HISTAMINE ACTIONS IN THE MAMMALIAN CENTRAL NERVOUS SYSTEM

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ABSTRACT

Microionophoretic investigations on histamine in the mammalian central nervous system are summarized. More recent investigations using the brain slice method have revealed the mechanism of a modulatory action: In the hippocampus histamine blocks a calcium activated potassium conductance and profoundly potentiates excitatory signals.

KEYWORDS

Histamine, microionophoresis, brain slices, modulation, calcium, potassium

INTRODUCTION

"Seeing is believing", this attitude is probably responsible for the neglect histamine has suffered for a long time. The more popular amines (acetylcholine, noradrenaline, dopamine, serotonin) whose cells of origin and projections have been clearly visualized in the past decades are no closer to meeting the strict criteria for the identification as transmitters in the central nervous system than histamine. Direct demonstration of histaminergic pathways is now also available (Pollard and colleagues, Steinbusch and Mulder, Watanabe and colleagues, this volume) and confirms the lesion studies of Garbarg and colleagues (1974). Advances of in vitro techniques have allowed a better insight in the basic mechanisms representing central histamine functions. These investigations give indications for a classical transmitter role - direct effects on membrane permeability of certain ions - but a typical modulator action seems to be predominant and has been much better characterized. This modulation is potentially very powerful ranging between suppression and maximal transmission of neuronal signals.

Microionophoresis of Histamine

This technique delivers a high concentration of histamine (or other substances) to the immediate environment of the tip of a multibarreled glasspipette. Pressure applied to the same pipettes has also succesfully been used to eject drugs in a highly localized manner. By these ways depressant actions of

histamine have been found on many neurones all over the central nervous system. Motoneurones of the cat were hyperpolarized and synaptic potentials reduced (Phillis, Tebecis and York, 1968a). Engberg, Flatman and Kadzielawa (1976) showed an increase in membrane resistance and a reduction in spike afterhyperpolarization. The specificity and physiological relevance of these observations was however questioned by the authors. Similar actions of histamine and several of its metabolites occur on the big medial reticular formation neurones in the brain stem of unanaesthetized and decerebrate cats. Some related imidazole compounds seem to activate GABA receptors, most notably imidazoleacetic acid (Haas, Anderson and Hösli, 1973).

In cortical regions of rat, cat and guinea pig, most responsive neurones are depressed by ionophoretic histamine (Phillis, Tebecis and York, 1968b) an action which seems to be mediated by H2-receptors (Haas and Bucher, 1975; Phillis, Kostopoulos and Odutola, 1975; Haas and Wolf, 1977) but may also involve H1 receptors (Sastry and Phillis, 1976a). The H2 agonists 4-methylhistamine and impromidine exert also depressions and these are blocked by the H2 antagonists metiamide and cimetidine. Excitatory and dual actions occur but cannot be clearly related to H1 or H2 receptors. Metiamide seems to specifically block the histaminergic medial forebrain bundle neocortical pathway (Sastry and Phillis, 1976b; Haas and Wolf, 1977). The complex synaptic response following afferent stimulation (comprising histaminergic fibers) in the hippocampus is also modified by ionophoretic metiamide (Haas and Wolf, 1977). Furthermore, lesions in the medial forebrain bundle of guinea pigs lead to an increased sensitivity of cortical neurones to local histamine administration. This supersensitivity occurs in parallel with the fall in histidine decarboxylase activity (Haas and colleagues, 1978).

In the hypothalamus, ionophoresis of histamine often leads to excitation (Haas, 1974). A slow (several seconds) and rarely a faster time course (less than 1 sec) was described for those actions which may be related to H1 receptors (Renaud, 1976; Haas and Wolf, 1977; Carette, 1978). Depression of firing is also found and is blocked by H2 antagonists. The catabolites of histamine, 2-methylhistamine and 2-methylimidazoleacetic acid were much weaker than histamine: in the absence of a high affinity reuptake mechanism, methylation could be the major way of histamine inactivation (Green, 1970; Haas and Wolf, 1977). The excitation of identified neurosecretory neurones projecting to the neurohypophysis can explain the antidiuretic action of histamine (Haas, Wolf and Nussbaumer, 1975; Haas and Wolf, 1977; Haas and Geller, 1982).

Brain Slices in Vitro: Hypothalamus

Inspection of the 400 - 500 uM thick slices in a perfusion chamber with a stereomicroscope allows clear identification of most hypothalamic nuclei. Response patterns similar to those observed in vivo were found in several nuclei. Comparable results were also obtained from tissue cultures, where metiamide blocked inhibitory (H2) actions and promethazine blocked excitatory (H1) actions (Geller, 1981). Intracellular recordings from presumed neurosecretory neurones in the paraventricular and supraoptic nuclei have revealed strong excitation by bath applied histamine, presumably as a result of increased epsps. This indicates that the direct effect of histamine took place on neigbouring elements (Haas and Geller, 1982).

Hippocampus

The hippocampal slice is not only the most investigated brain slice, it is also

quite suitable for studying the mechanism of action of histamine on the cellular and membrane level as histaminergic projections to this structure have been clearly identified (Garbarg and colleagues, 1974; Schwartz, Garbarg and Pollard, 1984). The manipulations of the ionic environment in a perfusion chamber allow an analysis hitherto unavailable on central neurones. In accordance with the in vivo studies, locally restricted application of histamine by ionophoresis or pressure injection depresses the spontaneous firing of the majority of CA 1 pyramidal and dentate granule cells. This is accompanied by a hyperpolarization and sometimes a moderate conductance change. The hyperpolarization appears to be postsynaptic and mediated by H2 receptors (Haas, 1981). Microdrops applied to the slice surface can also cause a slow depolarization without a conductance change. Extra- and intracellularly recorded epsps were found to be augmented by Segal (1980, 1981), who suggested that these effects are presynaptic and mediated by the H1 receptor. Experiments with bath applied histamine are described in the following sections.

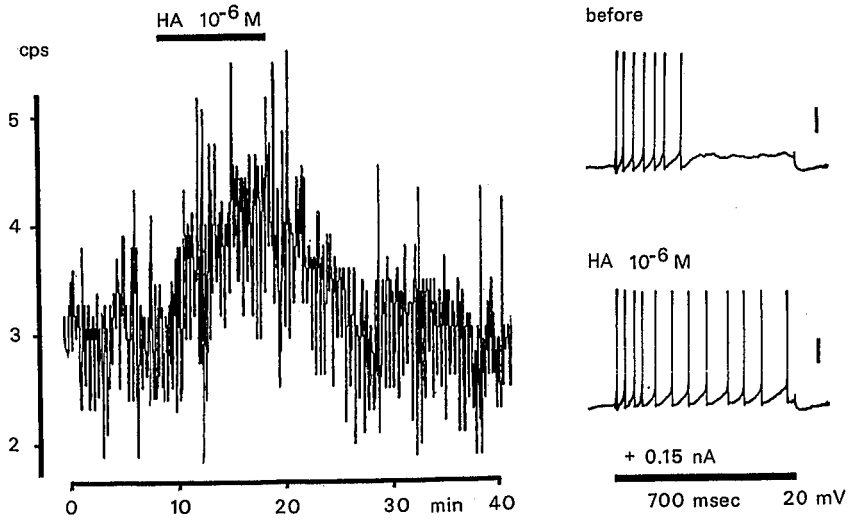

Fig. 1. Histamine blocks accommodation of firing and increases firing rate. Oscilloscope photographs on the right show responses of a CA 1 pyramidal cell to depolarizing current injection (+ 0.15 nA for 700 msec, bar below picture). In the presence of histamine (1 uM) firing continues through the whole pulse. The diagram on the left is a ratemeter record showing the number of action potentials per second (cps) versus time. Histamine (HA) was added to the perfusion fluid during the time indicated by the bar above the trace. About one half of the increase in frequency results from the increased response to the depolarizing pulses which were given every 10 sec, the other half represents increased spontaneous firing.

METHODS

Conventional techniques were used for preparation and incubation of transverse hippocampal slices from 48 Wistar rats in a perfusion chamber (Haas, Schaerer and Vosmansky, 1979). Microelectrodes for extracellular recording were filled

with 1 M NaCl, those for intracellular recording with 2-4 M KCl, K-acetate or CsCl. Drugs were added to the perfusion medium usually for periods of at least 5 - 10 min. Although equilibration was achieved within 1 min in the chamber the same concentration at the receptor sites in the slice was probably not reached within 10 min. Stimulation and recording electrodes were placed on the appropriate locations on the slices under direct observation through a stereomicroscope. Signals were recorded with a bridge amplifier, viewed on a storage oscilloscope and analysed with the aid of a microprocessor.

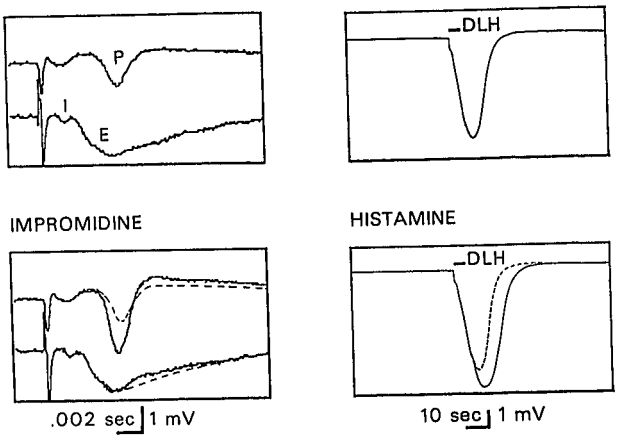

Fig. 2. H2 actions on extracellular epsp (E) population spike (P) and response to ionophoretic (10 nA, during bar) D,L-homocysteic acid (DLH). Upper records and broken lines in lower records are controls. Lower records show potentials in the presence of 1 uM impromidine and 10 uM histamine respectively. Left: Upper traces are recorded in pyramidal layer of CA 1, lower traces in stratum radiatum (I: input volley, E: epsp).

RESULTS

Resting Potential and Accommodation of Firing.

Micromolar concentrations of histamine and impromidine depolarized pyramidal cells in the CA 1 region slightly (2.5 +- 1.5 SD mV, n = 16) and increased their spontaneous firing rate (Fig. 1, left diagram). The response to low intensity depolarizing current injection usually displayed strong accommodation of the action potential frequency: In Fig. 1 (before) spike firing is only seen during the first 300 msec of a 700 msec, + 0.15 nA pulse, but occurs through the whole pulse when 1 uM histamine is present. This effect was observed in all 27 investigated neurones; in 9 of those careful examination showed that the effect was independent of changes in soma potential or conductance.

The firing caused by ionophoretic pulses of glutamic or D,L-homocysteic acids to the apical dendritic region was prolonged by histamine and impromidine (n = 7). This was often registered as an extracellular DC field representing the firing of several neurones (Fig. 2, right records). Furthermore, burst discharges in spontaneously epileptic slices (n = 2) were potentiated when histamine was added to their bathing fluid (Haas 1984, 1985).

Afterhyperpolarization (AHP)

Single action potentials or bursts of spikes in CA 1 pyramidal cells are followed by a two-component AHP (Figs. 3; 4C). The fast component is ascribed to the delayed rectifier potassium current while the long lasting component is due to a calcium activated potassium current (gK(Ca)). This late but not the early AHP is blocked by histamine and impromidine in micromolar concentrations. The block is completely reversed by adding the H2 antagonists metiamide or cimetidine (5 - 10 uM) to the medium. Neither mepyramine (H1 antagonist) nor propranolol (beta antagonist, which blocks a similar action of noradrenaline on the AHP) antagonized this effect (Madison and Nicoll, 1982; Haas and Konnerth, 1983).

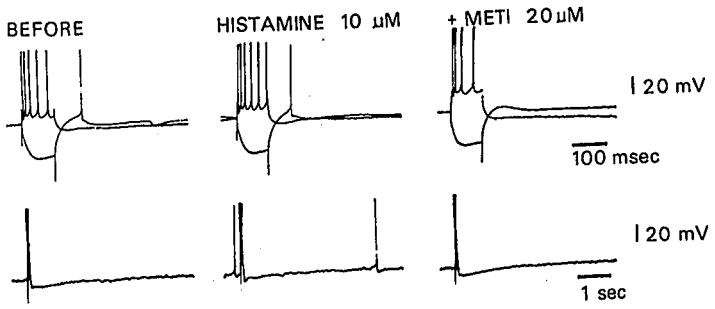

Fig. 3. Intracellular recordings from a CA 1 pyramidal cell before and during histamine action and after addition of metiamide. Upper records show responses to +- 1 nA lower records to + 1 nA, 100 msec current injection. Histamine blocks the late AHP after a burst of spikes (and the accommodation of firing) and this effect is (more than) fully reversed by metiamide.

The AHPs are also observed following slow (calcium) spikes in TTX poisoned preparations. The late component is blocked in this condition in the absence of a reduction in the calcium spike indicating that the block of gK(Ca) was not secondary to a reduction in calcium inflow. In fact an increase in calcium spike amplitude and the number of calcium spikes fired by a given depolarization was usually seen. In order to better analyse the calcium spike per se recording was performed with caesium chloride filled electrodes. Caesium ions diffusing into the cell quickly blocked the late AHP and revealed large calcium spikes. Now 10 uM histamine had no effect (Fig.4 A). Comparable data were also obtained when gK(Ca) was reduced by adding tetraethylammonium (10 uM) or barium ions (0.3 mM) to the perfusion fluid. The large calcium spikes recorded when restricting potassium currents were reduced were often followed by an afterdepolarization lasting for several 100 msec. This potential which presumably reflects a persistent calcium inflow was facilitated and prolonged by histamine.

Synaptic Potentials

Excitatory postsynaptic potentials (epsps) in CA 1 after stimulation of strata radiatum or oriens were found unchanged during perfusion with histamine (Fig. 2). This was investigated with intracellular and extracellular (field epsp) recording. However, the population spike, i.e. the compound action potential fired by a given stimulation and epsp, was always increased by histamine and

impromidine. The relation between field epsp and population spike is illustrated in Fig. 6. In the CA 3 region, an increase of epsps by histamine has been observed (Segal, 1982; Tagami and colleagues, 1984).

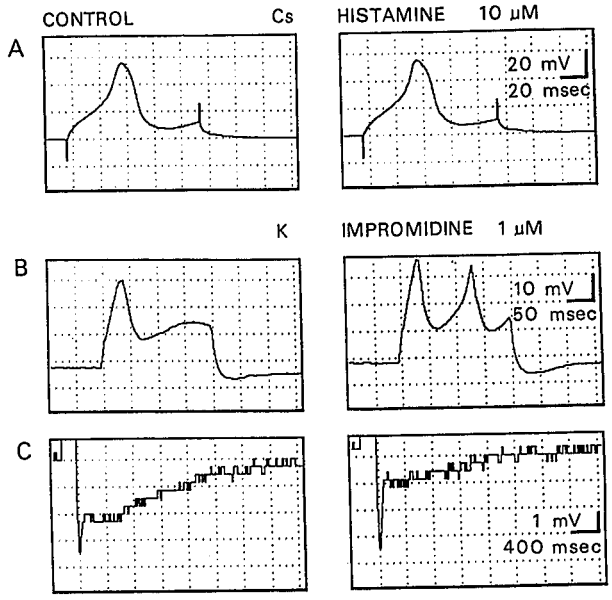

Fig. 4. Histamine and impromidine actions in a tetrodotoxin poisoned slice. Averaged (9 sweeps) intracellular records from 2 CA 1 pyramids. A: Calcium spike evoked by positive current injection (100 msec) recorded with a caesium chloride filled electrode. Intracellular caesium blocks potassium channels revealing a large calcium spike (58 mV) without late AHP. The addition of 10 uM histamine does not reduce the calcium spike and hence presumably calcium inflow; the spike is in fact slightly faster in onset and wider. B: Calcium spikes recorded with a potassium chloride filled electrode. The addition of 1 uM impromidine (H2 agonist) to the medium causes an increase of the calcium spikes and a block of accommodation: the same 200 msec pulse evokes now two slow spikes. C: Tails after the responses shown in B. Note different gain (x8) and time base (x8). The calcium spikes are (upward) out of scale, the first downward deflections are the early afterhyperpolarizations due to the delayed rectifier potassium current (unaffected). The late afterhyperpolarization is markedly reduced by 1 uM impromidine.

DISCUSSION

The widespread arborization of histaminergic (and other aminergic) projections to the forebrain suggest that they may regulate the functional state of target regions rather than transmit discrete signals. Such a function would be very well served by the modulatory action described here: A range of different excitatory signals are shown to be potentiated by histamine through activation of an H2 receptor. They include synaptically evoked population spikes, epileptiform bursts, responses to depolarization by current injection through

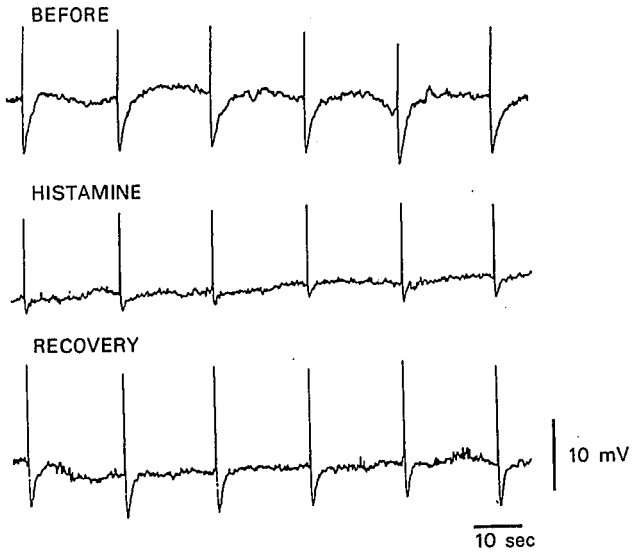

Fig. 5. Effect of histamine (1 uM) on the late afterhyperpolarization (AHP) in tetrodotoxin containing medium. Upstrokes are calcium spikes (elicited every 20 sec by depolarizing current injection), downward deflections are AHPs. Lowest trace obtained 20 min after withdrawal of histamine. Traces from pen recorder.

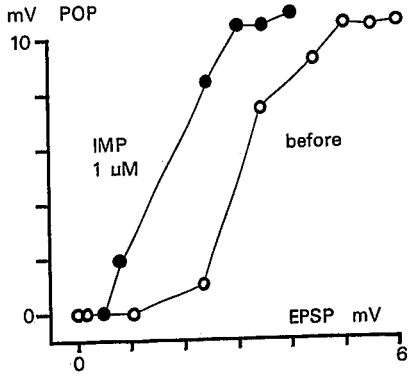

Fig. 6. Relationship between field epsp and population spike (POP) at varying stimulation strength in CA 1 (see Fig. 3). The epsp was unchanged (not shown) but the population spikes evoked by given epsps were enhanced by 1 uM impromidine (filled circles).

the recording electrode or by ionophoretic application of excitatory amino acids. All these actions could be explained by a block of gK(Ca), which was best illustrated by the long lasting AHP after excitatory signals. Strong and longer lasting depolarizations are selfrestricting by activation of gK(Ca). A release from this self-restriction by histamine may be described as an intrinisic disinhibition. Such an action would also increase signal to noise ratio by favoring larger potentials. No direct actions on calcium spikes were seen even in experiments optimizing their visibility. A voltage clamp study of CA 1 neurones however, has revealed a reduction in somatic calcium current by histamine (Pellmar, 1984). In low calcium high magnesium solutions an excitatory action of histamine (H2) is still present (Fig. 7) indicating that this effect is independent of extracellular calcium (Haas and colleagues, 1984): It may be a direct interaction with K channels or an influence on intracellular calcium level and sequestration. In each case cyclic AMP accumulation and, perhaps in the latter, phosphorylation of proteins leading to a larger calcium binding capacity may be involved (Haas, 1984, 1985).

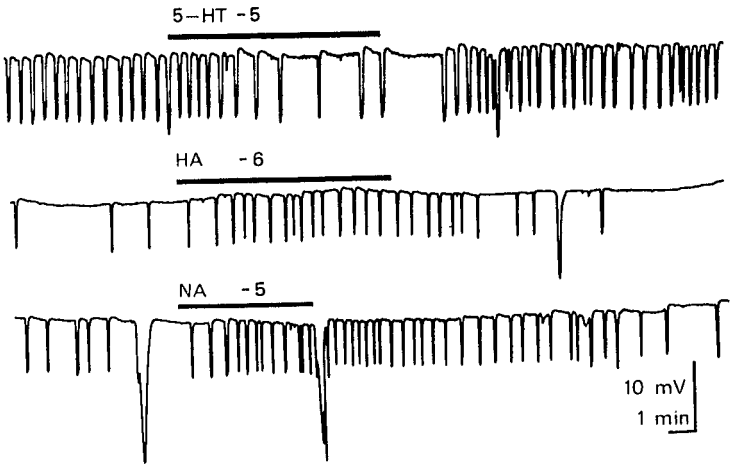

Fig. 7. Spontaneous field bursts (downward deflections), recorded in a low calcium high magnesium medium, are blocked by serotonin (5-HT, 10 uM) but accelerated by histamine (HA, 1 uM) and noradrenaline (NA, 10 uM). These effects parallel the actions on afterhyperpolarizations. (AHP-block = acceleration; AHP-enhancement = slowing) and argue for a mechanism of action which is independent of calcium inflow.

No direct data on presynaptic actions of histamine are available at present but the mechanisms described here on the postsynaptic level may well be operative in terminals and varicosities, where calcium inflow triggers release. Although a clearer picture of histamine's role in the central nervous system is emerging more information is needed to understand how it functions naturally. The mode of action of histamine (and the other amines) cannot be expected to serve very specific functions making it the transmitter of, for instance, thermoregulation or water balance. However, an involvement in many hypothalamic and forebrain

functions is highly probable. Together with other systems ascending from the brain stem histamine neurones may participate in regulation of states of awareness, circadian and other rhythms, neuroendocrine and vegetative functions. The anatomical disposition and modulatory mechanism allow setting of the neuronal responsiveness and thus the functional state in target areas.

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