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Histamine

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1. INTRODUCTION

1.1. Historical Perspective

Early in this century, histamine (imidazolethylamine) was detected by Sir Henry Dale and his co-workers as a uterine stimulant in extracts of contaminated ergot (Barger and Dale, 1910). In the following years, its potent effects on smooth muscle and its participation in the allergic response were established. Although originally suspected to be the result of bacterial action during putrefaction, the compound was later successfully isolated from several types of fresh tissue and was therefore given the name histamine, which is derived from the Greek word histos for tissue. In 1943, using the guinea pig ileum as bioassay, Kwiatkowski detected histamine in brain and observed that there was a higher concentration in the grey than in the white matter. More sensitive methods for the determination of histamine were subsequently developed, including fluorometric and enzymatic-isotopic assays, but until very recently it has not been possible to directly visualize histaminergic neurons in brain. Thus, histamine has attracted less attention among neurobiologists than other biogenic amines, although evidence that it acts as a neurotransmitter is at least as good (Green, 1970; Green et al., 1978, Schwartz et al., 1985).

1.2. Regional and Subcellular Distribution

Determination of histamine in small brain samples has provided information regarding its regional localization in brain. The highest levels are

found in the hypothalamus, particularly in the arcuate and suprachiasmatic nuclei in rat (Green, 1970; Brownstein et al., 1974b), and in the mammillary bodies in monkey and man (Snyder and Taylor, 1972; Lipinski et al., 1973). Moderate amounts are found in cortical areas, and low levels are present in cerebellum and spinal cord. Absolute histamine levels in brain average about 50 ng/g, ten times lower than the levels of some other amine transmitters. However, histamine turnover is faster and therefore more histamine may be released per unit time (Dismukes and Snyder, 1974; Pollard et al., 1974).

The histamine-specific biosynthetic enzyme histidine decarboxylase is considered a better marker than the amine itself for histaminergic neurons and their terminals. This enzyme is generally distributed in a parallel fashion to histamine except in the hippocampus, where enzyme activity is high but amine levels are low (Baudry et al., 1973). At the subcellular level, the major portion of histamine is found in the synaptosomal fraction associated with synaptic vesicles, while histidine decarboxylase is found in the cytoplasm. A significant amount of cerebral histamine is contained within the granules of mast cells. The turnover of this nonneuronal histamine is much slower than that of the vesicular histamine (Schwartz, 1975; Schwartz et al., 1985). A mouse mutant lacking mast cells is deficient in as much as 50% of normal brain histamine (Yamatodani et al., 1982; Grzanna and Schultz, 1983).

1.3. Pathways in Brain

Although fluorescent products can be formed by condensation of histamine with aldehydes, it has not been possible to visualize histaminergic neurons with histofluorescence techniques, as is the case for other biogenic amines. Immunohistochemistry using antibodies against a BSA-histamine conjugate or histidine decarboxylase is now providing this missing picture. Histaminergic fibers emanating from the posterior ventral hypothalamus and the mammillary nuclei innervate the whole forebrain in a diffuse manner. Thus, immunoreactive varicose fibers are observed in the diencephalon and telencephalon, with highest densities in the basal hypothalamus and the mammillary region. Two major ascending and a minor descending projection have been described (Wilcox and Seybold, 1982; Watanabe et al., 1983; Panula et al., 1984; Steinbusch and Mulder, 1984).

Prior to the development of immunohistochemical techniques for the visualization of histaminergic neurons, lesion studies had suggested the existence of long histaminergic pathways in the brain. Appropriately placed lesions cause anterograde degeneration of histaminergic neurons resulting in a disappearance of histamine and histidine decarboxylase from target regions. Using this method, a projection pattern similar to the catecholamines and serotonin was revealed (Fig. 1). For example, unilateral lesions of the medial forebrain bundle lead to a fall of histidine decarboxylase activity in the whole ipsilateral forebrain, indicating that histaminergic fibers form a widespread, diffuse projection but do not cross the midline to a significant extent (Garbarg et al., 1974). Quantitating histidine decarboxylase activity

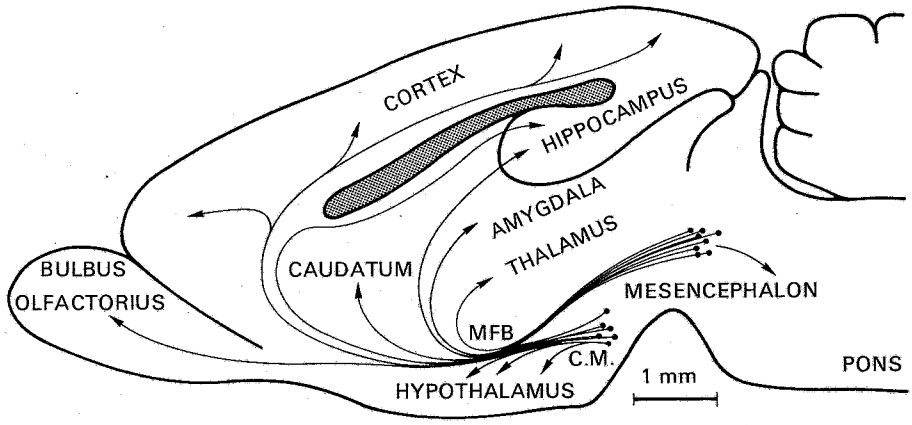

Figure 1. Histaminergic pathways in the mammalian (rat) brain, as determined by lesion experiments and confirmed by immunohistochemistry and electrophysiology. Histaminergic neurons are situated in the mammillary bodies and a supramammillary mesencephalic area. The widespread projection to the whole forebrain is similar to the pattern of other aminergic fibers but is, in contrast to these, largely unilateral.

in the cortex after small lesions at different locations along the midbrain and hypothalamus has allowed a relatively precise localization of the histaminergic neurons in the diencephalon. Thus, lesions caudal to the supramammillary region have no effect on histidine decarboxylase activity, whereas selective destruction of cell bodies in this area by localized injection of kainic acid does reduce enzyme levels (see Schwartz et al., 1985).

The hippocampus receives its afferents through the medial forebrain bundle and fibers enter by both a dorsal (fornix) and a ventral (perforant path) route. Transection of either of these inputs results in about a 50% decrease of histidine decarboxylase, while destruction of both inputs together results in a complete loss of the enzyme. By a similar approach, it has been possible to characterize projections to the striatum, olfactory bulb, thalamus, hypothalamus, the bed nucleus of the stria terminalis, and the amygdala (Ben-Ari et al., 1977; Garbarg et al., 1974) (Fig. 1).

1.4. Metabolism and Release

Histamine is synthesized in brain from histidine by a specific decarboxylase, which is distinct from the aromatic-L-amino acid decarboxylase found in other aminergic neurons. The enzymes differ in kinetics and regional distribution and can be selectively blocked by specific inhibitors (Garbarg et al., 1980; Schwartz, 1975). Histamine synthesis may be regulated by the local availability of its amino acid precursor. The major pathway for histamine degradation is methylation by histamine methyltransferase, which uses S-adenosylmethionine as methyl donor (Snyder and Taylor, 1972). Ox-

idative deamination and dehydrogenation subsequently lead to methylimidazoleacetic acid, which is eventually excreted by the kidney. There is no high-affinity uptake system for histamine, and therefore methylation could be the major means of inactivation of the transmitter (Green, 1970).

Endogenous histamine is released by potassium-evoked depolarization from brain slices in a calcium-dependent fashion. Histamine inhibits its own release from depolarized slices of rat cerebral cortex by an action on receptors that are pharmacologically distinct from conventional histamine receptors (see Section 1.5; Arrang et al., 1983). Reserpine releases histamine along with other amines, suggesting that they have similar vesicular storage sites. Lesions in the medial forebrain bundle cause a transient increase in the histamine content in cortex and hippocampus, which may reflect an interruption of ongoing release. The mast cell degranulator 48/80 also releases histamine from brain slices, but this histamine comes from the slowly metabolized pool in mast cells (Schwartz et al., 1985).

1.5. Histamine Receptors

The classical antihistamines developed in the 1940s are now classified as H_1 receptor antagonists, the prototype being pyrilamine (for mepyramine). At low concentrations, these drugs antagonize most of the actions of histamine on smooth muscle but are ineffective in blocking histamine induced stimulation of heart rate and gastric secretion. The H_2 receptors mediating these latter actions were defined in the early 1970s when Black and his colleagues (Black et al., 1972) synthesized burimamide, metiamide, and cimetidine, substances that antagonized these responses. Highly specific H_2 receptor agonists such as dimaprit and impromidine are now also available. To date however, all H_1 receptor agonists that have been synthesized, such as 2-methylhistamine, 2-pyridylethylamine, and 2-thiazolethylamine, have considerable H_2 agonist activity (Schwartz, 1979).

Histamine H_1-receptors can be labeled in brain membranes with either [^{3}H]mepyramine (Hill et al., 1978; Chang et al., 1979) or [^{3}H]doxepin, an antidepressant (Tran et al., 1981). The binding sites display pharmacological specificity characteristic of histamine H_1 receptors with some differences in drug selectivity in various brain regions and species. An autoradiographic study in the rat has revealed high receptor densities in the bed nucleus of the stria terminalis, the area dentata, the hypothalamus, and the brain stem (Palacios et al., 1981). A small fraction of these receptors are on vascular smooth muscle (see Green, 1983; Schwartz, 1979; Schwartz et al., 1985). The hypothalamus (especially the supraoptic and suprachiasmatic nuclei) and the hippocampus are particularly rich in H_1 receptors. In guinea pig, however, the highest density is surprisingly in the cerebellum, which seems devoid of endogenous histamine.

The criteria for specific labeling of the H_2 receptor seem to be met by [^{3}H]tiotidine (Gajtkowski et al., 1983). High affinity for H_2 receptor binding was found in hippocampus, cortex and striatum (in this order) while cere-

bellum and pons displayed no significant binding (Norris et al., 1984). Histamine H_2 receptors in brain are coupled to adenylate cyclase, and it has been possible to demonstrate histamine stimulation of cyclic AMP production in intact tissues (brain slices) as well as cell-free preparations of guinea pig and rat brain via this receptor (Daly, 1976; Green, 1983; Kanof and Greengard, 1979). In intact cells, however, the situation is complicated by the fact that H_1 receptors can modulate the H_2 effect on cyclic AMP accumulation (Palacios et al., 1978). The brain regions richest in histamine-stimulated adenylate cyclase are neocortex and hippocampus. Because the cyclic AMP response is abolished by intrahippocampal injections of the neurotoxin kainic acid, it is likely that the histamine-stimulated adenylate cyclase is present in neurons and not in glial cells.

H_1 receptor antagonists are used clinically because of their antiallergic and antiemetic actions; their major side effect is sedation. The phenothiazine and butyrophenone neuroleptics also block H_1 receptors (Green, 1983). On the other hand, tricyclic antidepressants such as imipramine block H_1 and H_2 receptors (as well as muscarinic cholinergic receptors), but the highest affinity is for the H_1 receptor (Schwartz et al., 1981). H_2 receptor antagonists such as cimetidine and ranitidine are widely used clinically to suppress gastric acid secretion.

1.6. Histamine Neurons in Invertebrates

Excellent evidence supporting a role for histamine as a neurotransmitter is provided by studies in invertebrates. Histamine and histidine decarboxylase are present in a number of identified molluscan neurons (Weinreich, 1977; Brownstein et al., 1974a; Turner and Cottrell, 1977), and several types of excitatory and inhibitory responses to histamine have been reported. Excitatory, depolarizing responses in *Aplysia* and *Onchidium* are mediated by an H_1 type receptor and act through an increase in sodium conductance (Carpenter and Gaubatz, 1975; Gotow et al., 1980). A slow hyperpolarization, mediated by H_2 receptors, seems to be due to an increase in potassium conductance.

In *Aplysia*, histamine also causes a fast hyperpolarizing response that is due to chloride ion efflux and is not blocked by H_1 or H_2 antagonists but is reduced by curare (Gruol and Weinreich, 1979). A pharmacologically similar chloride-dependent inhibitory response to histamine is present in neurons of the lobster stomatogastric ganglion (Claiborne and Selverston, 1984). However, Gotow et al. (1980) ascribe the H_2-mediated hyperpolarizing response in *Onchidium* mainly to stimulation of an electrogenic pump. Excitatory and inhibitory responses to histamine have also been observed in *Helix* and *Achatina* but could not be clearly classified.

The best demonstration of histaminergic transmission in any nervous system is provided by McCaman and Weinreich (1982), who were able to simultaneously record from a single identified histamine-containing neuron and its follower cell in the cerebral ganglion of *Aplysia*. Stimulation of the

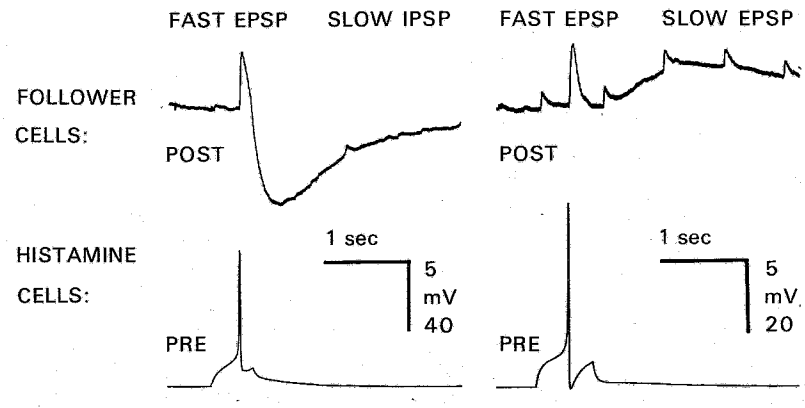

Figure 2. Simultaneous intracellular recording from histamine-containing neurons and their follower cells in *Aplysia*. A single action potential, evoked by intracellular current injection in the histamine cells, causes synaptic potentials in the follower cells. (Courtesy of D. Weinreich.)

presynaptic neuron evoked several histamine mediated synaptic potentials (Fig. 2). IPSPs and hyperpolarizing histamine effects, due to an increase in potassium conductance, were selectively blocked by cimetidine.

2. CENTRAL NERVOUS SYSTEM: STUDIES *IN VIVO*

2.1. Spinal Cord

Lesion and immunohistochemical mapping studies have demonstrated the existence of descending projections of diencephalic histamine neurons to the brain stem and spinal cord. In extracellular recordings in the cat spinal cord it was observed that ionophoretically applied histamine depresses the firing of many spinal interneurons and motoneurons. Early intracellular experiments by Phillis et al. (1968a) revealed that histamine hyperpolarized motoneurons and caused a reduction of synaptic potentials. Later, Engberg et al. (1976) reported that histamine caused an increase in membrane resistance and a decrease in the afterhyperpolarization following the spike. However, the physiological relevance of these observations was questioned by the authors, as a number of phenolic amines, as well as local anesthetics, calcium, and protons, had similar effects.

2.2. Brainstem

In the unanesthetized decerebrate cat, neurons in the medial reticular formation of the medulla, including identified bulbospinal neurons, respond

to iontophoretic histamine with a depression of firing. Histamine metabolites have a similar but usually weaker activity (Anderson et al., 1973; Haas et al., 1973). (Imidazoleacetic acid, however, is as strong a depressant as GABA. Since its inhibitory action is blocked by the GABA antagonist bicuculline it may not act at histamine receptors.) Most vestibular neurons are also inhibited by histamine, although some cells are excited. Metiamide selectively blocks the inhibitory response, indicating that it is mediated by H_2 receptors (Satayavivad and Kirsten, 1977). Histamine also depresses dorsal raphe serotonergic neurons in the rat via H_2 receptors (Lakoski et al., 1984).

2.3. Hypothalamus

In contrast to other brain regions, iontophoresis of histamine into the environment of hypothalamic neurons often results in excitation (Haas, 1974). Usually the excitation is prolonged, lasting several seconds, although occasionally it is more rapid. These excitatory effects may be related to H_1 receptors. Depression of firing is found in a variable percentage of cells as well; these responses are mimicked by H_2 agonists and blocked by H_2 antagonists. The catabolite of histamine, tele-methylhistamine, displays actions similar to histamine but is far less potent (Haas and Wolf, 1977).

Specific responses to histamine have been observed in certain functionally or electrophysiologically identified hypothalamic neurons. Vasopressin- and oxytocin-secreting neurons in the supraoptic nucleus can be identified by antidromic invasion from the hypophyseal stalk and by their response to changes in blood osmolarity (Barker et al., 1971). These neurons are excited by histamine (Fig. 3), and the excitation is blocked by the H_1 antagonist mepyramine (Haas et al., 1975; Haas and Wolf, 1977). This is in keeping with experiments showing that local injection of histamine into the supra-

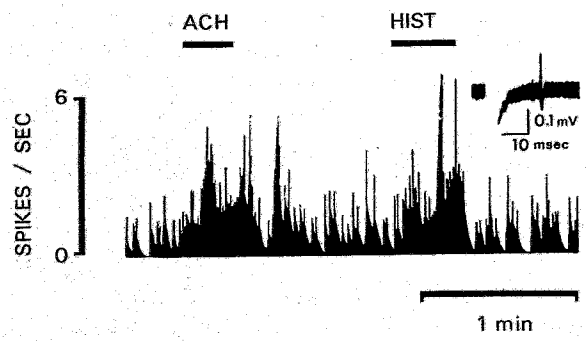

Figure 3. Ratemeter record from a neurosecretory neuron in the cat supraoptic nucleus. Inset shows antidromic action potential after stimulation of the neurohypophysis. Acetylcholine and histamine iontophoretically ejected from a micropipette (60 nA) increase the firing rate.

optic nucleus causes a mepyramine-sensitive antidiuretic effect, presumably due to stimulation of vasopressin release (Bennett and Pert, 1974).

Some thermosensitive neurons in the rostral hypothalamus also respond to histamine (Sweatman and Jell, 1977), as do preoptic-septal neurons projecting to the median eminence and arcuate nucleus (Carette, 1978) and neurons located in the ventromedial nucleus (Renaud, 1976).

2.4. Cortex

Histamine actions have been studied on cortical neurons of the rat, cat, and guinea pig. The firing of most responsive neurons is reduced by iontophoretic histamine (Phillis et al., 1968b), and this action seems to be mediated by H_2 receptors (Haas and Bucher, 1975; Phillis et al., 1975; Haas and Wolf, 1977; Haas et al., 1978) but may also involve H_1 receptors (Sastry and Phillis, 1976a). Recordings from unidentified deep cortical neurons and from pyramidal cells projecting to the brainstem or spinal cord have yielded similar results. Specific H_2 agonists (4-methylhistamine, impromidine) mimic the depressant actions, and these effects are blocked by the H_2 antagonists metiamide and cimetidine. Excitatory and dual actions are occasionally observed; however, only the depressant component is reversed by metiamide (Haas and Wolf, 1977). Although there is some suggestive evidence to support the view that the excitatory effects are due to stimulation of H_1 receptors, this cannot be stated with confidence, since truly specific H_1 antagonists are not yet available. The H_1 antagonist mepyramine unfortunately has local anesthetic properties and in iontophoretic studies blocks the actions of histamine (as well as other agents) in a nonspecific fashion.

Evidence for the physiological relevance of H_2 receptor-mediated depressant effects in neocortex is provided by the observation that the H_2 antagonist metiamide seems to specifically block the presumed histaminergic medial forebrain bundle–neocortical pathway (Sastry and Phillis, 1976b; Haas and Wolf, 1977). Electrical stimulation of the medial forebrain bundle produces inhibition of cortical neurons, which is reversed by iontophoretic metiamide. The selectivity of this effect is demonstrated by the finding that the inhibitory pause caused in response to direct cortical stimulation (presumably due to activation of intrinsic inhibitory neurons) is unaffected.

Lesions in the ascending histaminergic pathway to the cortex at the level of the medial forebrain bundle produce an increased sensitivity to iontophoretic histamine, but not GABA. This supersensitivity parallels the fall in histidine decarboxylase activity and appears only on the side ipsilateral to the lesion (Haas et al., 1978). In studies of the hippocampal histaminergic projection, it was observed that the late component of the IPSP (as judged from peristimulus histograms) produced in response to fimbria stimulation can be specifically reduced by metiamide, suggesting that the inhibition is at least partially mediated by histamine acting via H_2 receptors.

3. CENTRAL NERVOUS SYSTEM: STUDIES *IN VITRO*

3.1. Hypothalamus

3.1.1. Tissue Culture

Tuberal hypothalamic neurons in tissue culture can respond with either excitation or depression to locally applied histamine. About one half of the cells are depressed, one quarter are excited, and the remainder are unaffected. The general pharmacological principles derived from *in vivo* studies seem to apply to these neurons *in vitro*. The antagonists metiamide (H_2) and promethazine (H_1), added to the perfusion fluid, selectively block the inhibitory and excitatory responses to iontophoretic histamine, respectively. Moreover, the H_2 agonist dimaprit causes only depressions, while the partial H_1 agonist 2-pyridylethylamine elicits both effects (Geller, 1976, 1981). The depressions persist in calcium-free medium, indicating a direct postsynaptic effect, and are potentiated by phosphodiesterase inhibitors, supporting a role for cyclic AMP in mediating the response (Geller, 1979).

3.1.2. Tissue Slices

Most hypothalamic nuclei can be easily identified by inspection in unfixed slices. Spontaneously firing cells in several nuclei respond well to locally applied or bath perfused histamine with similar patterns as observed *in vivo*. Intracellular recordings have been obtained from presumed neurosecretory neurons in the paraventricular nucleus. These cells, identified by their location and typical firing pattern, showed a clear excitatory response to bath applied histamine. However, this seemed to result from an increased frequency of EPSPs, rather than a direct postsynaptic action. Therefore in these experiments histamine appeared to activate neighboring cells with excitatory connections to the neurosecretory neurons instead of the endocrine cells themselves (Haas and Geller, 1982).

3.2. Hippocampus

The action of histamine in the hippocampus has been clarified by intracellular recordings in tissue slices. In keeping with the observations from *in vivo* studies, local application of histamine by iontophoresis or pressure ejection depresses the spontaneous or evoked firing of the majority of CA_1 pyramidal and dentate granule cells. This depression of firing is associated with hyperpolarization of the somal membrane and in some cases with a moderate conductance increase (Fig. 4). As in other systems, this hyperpolarization appears to be mediated by H_2 receptors, as it is mimicked by

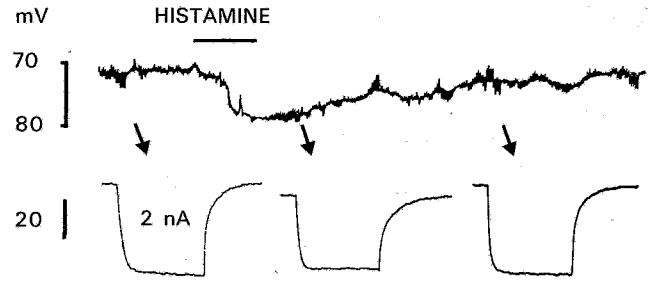

Figure 4. Hyperpolarization of a dentate granule cell in a rat hippocampal slice. Histamine was ejected by pressure from a micropipette during the period indicated by the bar (3 min). Lower traces are the voltage responses to hyperpolarizing current injections (2 nA, 100 msec) illustrating a conductance increase during the histamine effect.

the H_2 agonist impromidine. The hyperpolarizing effect of histamine is due to a direct postsynaptic action as it persists in low calcium/high magnesium or tetrodotoxin-containing media (Haas, 1981).

Application of histamine microdrops to the slice surface can also cause a slow depolarization with no observable conductance change, which is blocked by the H_1 antagonist promethazine (1 mM). In addition, the EPSP, recorded extra- and intracellularly in the CA_1 and the CA_3, area, was found augmented by histamine (Segal, 1980, 1981). These effects are believed to be generated by a *presynaptic* action of histamine because the responsiveness to direct application of glutamate was unaffected and because they could not be demonstrated in low calcium/high magnesium or tetrodotoxin-containing media. Other extra- and intracellular experiments in the CA_1 area, however, showed a reduction or no change in EPSPs, but an enhanced response to glutamate ionophoresis in the presence of histamine (Haas, 1984; Greene and Haas, 1985).

When histamine or the H_2 agonist impromidine are added to the perfusion fluid of hippocampal slices, the population spike in the CA_1 region is increased with no change in the EPSP (Fig. 5A), indicating a postsynaptic action (Haas, 1984). Intracellular recording disclosed a slight membrane depolarization; however, the major effect was on the afterhyperpolarization following a burst of spikes. In CA_1 pyramidal neurons, as in other cell types, the long-lasting (several second) afterhyperpolarization is believed to be due to the activation of a calcium-dependent potassium conductance. [This conductance has been related to a specific membrane current I_{AHP} (Lancaster and Adams, 1984), which may be distinct from the well-known I_C (Brown and Griffith, 1983).] As is the case for norepinephrine (see Chapter 8), histamine depresses amplitude and time course of this afterhyperpolarization (Haas and Konnerth, 1983; Haas, 1984), which results in enhanced repetitive firing (block of "accommodation"; Madison and Nicoll, 1984).

The H_2 agonist impromidine, but not the H_1 agonist thiazolethylamine, mimicks these effects of histamine. Moreover, the H_2 antagonists metiamide

and cimetidine block the action of histamine on the afterhyperpolarization, whereas the H_1 antagonist mepyramine and the β-antagonist propranolol do not. These observations provide strong evidence that the effect is due to activation of H_2 receptors.

In the presence of tetrodotoxin, which blocks the sodium component of action potentials, calcium-dependent spikes can be evoked in CA_1 neurons that are of markedly prolonged duration. An afterhyperpolarization occurs following these calcium spikes. Histamine specifically depresses the slow (but not the fast) component of this afterhyperpolarization (Fig. 5C,D). A reduction in the afterhyperpolarization might be secondary to a block of calcium entry as, for example, occurs when cadmium ions eliminate calcium spikes and the resultant afterhyperpolarization. This is unlikely, however, as calcium spikes are actually enhanced and prolonged, rather than reduced by the amine. Blockers of potassium channels such as tetraethylammonium, barium, and intracellular cesium maximize the visibility of calcium spikes. Even under these circumstances the calcium spikes are not reduced by histamine. When calcium currents are blocked by adding cadmium to the medium, histamine still has a depolarizing action, but intracellular EGTA (which chelates calcium ions) prevents it. Furthermore, in calcium-deficient, magnesium-enriched medium where the slow afterhyperpolarization is blocked, histamine (acting through H_2 receptors at concentrations as low as 10 nM) can still produce the depolarization. This depolarizing response has been attributed to depression of a steady potassium conductance and it has been speculated that histamine reduces the intracellular availability of calcium ions leading to a reduction in a resting calcium-activated potassium current (Haas et al., 1984; Haas, 1984).

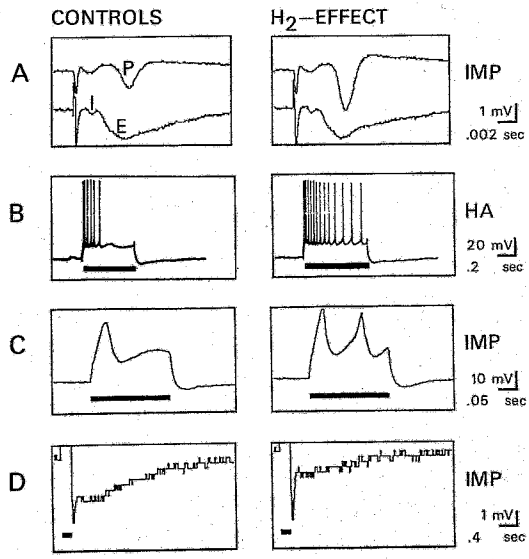

Figure 5. Effect of histamine (HA) and impromidine (IMP) on excitation of CA_1 pyramidal cells in hippocampal slices of the rat. (A) Somatic population spikes (P), input fiber volleys (I), and dendritic extracellular EPSPs (E) after stimulation of str. radiatum. The population spike, but not the EPSP, is significantly increased by 1 μM impromidine. (B, C, D) Responses to intracellular depolarizing current injection, indicated by black bars. (B) Normal medium; 1 μM histamine blocks accommodation of firing. (C, D) Tetrodotoxin-treated slice; 1 μM impromidine facilitates calcium spikes (C) and blocks the long-lasting afterhyperpolarization (D).

As noted in Section 1.5, there is evidence from biochemical studies that H_2 receptors in brain are coupled to adenylate cyclase. The effect of histamine on the afterhyperpolarization can be mimicked by the nonhydrolyzable, lipid-soluble cyclic AMP analog 8-bromo cyclic AMP and the histamine response is potentiated by the phosphodiesterase inhibitor Ro 20-1724 (Haas, 1985). Thus, as for norepinephrine, there is reason to believe that cyclic AMP mediates the effect. Additional evidence in favor of this concept is the observation that only amines that stimulate adenylate cyclase in brain slices (i.e., histamine and norepinephrine; Green, 1983; Etgen and Browning, 1983) produce the effect on the afterhyperpolarization. Dopamine and serotonin are ineffective in either regard.

In addition to an action on pyramidal cells, histamine also seems to affect interneurons in the hippocampal slice. This has been inferred from intracellular recordings in pyramidal cells where there is an increase in the frequency of IPSPs during perfusion with histamine.

4. SYMPATHETIC GANGLIA

Like many other substances, histamine can affect synaptic transmission in sympathetic ganglia. In the rabbit isolated superior cervical ganglion, histamine produces two antagonistic effects, an H_1 receptor-mediated facilitation and an H_2 receptor-mediated depression of ganglionic transmission (Brimble and Wallis, 1973). Moreover, the actual effect of histamine itself depends on the type of ganglionic response involved. Thus, micromolar concentrations of histamine reduce the compound action potential evoked by a single stimulus but facilitate the response to repetitive stimulation. In rat sympathetic ganglia, histamine has also been shown to cause a depression of the compound action potential (Lindl, 1978). Although a dual action of histamine on blood pressure is known, the physiological significance of the ganglionic responses in mediating these effects are uncertain. As in brain, histamine stimulates cyclic AMP accumulation in sympathetic ganglia via an action on H_2 receptors; H_1 receptor activation causes an increase in cyclic GMP levels (Study and Greengard, 1978). However, the role of cyclic nucleotides in mediating ganglionic responses to histamine remains to be elucidated.

5. CONCLUSION

Recordings from brain and spinal cord neurons in conjunction with iontophoresis of histamine, its metabolites, agonists, and antagonists have significantly advanced our understanding of the functional neuropharmacology of central histamine receptors and have provided good circumstantial evidence that histamine serves as a central transmitter. Inhibitory effects of

ionophoretically applied histamine have been described for most regions in the central nervous system and are usually mediated by H_2-receptors. At least in the hippocampus, this action seems to reflect membrane hyperpolarization, which involves a conductance increase probably to potassium ions. On the other hand, excitatory responses to histamine, such as occur in the hypothalamus, may be due to H_1 receptor activation, but the underlying membrane mechanisms are unknown.

Perhaps more important than its effects on passive membrane properties in hippocampal neurons is the ability of histamine to cause a decrease in a calcium-activated potassium conductance. This may occur through an interference with intracellular calcium sequestration mediated by H_2 receptors linked to adenylate cyclase. As histamine releases the neurons from an endogenous potassium current, its action could be described as an "intrinsic disinhibition." From a functional point of view, reduction of the spike afterhyperpolarization through a suppression of the calcium-activated potassium conductance allows a powerful facilitation of repetitive firing in response to depolarizing signals. In concert, the hyperpolarizing action of histamine and its potentiation of excitatory stimuli could act to increase the response to strong synaptic inputs while suppressing weaker ones, so that the "signal-to-noise" ratio is increased (see also Chapter 8). Of course, more information is needed to understand how these mechanisms operate naturally.

The widespread distribution of histaminergic neurons suggests that they, like other amine pathways, may influence the functional state of target regions rather than transmit discrete signals. Together with other systems ascending from the reticular formation, histamine neurons may be involved in the regulation of states of awareness, circadian and other biological rhythms, cerebral circulation and energy metabolism, and neuroendocrine and vegetative functions (Gross, 1982; Schwartz et al., 1985). The sedative action of H_1 antagonists has led to speculations of an involvement of histamine in the regulation of sleep and waking. The desynchronization of the EEG by centrally applied histamine (Wolf and Monnier, 1973) and the fluctuation of endogenous brain histamine during the day and night cycle (Schwartz et al., 1985) are in keeping with this possibility.

Histaminergic systems also seem to participate in the regulation of water balance and drinking behavior, in part through an action on the hypothalamic supraoptic and paraventricular neurons that project to the posterior pituitary. Thus, microinjection of histamine into the region of the supraoptic and paraventricular nuclei stimulates vasopressin release via H_1 receptors, and this is probably due to the excitatory effects of histamine on these neurons.

Anterior pituitary functions may also be controlled by histamine neurons in the hypothalamus (Weiner and Ganong, 1978; Roberts and Calcutt, 1983). For example, prolactin secretion is increased by H_1 and decreased by H_2 receptor activation, perhaps explaining the rise in plasma prolactin occurring in some patients receiving cimetidine (see Schwartz et al., 1985).

Histamine neurons may also be involved in the control of autonomic functions. Centrally administered histamine causes a transient increase in

blood pressure and heart rate. Interestingly, spontaneously hypertensive rats display increased histamine levels in the hypothalamus. Temperature regulation may also involve histamine neurons as hypothermia can be induced through H_2 receptor activation (Green et al., 1976). H_1 receptor antagonists are well known to have an antiemetic action on the chemoreceptor trigger zone in the area postrema, but the role of histamine neurons in the vomiting reflex is unknown. The recent availability of neuroanatomical maps precisely localizing brain histamine neurons and their projections and the growing understanding of the cellular mechanisms underlying the transmitter actions of histamine should allow clarification of the role of histamine in these diverse behavioral functions.

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