yet significant desensitization of this response is not observed. Thus, we propose that desensitization of the histamine-induced facilitation represents homologous desensitization of the histamine mediated component of the facilitation. Responses mediated by the histamine H_1 receptor exhibit homologous desensitization (Hill, 1990; Bristow *et al*., 1993). The presence of desensitization is therefore consistent with the involvement of the histamine H_1 receptor.

The H_1 receptor is linked to phospholipase C (Hill & Donaldson, 1992) and activation of the receptor on cortical neurones stimulates phosphoinositol hydrolysis (Daum *et al*., 1984; Donaldson & Hill, 1986; Carswell *et al*., 1987; Bristow *et al*., 1993). Thus, in so far as histamine acts through the H_1 receptor to enhance the NMDA induced depolarization, it resembles other neuromodulators including acetylcholine, glutamate acting at Group I metabotropic glutamate receptors, noradrenaline and 5-HT in facilitating NMDA responses (Nedergaard *et al*., 1987; Markram & Segal, 1990; 1992; Aniksztejn *et al*., 1991; 1992; Mally *et al*., 1991; Kelso *et al*., 1992; Harvey & Collingridge, 1993; Kinny & Slater, 1993; Rahman & Neuman, 1993a, b; 1996a).

Desensitization may in part explain the narrow, bell-shaped concentration-response relationship. The facilitation mediated by 5-HT_{2A} receptors undergoes desensitization, which accounts for the bell-shaped concentration-response relationship observed with 5-HT (Rahman & Neuman, 1993a, b, c). Addition of *myo*-inositol to the bathing medium reduces the loss of substrate available for phospholipase C that normally occurs when brain slices are prepared (Sherman *et al*., 1986) and reduces, but does not eliminate, homologous desensitization of the 5-HT_{2A} receptor-mediated facilitation (Rahman & Neuman, 1993c). Thus, adding *myo*-inositol results in 5-HT inducing both a larger facilitation and a broadening of the effective concentration range. *Myo*-inositol was present in the ACSF throughout the present investigation. In the absence of added *myo*-inositol, we suggest that the histamine-induced facilitation would be smaller in magnitude and exhibit greater homologous desensitization (see Rahman & Neuman, 1993c). Low substrate levels may account for the lack of a histamine H_1 receptor-induced facilitation observed in hippocampal slices perfused with Mg^{2+}-containing ACSF (Brown *et al*., 1995). Desensitization would be most apparent with high concentrations of histamine, which among other actions would be expected to deplete substrate rapidly (Rahman & Neuman, 1993b, c). Depending on the kinetics of the processes underlying the facilitation, the facilitation may be absent when substrate concentrations are low.

The absence of a histamine H_1 component in previous investigations was also probably due in part to the use of Mg^{2+}-free ACSF. The perfusion of Mg^{2+}-free ACSF for short per-

iods to eliminate the voltage-dependence of the NMDA response does not reduce the extent of the 5-HT-or acetylcholine-induced facilitation (Nedergaard *et al*., 1987; Markram & Segal, 1990). However, Mg^{2+} appears to be necessary for the expression of at least some G-protein linked responses, which are lost following prolonged perfusion of Mg^{2+}-free ACSF. Thus, depolarization of cortical neurones mediated by muscarinic acetylcholine receptors is eliminated in nominally Mg^{2+}-free ACSF (El-Beheiry & Puil, 1990). Moreover, the facilitation induced by phenylephrine and 5-HT is also abolished in Mg^{2+}-free ACSF, whereas the facilitation induced by calcimycin persists (Rahman & Neuman, 1996b). This suggests that it is signal transduction associated with the receptors which is altered and not the mechanism subserving the facilitation at the level of the NMDA receptor. The histamine H_1 receptor appears to operate in a manner similar to the 5-HT_{2A} receptor, the α_1-adrenoceptor and muscarinic receptors in that reducing Mg^{2+} in the medium apparently eliminates or at least significantly reduces signal transduction associated with the receptor.

Evidence has been presented that histamine directly influences a binding site on the NMDA receptor and it has been suggested that this accounts for the histamine receptor-independent facilitation (Bekker, 1993; Vorobjev *et al*., 1993; Williams, 1994). The characteristics of the facilitation observed in the present experiments during perfusion with Mg^{2+}-free ACSF are consistent with this type of facilitation, i.e., (i) the facilitation induced by 10 μM histamine was 15 to 40% larger than the NMDA control, (ii) desensitization was absent, (iii) the facilitation was insensitive to histamine H_1 receptor antagonists.

Based on the foregoing data we propose that there are two distinct mechanisms underlying the histamine-induced facilitation of NMDA responses in rat neocortical neurones. The first mechanism is dependent on the activation of the histamine H_1 receptor and probably results from stimulation of phospholipase C. The second mechanism is independent of histamine cell surface receptor activation and may depend on the direct interaction of histamine with the NMDA receptor (Bekkers, 1993; Vorobjev *et al*., 1993; Williams, 1994).

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