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RESEARCH PAPER

Influence of the hippocampus on amino acid utilizing and cholinergic neurons within the nucleus accumbens is promoted by histamine via H_1 receptors

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BACKGROUND AND PURPOSE
The influence of the neurotransmitter histamine on spontaneous and stimulation-evoked release of glutamate, aspartate, GABA and ACh in the nucleus accumbens (NAc) was investigated *in vivo*.

EXPERIMENTAL APPROACH
Using the push–pull superfusion technique, histaminergic compounds were applied to the NAc and neurotransmitter release was assessed. In some experiments, the fornix/fimbria of the hippocampus was electrically stimulated by a microelectrode and evoked potentials were monitored in the NAc.

KEY RESULTS
Superfusion of the NAc with the H_1 receptor antagonist triprolidine (50 μM) decreased spontaneous outflow of glutamate, aspartate and ACh, while release of GABA remained unaffected. Superfusion with histamine elevated release of ACh, without influencing that of the amino acids. Electrical stimulation of the fornix/fimbria enhanced the output of amino acids and ACh within the NAc. The evoked outflow of glutamate and ACh was diminished on superfusion with triprolidine, while release of aspartate and GABA was not affected. Superfusion of the NAc with histamine intensified the stimulation-evoked release of glutamate and Ach. Histamine also elevated the stimulation-induced release of aspartate, without influencing that of GABA. Presuperfusion with triprolidine abolished the reinforced effect of histamine on stimulation-evoked transmitter release within the NAc.

CONCLUSION AND IMPLICATIONS
Neuronal histamine activates H_1 receptors and increases spontaneous release of glutamate, aspartate and ACh within the NAc. Stimulation of the hippocampal fornix/fimbria tract also enhances release of glutamate and ACh within the NAc and this effect is intensified by H_1 receptor stimulation within the NAc. The latter effects, which are mediated by hippocampal afferences, might play an important role in mnemonic performance and in emotional processes such as anxiety and stress disorders.

LINKED ARTICLES
This article is part of a themed issue on Histamine Pharmacology Update. To view the other articles in this issue visit http://dx.doi.org/10.1111/bph.2013.170.issue-1

Abbreviations
NAc, nucleus accumbens; OPA, ortho-phthaldialdehyde

Introduction

Tuberomamillary nuclei of the posterior hypothalamus innervate many brain areas such as cortex, hypothalamus, amygdaloid complex and hippocampus (Wilcox and Seybold, 1982; Panula *et al.*, 1984; Watanabe *et al.*, 1984), but also striatal brain structures such as caudate putamen and nucleus accumbens (NAc; Watanabe *et al.*, 1984). The histaminergic influence on glutamate-mediated processes is of particular interest because activation of NMDA receptors induces long-term potentiation (for a review, see Bliss and Collingridge, 1993), which has been suggested to be implicated in mnemonic processes (Eichenbaum, 1996; Holscher, 1999). Furthermore, NMDA-mediated synaptic transmission is elevated by histamine in acutely isolated hippocampal neurons (Vorobjev *et al.*, 1993). Histamine also facilitates release of glutamate from hippocampal synaptosomes via H_1 and H_2 receptors (Rodriguez *et al.*, 1997). However it is not known whether histamine modulates glutamate-mediated responses under *in vivo* conditions.

The NAc is a part of the basal forebrain that seems to participate in emotional processes such as stress response (Abercrombie *et al.*, 1989; Lemos *et al.*, 2012) and anxiety (Morales-Mulia *et al.*, 2012), antipsychotic drug actions (O'Donnell and Grace, 1996), sensorimotor gating (Wan and Swerdlow, 1996), and the pathophysiology of schizophrenia (O'Donnell and Grace, 1998). This aspect of the ventral striatum is innervated by the hippocampal formation via the fornix/fimbria tract (Kelley and Domesick, 1982; Groenewegen *et al.*, 1987). Fibres arising from the subiculum of the hippocampus mainly utilize glutamate as neurotransmitter (Walaas and Fonnum, 1979; Yang and Mogenson, 1984). This projection is supposed to elevate the excitability of accumbal neurons, thus inducing their susceptibility to signals from the frontal cortex (Walaas and Fonnum, 1979; Walaas, 1981; Yang and Mogenson, 1984; O'Donnell and Grace, 1995). Because the NAc possesses histaminergic nerve terminals (see earlier), it seems possible that histaminergic neurons modulate glutamate-mediated processes within the NAc. In this study, we investigated whether locally applied histamine and the histamine H_1 receptor antagonist triprolidine modulate basal release of glutamate, aspartate, GABA and ACh within the NAc and release of these transmitters during stimulation of hippocampal afferents to the NAc. For the latter purpose, fibres arising from the subiculum of the hippocampus were electrically stimulated and neurotransmitter release within the NAc was assessed, using the push–pull superfusion technique.

Methods

Animals

Protocols of experiments comply with the guidelines for animal care of national guidelines and were approved by the Bundesministerium für Wissenschaft, Forschung und Kunst, Austria, Kommission für Tierversuchsangelegenheiten. All procedures used were as humane as possible. Every effort was made to minimize number of animals used and their suffering. ARRIVE guidelines for reporting experiments involving animals and the BJP editorial explaining how this applies to pharmacological studies have been consulted (Kilkenny *et al.*, 2010; McGrath *et al.*, 2010).

Animals were housed under constant temperature (23 ± 2°C) and a 12 h light/dark cycle (light period: 0700–1900 h). Water and food were freely available.

Surgery and push–pull technique

Experiments were carried out on 68 male Sprague–Dawley rats (250–270 g). For the determination of glutamate, aspartate, GABA and ACh in the NAc the animals were anaesthetized with urethane (1.3 $g \cdot kg^{-1}$), the head was fixed in a stereotaxic frame and a push–pull cannula (outer tubing: o.d. 0.83 mm, i.d. 0.51 mm; inner tubing: o.d. 0.31 mm, i.d. 0.16 mm) was stereotaxically inserted into the NAc (AP +1.3, L +2.5, V −7.5; coordinates according to Paxinos and Watson, 1998). The NAc was superfused with artificial CSF (aCSF) pH 7.2. aCSF consisted of (mmol l^{-1}) NaCl 140.0, KCl 3.0, $CaCl_2$ 1.2, $MgCl_2$ 1.0, Na_2HPO_4 1.0, NaH_2PO_4 0.3 and glucose 3.0. The superfusate was continuously collected in time periods of 10 min and stored at −80°C until transmitters were determined. For ACh determination, the aCSF additionally contained 1 $\mu mol \cdot L^{-1}$ neostigmine. The superfusion rate was 15 $\mu L \cdot min^{-1}$. At the end of the experiment the rat was sacrificed with an overdose of sodium pentobarbital, the brain removed and immersed in formaldehyde solution (4%). The position of the cannula was verified in histological slices stained with cresyl violet and luxol fast blue.

Stimulation of the fornix/fimbria tract

The fornix/fimbria tract (coordinates, from bregma: AP −1.5, L +1.5, V −3.5; Paxinos and Watson, 1998) was stimulated with a concentric bipolar stimulation electrode (0.25 mm exposed outer shaft and inner tip, separated by 0.75 mm) for 10 min (50 Hz for 100 ms, followed by 100 ms pause), mounted on a microdrive and introduced stereotaxically (Kraus and Prast, 2001). Correct application of current pulses was controlled by oscilloscope. To investigate the effect of electrical stimulation on the transmitter release in the NAc, the following parameters were used: 2.4 mA, 0.4 ms (amino acids) and 1.2 mA, 0.8 ms (ACh).

Determination of amino acids and ACh

Neurotransmitters were determined in the superfusate after separation by HPLC. Glutamate, aspartate and GABA were determined using precolumn derivatization with orthophthaldialdehyde (OPA) using a solvent gradient delivery pump (JASCO PU-1580; JASCO Corporation, Tokyo, Japan), an autosampler (CMA 200; CMA Microdialysis, Stockholm, Sweden) and an analytical column (Nucleosil 100-5 C18 5 µm, Seibersdorf Laboratories, Seibersdorf, Austria; Kraus and Prast, 2001). Briefly the mobile phase consisted of a 0.1 M sodium acetate buffer (adjusted with acetic acid to pH 6.95) : methanol : tetrahydrofurane = 92.5:5:2.5, vol% (eluent A). This solution was mixed in a stepwise gradient with eluent B (methanol: tetrahydrofurane = 97.5:2.5, vol%), initially concentration of eluent B was 10%. The gradient was changed as follows: eluent B 10–25% (0–0.5 min), isocratic run (0.5–14 min), 25–40% (14–18 min), 40–100% (18–24 min), 100–0% (24–26 min), isocratic run (26–36 min). Over the next 5 min the gradient

returned to initial composition. For the pre-derivatization, 50 μL of the superfusate were mixed automatically within the autosampler with 10 μL OPA and after a reaction time of 60 s, 50 μL were injected. The fluorescence detector (JASCO FP-920; JASCO Corporation) was set at 365 and 450 nm excitation and emission wave lengths respectively. The retention times were (min): 6 aspartate, 8 glutamate, 25 GABA. All amino acids were quantified using calibration curves of external standards injected at the beginning and the end of the sample analyses. The detection limits were (fmol per sample): 10 (aspartate), 20 (glutamate) and 40 (GABA).

ACh was electrochemically detected as previously described (Prast *et al.*, 1999b). Briefly mobile phase, which consisted of 100 mmol·L^{-1} K_2HPO_4, 5 mmol·L^{-1} KCl, 1 mmol·L^{-1} tetramethylammonium hydroxide, 1 mmol·L^{-1} Na-EDTA and 0.5 ml·L^{-1} of the microbiocide kathon GC, pH 7.9, was pumped at a flow rate of 0.4 mL·min^{-1}. ACh and choline were seperated on an analytical column (80 × 3 mm, chromspher C18) loaded with lauryl sulfate (100 mg 20 mL^{-1}). At the postcolumn enzyme reactor (20 × 1 mm Nucleosil-NH_2) to which ACh esterase and choline oxidase were bound covalently, ACh was hydrolysed to acetate and choline. Subsequently choline was oxidized to betaine and hydrogen peroxide. The peroxide was electrochemically detected by a platinum electrode at +500 mV with an amperometric detector (BAS LC-4B; West Lafayette, IN, USA). ACh was quantified using calibration curves from external standards injected at the beginning and the end of the sample analyses. The detection limit for ACh (signal/ratio = 3) was 5 fmol per sample.

Drugs

Histamine (Sigma, Deisenhofen, Germany), triprolidine hydrochloride (Research Biochemicals International, Natick, MA, USA)

Statistical analysis

Data are expressed as means ± SEM. Kolmogorof–Smirnof normality test was used to assess normality of variables. Neurotransmitter release rates were analysed by ANOVA, followed by paired *t*-test for paired data, using the means of the three values before superfusion with drugs or electrical stimulation as controls. For comparison of stimulation-evoked release, data were analysed by *t*-test.

Results

Samples were collected about 80 min after the start of superfusion, when stable basal levels were reached.

The mean basal outputs in the NAc were (fmol min^{-1}; mean values ± SEM): glutamate 450.2 ± 87.1 (n = 33), asparate 277.2 ± 40.7 (n = 28), GABA 36.0 ± 2.0 (n = 28), ACh 63.2 ± 19.2 (n = 35).

Effects of triprolidine (H_1 receptor antagonist) and histamine on basal release of glutamate, aspartate, GABA and ACh in the NAc

Superfusion of the NAc for 40 min with the H_1 receptor antagonist triprolidine (50 μM) decreased basal release of glutamate, aspartate and ACh in the NAc, while GABA release rate was not affected. Histamine (25 μM), superfused for 10 min did not influence basal release of glutamate, aspartate and GABA, but ACh outflow was elevated (Figure 1).

Effect of triprolidine on transmitter release in the NAc evoked by hippocampal stimulation

Electrical stimulation of the hippocampal fornix/fimbria for 10 min markedly increased amino acid release in the NAc. In the presence of triprolidine (50 μM), stimulation-evoked release of glutamate was abolished. In the presence of triprolidine, stimulation-evoked aspartate and GABA release rates were not influenced (Figure 2). Hippocampal stimulation also elevated ACh release rate in the NAc. Triprolidine greatly diminished the stimulation-induced release of ACh (Figure 3).

Influence of histamine and triprolidine on stimulation-evoked release of glutamate, aspartate, GABA and ACh in the NAc

When electrical stimulation was carried out during superfusion of the NAc with histamine (25 μM), stimulation-evoked release of glutamate was greatly enhanced. Outflow of aspartate was intensified 10 min after termination of electrical stimulation and superfusion with histamine, while stimulation-evoked release of GABA remained unaffected. The H_1 receptor antagonist triprolidine (50 μM) abolished effect of histamine on stimulation-evoked release of glutamate and aspartate outflows in the NAc (Figure 4). Histamine also greatly increased the stimulation-evoked release of ACh and triprolidine abolished effect of histamine on stimulation-evoked release of ACh (Figure 5).

Discussion and conclusions

Binding studies have shown that H_1 receptors are present in the NAc of guinea pigs (Bouthenet *et al.*, 1988) and in the NAc of rats (Watanabe *et al.*, 1984). In this study, the influence of histamine on neurotransmitter release in the NAc was investigated during the resting and activated state of neurons. H_1 receptor blockade elicited by superfusion of the NAc with triprolidine, diminished basal release rates of glutamate, aspartate and ACh. Hence, it seems likely that endogenously released histamine facilitates outflow of these neurotransmitters via H_1 receptor activation. In fact, superfusion of the NAc with 25 μM histamine elevated release of ACh. Also the H_3 receptor antagonist clobenpropit increases, by blocking presynaptic H_3 autoreceptors, outflow of ACh in the NAc (Prast *et al.*, 1999a). Similar results concerning the effect of histamine on ACh release in conscious rats have been published elsewhere (Prast *et al.*, 1999b). Therefore, histamine, acting on H_1 receptors, exerts a constant tonic effect on glutamatergic and cholinergic neurons in the NAc.

It might be postulated that the effect elicited by triprolidine is not a specific one, but due to its local anaesthesia. The low concentrations of triprolidine used and the low local anaesthetic activity of this compound do no support this idea. Furthermore, if this were so, then triprolidine should

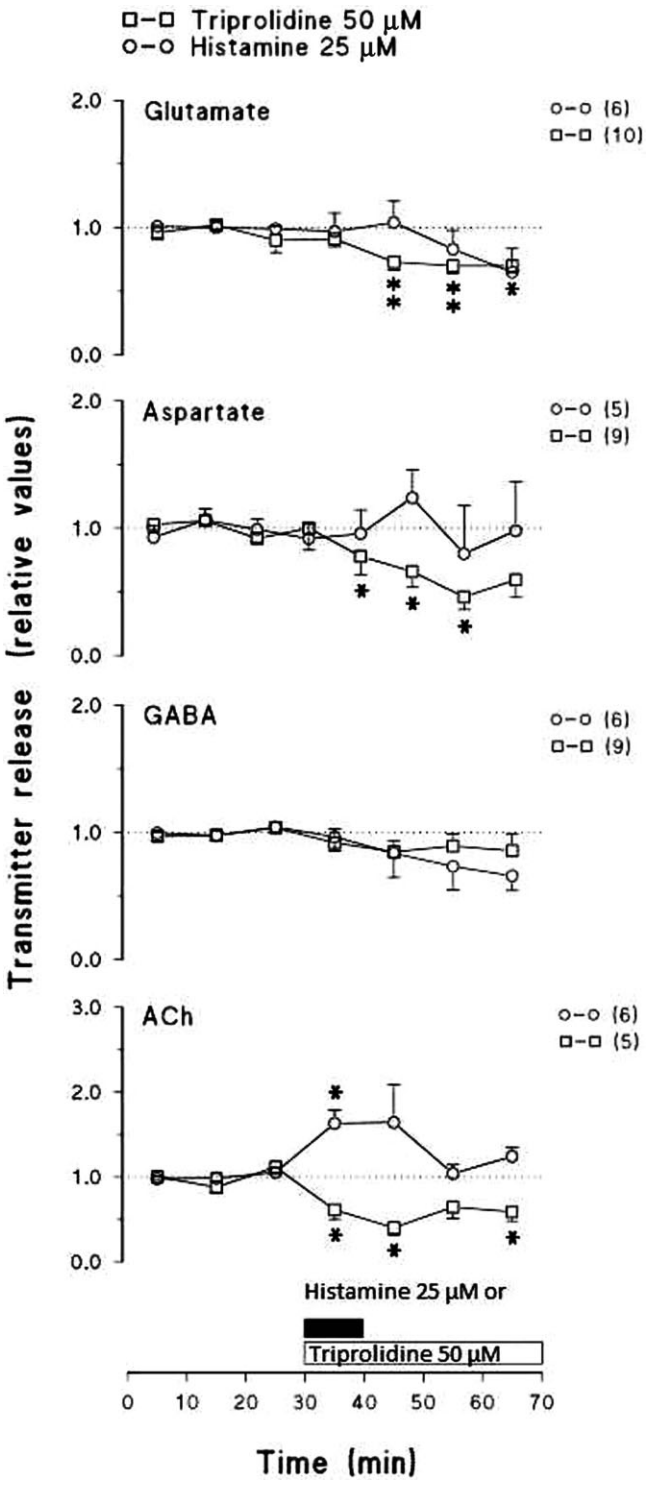

Figure 1

Effects of triprolidine and histamine on basal release of glutamate, aspartate, GABA and ACh in the NAc. Boxes indicate the time interval of superfusion of either triprolidine (50 µM; open box) or histamine (25 µM; closed box). The basal release rates in three samples preceding superfusion with histaminergic compounds were taken as 1. Mean values ± SEM, number of rats are indicated in parentheses, *$P < 0.05$, **$P < 0.01$.

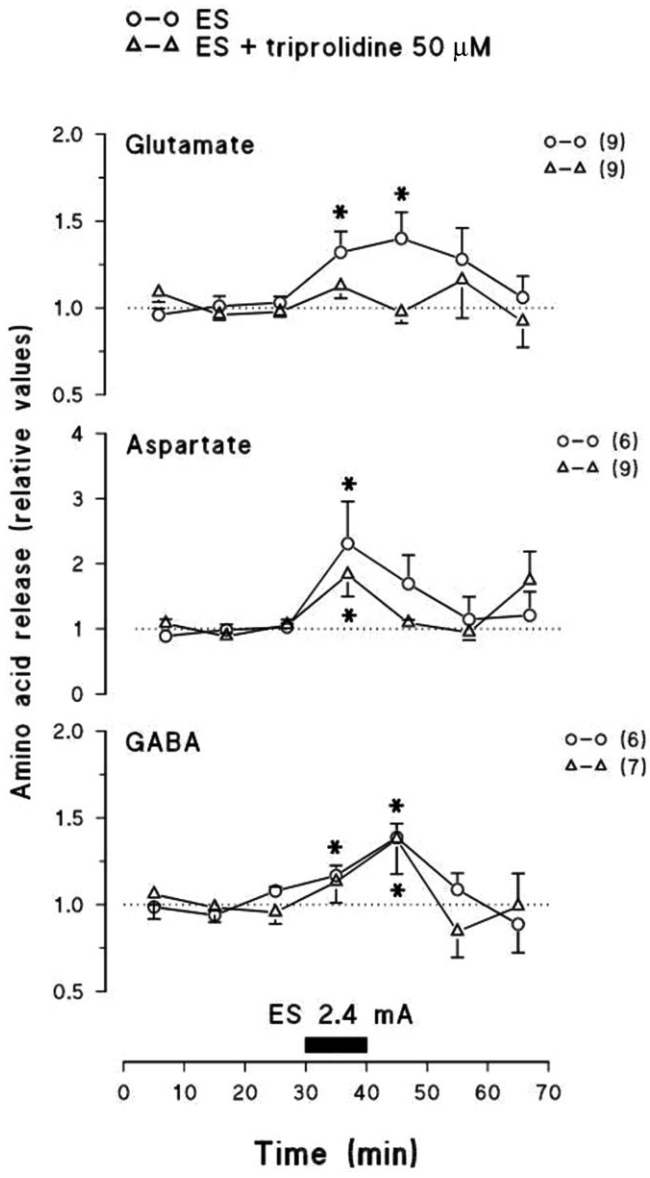

Figure 2

Effect of triprolidine on hippocampal stimulation-evoked release of glutamate, aspartate and GABA in the NAc. Box indicates the time interval of electrical stimulation (ES). Superfusion with triprolidine (50 µM) started 40 min prior to ES. The basal release rates in three samples preceding ES were taken as 1. Mean values ± SEM, number of rats are indicated in parentheses, *$P < 0.05$.

affect release of all neurotransmitters. However, release of GABA was not affected by triprolidine.

As mentioned in the *Introduction*, the NAc receives glutamatergic innervation originating from the hippocampus via the fornix/fimbria tract. Electrical stimulation of the hippocampus evokes action potential-dependent release of glutamate, aspartate, GABA and ACh in the NAc (Kraus and Prast, 2001, 2002), thus showing that impulses from neurons of this limbic structure modulate accumbal neuron activity. Cholinergic interneurons in the NAc possess NMDA receptors (Vuillet *et al.*, 1992; Landwehrmeyer *et al.*, 1995,

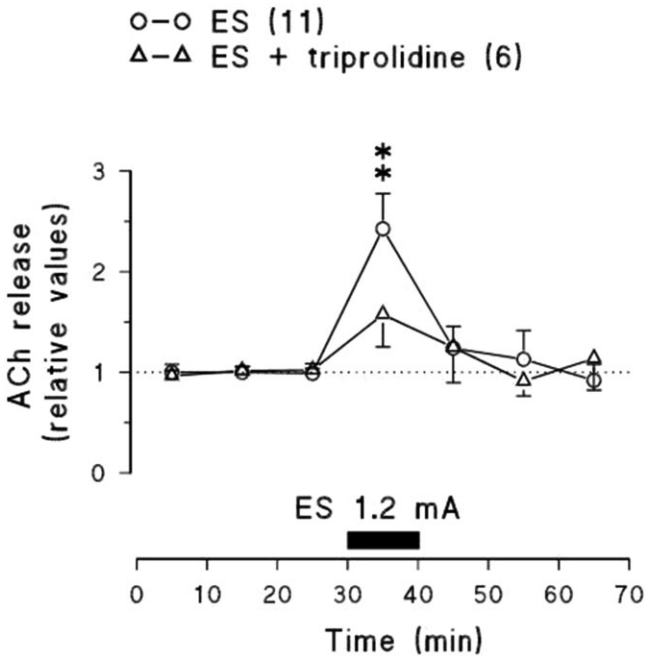

Figure 3

Effect of triprolidine on hippocampal stimulation-evoked release of ACh in the NAc. Box indicates the time interval of electrical stimulation (ES). Superfusion with triprolidine (50 μM) started 40 min prior to ES. The basal release rate in three samples preceding ES were taken as 1. Mean values ± SEM, number of rats are indicated in parentheses, $^{**}P < 0.01$.

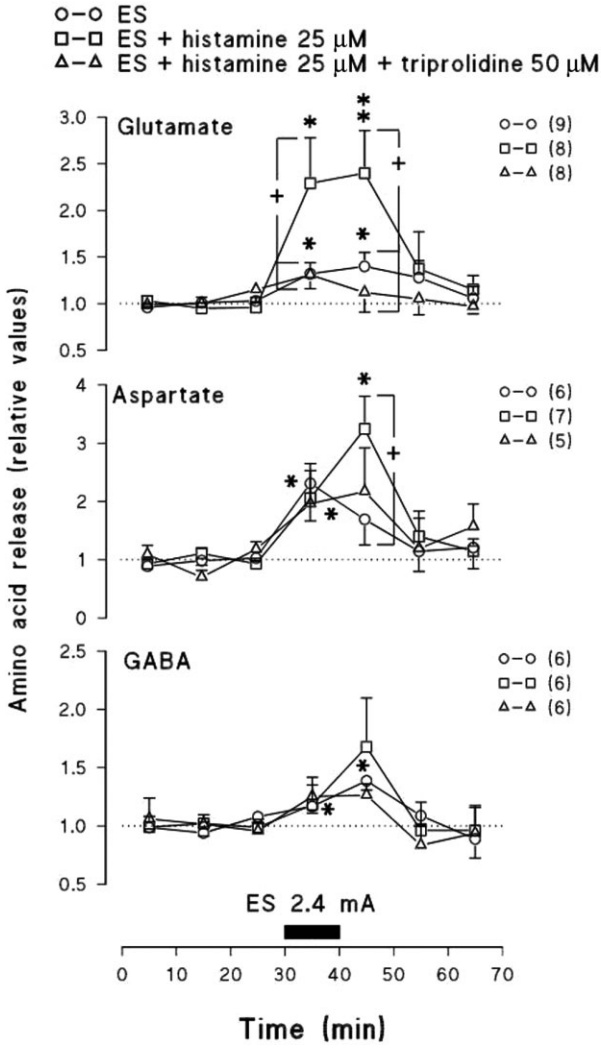

Figure 4

Effects of histamine and triprolidine on hippocampal stimulation-evoked release of glutamate, aspartate and GABA in the NAc. Box indicates the time interval of electrical stimulation (ES) or ES together with superfusion with histamine (25 μM). Superfusion with triprolidine (50 μM) started 40 min prior to ES and superfusion with histamine. The basal release rates in three samples preceding ES were taken as 1. Mean values ± SEM, number of rats are indicated in parentheses, $^{*, +}P < 0.05$, $^{**}P < 0.01$.

Küppenbender *et al.*, 1999), which might be activated by excitatory amino acids released during electrical stimulation of the hippocampus. Glutamatergic receptors seem to be located on striatal GABAergic neurons, because elevation of glutamate levels within the NAc increases GABA release (Segovia *et al.*, 1999). In our experiments, the H_1 receptor antagonist triprolidine diminished stimulation-evoked release of glutamate and ACh. On the other hand superfusion of the NAc with histamine exerted the opposite effect. H_1 receptor blockade abolished histamine-induced reinforced effect upon stimulation-evoked release of glutamate, aspartate and ACh.

These findings suggest that histaminergic neurons facilitate spontaneous and stimulation-induced neurotransmitter release via H_1 receptors located on accumbal neurons. Interestingly, histamine enhanced the basal release of ACh, but failed to modulate the release of glutamate and GABA. In contrast to the selective H_1 selective antagonist triprolidine, histamine stimulates all histamine receptors. Hence, the modulation of ACh release by histamine seems to be the sum of its action on H_1, H_2 and H_3 receptors. Moreover histamine released from histaminergic nerve terminals enhances the release of ACh partly by inhibition of dopamine release. In turn, dopamine increases GABAergic transmission, thus inhibiting ACh release (Prast *et al.*, 1999a,b). The complexity of these mutual neuronal interactions mirrors how the living brain is working.

Histaminergic neurons in the hypothalamus possess subtypes of NMDA receptors (Yanai *et al.*, 1997). It seems therefore possible that NMDA receptors located on histaminergic neurons projecting to the striatum are activated by glutamate released on hippocampal stimulation. Stimulation-evoked elevated histamine levels might in turn facilitate release of glutamate, aspartate and ACh in the NAc. GABAergic neurons of the NAc seem not to be affected by histamine, either under spontaneous or under activated conditions. It seems likely that GABAergig neurons within the NAc are deprived of histamine receptors.

In vitro and *ex vivo* studies have shown that histamine binds at the polyamine binding side of the NMDA receptor

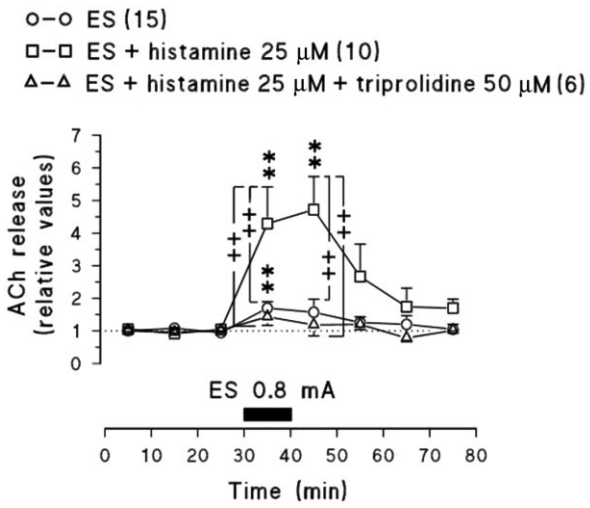

Figure 5

Effects of histamine and triprolidine on hippocampal stimulation-evoked release of ACh in the NAc. Box indicates the time interval of electrical stimulation (ES) or ES together with superfusion with histamine (25 μM). Superfusion with triprolidine (50 μM) started 40 min prior to ES or ES together with superfusion with histamine (25 μM). The basal release rates in three samples preceding ES were taken as 1. Mean values ± SEM, number of rats are indicated in parentheses, $^{**,\,++}P < 0.01$.

complex (Vorobjev *et al.*, 1993; Williams, 1994) and facilitates transmission mediated by NMDA receptor activation (Saybasili *et al.*, 1995; Yanovsky *et al.*, 1995). On the contrary other *in vitro* experiments indicate that histamine modulates NMDA receptor activity via an allosteric site of NMDA receptors, different from the polyamine binding site (Burban *et al.*, 2010). It is not known, however, whether triprolidine possesses affinity to any of these binding sides. Thus, it remains to be elucidated whether the facilitating role of histamine upon NMDA receptors might partly contribute to effects we found in this study.

Various studies verify the significance of histaminergic signalling in physiological and pathophysiological cognitive processing such as memory consolidation (Philippu and Prast, 2001; Gianlorenco *et al.*, 2012), postnatal maternal deprivation-induced memory deficit (Benetti *et al.*, 2012), vascular dementia (Stasiak *et al.*, 2011) and drug-related cognitive disorders (Alleva *et al.*, 2012).

In conclusion, the findings of the present study indicate that histamine liberated from histaminergic neurons within the NAc stimulates H_1 heteroreceptors, which in turn increase spontaneous release of glutamate, aspartate and ACh in the NAc. Furthermore stimulation of H_1 receptors by endogenous histamine within the NAc intensifies release of glutamate and ACh in the NAc elicited by stimulation of the hippocampal fornix/fimbria. This H_1 receptor-mediated effect of endogenous histamine on the neuronal activity of NAc, induced by hippocampal afferences, might play a key role in mnemonic performance as well as in emotional processes such as anxiety and stress disorders.

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Conflict of interest

None.

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