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Electrophysiology of Histamine-Receptors

Helmut L. Haas

Department of Physiology, Heinrich-Heine-University, D-4000 Düsseldorf 1, Germany

INTRODUCTION

Histamine actions on excitable cells are studied by electrophysiological methods. The identification of a transmitter or modulator at a given site requires demonstration that the exogenously applied transmitter candidate mimics the action of the endogenously released substance (Werman, 1966). This goal is often only approachable by accumulating indicative evidence, mainly through pharmacological manipulations. This has largely been the research strategy in the study of histaminergic systems, in particular the mechanisms at the effector sites. Major advances have long been precluded by the technical difficulty of investigating histamine actions at the cellular or molecular level with microelectrodes. A technique called microionophoresis has dominated the field in the 1960s and 1970s: small amounts of transmitter or interacting substances were ejected from multiple micropipettes into the immediate environment of single neurons by applying small currents to the pipettes. One of the pipettes was used for recording the activity of single units or a few neurons simultaneously. Although concentrations of the applied substances at receptor sites could not be accurately determined, a number of qualitative pharmacological investigations have convincingly attributed certain actions to one or another of the histamine receptors. More precise information on mechanisms of action can be obtained with intracellular recording of membrane potential and conductances. This was first achieved in large mollusc neurones but has become feasible in vertebrates with the advent of in vitro preparations such as brain slices and neuronal cultures. This article describes mainly results from neurones: electrophysiological methods have also been used for the investigation of other tissues such as smooth muscles or the heart. These are treated in other chapters.

HISTAMINE ACTIONS

H_1-Receptor

These actions are almost exclusively excitatory: increase in firing rate, depolarization, and facilitation of signal transmission. The ionic mechanisms involved have been investigated in some cases: inward Na^+-currents are responsible in molluscs, a reduced potassium current in vegetative ganglia and in the brain stem. An inhibitory action of the H_1-agonist thiazole-ethylamine, and of histamine in the presence of cimetidine was seen in hippo-

campal slices bathed in low Ca^{++} high Mg^{++} media (Haas et al., 1984). This preparation reacts sensitively to measures which change intracellular Ca^{++}. Excitation can be caused by reduced, inhibition by increased intracellular Ca^{++}, through Ca^{++}-dependent K^+-channels. Dinitrophenol and azide which are known to increase intracellular Ca^{++} by releasing it from mitochondria reduce the firing. The product of histamine evoked phosphatidyl-inositolbisphosphate (PIP_2) breakdown, inositoltrisphoshate ($InsP_3$), releases Ca^{++} from the endoplasmatic reticulum (e.g., Daum et al., 1984) and might reduce neuronal excitability in this way. H_1-receptors do not by themselves stimulate adenylate cyclase but they can potentiate the action of direct activators of this enzyme, an effect which is dependent on intracellular Ca^{++} availability as is the case for H_1-mediated cyclic GMP formation and glycogenolysis (see Green, 1983; Schwartz et al., 1986). The observation that impromidine, the H_2-agonist with 50 times higher potency than histamine is hardly more potent in blocking a Ca^{++}-dependent K^+-conductance (gK(Ca), see below) might reflect this helping action of H_1-receptor activation in electrophysiological experiments. H_1-receptors bear similarities to adrenergic α_1-receptors: both are coupled to PI-turnover, an α_1-receptor mediated depolarization and reduced potassium conductance (McCormick and Prince, 1987) is reminiscent of the H_1 mediated excitation of hypothalamic and pontine reticular neurones Greene et al., 1989). In contrast, H_2-receptors are more akin to adrenergic β-receptors.

H_2-Receptor

These actions are mostly inhibitory: decreased firing rate, hyperpolarization and depression of signal transmission have been demonstrated. There are exceptions however: a potentiation of excitation on cortical (hippocampal) neurones. The former effect is mediated by induction, the latter by block of a potassium current. β-receptor activation causes a very similar pattern of opposite effects (Madison and Nicoll, 1982; Haas and Konnerth, 1983). In both cases potentiation of excitatory signals with reduced background excitability represents a very effective way of increasing signal to noise ratio. It can be described as an intrinsic disinhibition as it relieves the sensitive neurones from a specific inhibitory K^+-conductance (gK(Ca)). The evidence for mediation of this excitation-potentiating effect by H_2-receptors and cyclic AMP is very good, the inhibitory H_2-and β-receptor dependent effects are probably not mediated by cyclic AMP. Electrical stimulation of the histaminergic pathway evokes a metiamide sensitive depression of firing in a poststimulus histogram (Sastry and Phillis, 1976a; Haas and Wolf, 1977). The potentiation of excitation as a result of medial forebrain bundle stimulation is likely to have escaped the detection in these experiments as it would presumably have appeared as a small and long lasting enhancement of firing.

A direct excitation of vestibular neurones unrelated to gK(Ca) has been ascribed to H_2-receptor activation (Phelan et al., 1990). In a mollusc, hyperpolarization (H_2) was suggested to be mediated by an electrogenic Na^+-Ca^{++}-exchange which can be modulated by cyclic nucleotides (Gotow and Hashimura, 1982).

The electrophysiological effect mediated by H_2-receptors and cyclic AMP on heart muscle is different although functionally rather similar: positive inotropy is achieved by a prolongation of the action potential and an increase in its plateau amplitude (Eckel et al., 1982). A whole cell patch clamp study revealed an increased Ca^{++} current probably through a GTP dependent transducer protein and cyclic AMP mediated protein phosphorylation (Hescheler et al., 1987).

H_3-Receptor

Histamine synthesis and release are regulated by H_3-receptors (see Chapter 7, this volume). Where direct electrophysiological

evidence of histamine release is available drugs interacting with H_3-receptors have not yet been tested. Tuberomammillary histamine neurones which bear these receptors on pericarya and axon varicosities are inhibited by an H_3-agonist, possibly by a block of Ca^{++}-inflow (Reiner and Haas, 1987). Such an action could account for the autoreceptor mediated block of histamine release. GABA, opioid peptides and galanin, transmitters colocalized in these neurones inhibit them as well (Reiner and Haas, 1988; Schönrock et al., 1990). The H_3-receptor is probably negatively coupled to a Ca^{++}-channel to inhibit release and excitability through mediation of a G-protein (Takemura et al., 1989; Arrang et al., 1990). Autoreceptors in the locus coeruleus are of the α-type and positively coupled to K^+-channels through a G-protein (Williams et al., 1985). This is an indirect way to prevent (presynaptic) Ca^{++}-inflow which has not been excluded for H_3-receptor dependent actions.

GLIA

Glial cells possess receptors for several neurotransmitters, histamine is no exception (Hösli and Hösli, 1984). Although significant active currents do not seem to normally occur in glial membranes their potentials are important functional parameters which respond to histamine: H_1-receptor activation causes a depolarization and H_2-receptors mediate a hyperpolarization (Hösli et al., 1984). Histamine may be inactivated by methylation predominantly in astrocytes (Rafalowska et al., 1987) and the abovementioned actions could participate in the regulation of ionic homoeostasis in the extracellular space, which has repercussions on neuronal excitability.

INVERTEBRATE NEURONES

The marine mollusc Aplysia californica, a well known study object for electrophysiology, possesses histaminergic and histaminoceptive cells (Brownstein et al., 1974; Weinreich et al., 1975). The histaminergic neuron C 2 conveys mechanosensory information from the mouth and plays a complex role in feeding and the behavioural state of the sea slug (Weiss et al., 1986). A number of different depolarizing and hyperpolarizing re-

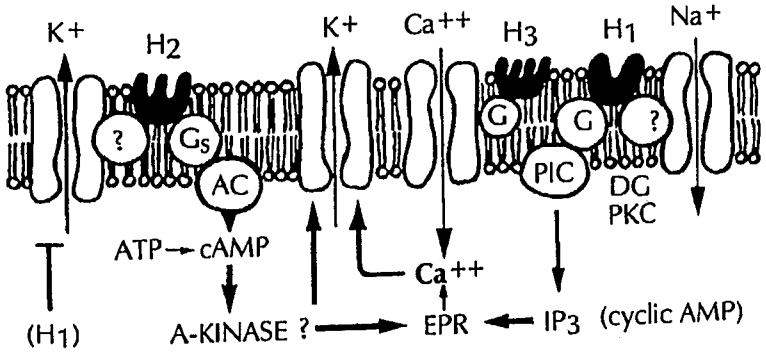

Fig. 1. Possible mechanisms of electrophysiological actions of histamine. H_1-receptors are coupled to potassium channels (negatively: excitation), to sodium channels (positively: excitation) and PIP_2 breakdown (decrease excitability through increased intracellular Ca^{++} and increase excitability through helping cyclic AMP production by H_2-receptor activation). H_2-receptor activation can open potassium channels or close Ca^{++}-dependent K^+ channels causing depression or potentiation of excitation. H_3-receptor activation blocks Ca^{++}-channels (N-type, through a G-protein) to depress release of histamine or other transmitters from varicosities and to inhibit histamine neurones themselves.

sponses to histamine were identified and pharmacologically characterized. A Na^+ dependent, H_1-receptor mediated response (Carpenter and Gaubatz, 1975) may correspond to the fast excitatory postsynaptic potential (epsp) observed by Weinreich (1977) and McCaman and Weinreich (1982). Fast Cl^--dependent inhibitory postsynaptic potentials (ipsps) and hyperpolarizing responses are not H_1-receptor mediated and could not clearly be ascribed to H_2-receptor activation either. A slow ipsp and hyperpolarizing response however is mediated by H_2-receptors and induces a K^+-conductance (Carpenter and Gaubatz, 1975; Gruol and Weinreich 1979a,b). This K^+-conductance is regulated by a GTP-binding protein such as Gi (Sasaki and Sato, 1987). A very good case has been made for the identity of histamine with the natural transmitter of these synaptic potentials (McCaman and Weinreich, 1982; 1985).

The first report of inhibitory and excitatory responses of snail (Helix aspersa) neurones to histamine appeared in 1968 (Kerkut et al., 1968). Takeuchi et al. (1976) found an excitation of a neurone in Achatina fulica Ferussac which was insensitive to both, mepyramine (H_1-antagonist) and burimamide (H_2-antagonist). Gotow et al. (1980a,b) detected, in the marine mollusc Onchidium verruculatum, excitatory H_1-receptor and inhibitory H_2-receptor dependent effects. The excitatory response is due to a Na^+-channel activation, and an electrogenic Na^+-Ca^{++} exchange was suggested as mechanism for the latter action which inhibits intrinsic beating activity in an identified neurone. Although cyclic nuleotides have no direct effect on this cell they are able to modulate the H_2-response: cAMP enhances, cGMP depresses it (Gotow and Hashimura, 1982).

Histamine is likely to be a (the ?) transmitter released from arthropod photoreceptors. Hardie (1987, 1989) has described a histaminergic potential and a histamine-gated chloride channel in the large monopolar cells following the photoreceptors. The pharmacological receptors involved have not yet been determined.

VERTEBRATE NEURONES

Vegetative Ganglia

Vegetative ganglia contain, apart from the projecting neurons, small intensely fluorescent (SIF) cells. These interneurones, not the principal cells, can store histamine (Häppölä et al., 1985; Weinreich, 1985; Päivarinta et al., 1987) and presumably modulate transmission by releasing it. An H_1-receptor mediated facilitation and an H_2-receptor mediated depression have been reported (Trendelenburg, 1954; Brezenoff and Gertner, 1972; Brimble and Wallis, 1973). These ganglia are probably not the source of peripheral histamine containing nerve fibers. Snow and Weinreich (1987) employed extra- and intracellular recording to disclose pre- and postsynaptic effects of histamine in the guinea pig. Histamine left the postsynaptic neuronal membrane properties unaltered but modulated the signal transfer: pre- and postsynaptic compound action potentials were reduced by histamine: impromidine (H_2-agonist) reduced only the postsynaptic action potential, an effect which was dose-dependently antagonized by cimetidine. This H_2-receptor antagonist caused a parallel shift of the dose-response curve. The reduction of the intracellularly recorded epsp was attributed to a decrease in acetylcholine release caused by a presynaptic volley. The facilitation of ganglionic transmission is seen as an H_1-receptor mediated increase in acetylcholine release. Some of the principal neurons display long lasting (more than 1s) afterhyperpolarizations (ahp) which can be blocked by cooling and histamine (Christian and Weinreich, 1988). This effect increases the postsynaptic excitability and allows higher frequency signal transfer. The H_1- and H_2-receptor activations are associated with increases of cyclic GMP and cyclic AMP respectively (Study and Greengard, 1978). Antigen exposure of superior cervical

ganglia taken from sensitized guinea pigs readily released histamine presumably from mast cells in the ganglia and lead consequently to a transient depolarization, an increase in neural input resistance and a block of the long lasting ahp. This effect was H_1-receptor mediated and not blocked by H_2- or H_3-receptor antagonists (Christian et al., 1989). Histamine could, by this mechanism, link immune-responses to the vegetative nervous system. The release of histamine from mast cells, which constitute a significant histamine pool in the brain, may well cause physiologically important effects on neurones or other effectors. H_1-receptor antagonists reduce postsynaptic potentials in bullfrog sympathetic ganglia (Tasaka et al., 1988) perhaps by removing a tonic histaminergic facilitation.

In the gut, apart from mast cells and enterochromaffine-like cells, neurones in the plexus submucosus and myentericus contain histamine. In the stomach, histaminergic fibers are sparse and they seem to be absent in the mucosa (Panula et al., 1985). The actions of histamine on myenteric neurones were depolarization of the membrane, increase of input resistance, suppression of ahps, augmented excitability, and repetitive spike discharges. These actions were predominantly but not exclusively mediated by H_2-receptors. Release of histamine from neuronal and non-neuronal sources, for instance during anaphylaxia, could therefore influence enteric functions also in this way (Nemeth et al., 1984). In the plexus submucosus (Meissneri) H_2-receptors are responsible for postsynaptic excitation and presynaptic inhibition. The excitation is achieved by block of a potassium conductance available at resting potential and a block of the long lasting ahp. A depression of both, fast and slow excitatory postsynaptic potentials (epsps) resultet from presynaptic inhibition of acetycholine- and presumably peptide release respectively. Pre- and postsynaptic actions of histamine were blocked by H_2-(cimetidine, ranitidine) but not H_1-receptor (mepyramine) antagonists. The adrenergic inhibitory postsynaptic potential (ipsp) was not affected by histamine suggesting the lack of histamine receptors on sympathetic nerve fiber varicosities (Tokimasa and Akasu, 1989). However, histamine depresses sympathetic neurotransmission in the guinea pig mesenteric artery by interacting with H_3-receptors on perivascular nerve terminals (Ishikawa and Sperelakis, 1987). Tamura et al. (1988) found epsps at nicotinic synapses on myenteric neurones reduced or abolished by histamine, acting through activation of the H_3-receptor. Thus histamine can modulate transmitter release on terminals other than those of histaminergic neurones themselves.

Central Nervous System

The exclusive source of the widespread histaminergic innervation of the central nervous system in vertebrates including man seems to be the tuberomammillary nucleus in the posterior hypothalamus. The location of this nucleus and its projections were predicted by the lesion studies of the group around J.C. Schwartz (1986) in Paris (Garbarg et al., 1974). Several hypothalamic nuclei are strongly innervated (e.g., the suprachiasmatic, supraoptic and paraventricular nuclei, Panula et al., 1989), the bulk of the fibers joins the medial forebrain bundle and projects to the olfactory bulb, most subcortical structures, the hippocampus and the cerebral cortex (Wilcox and Seybold, 1982; Panula et al., 1984; Steinbusch and Mulder, 1984; Takeda et al., 1984; Watanabe et al., 1984; Köhler et al., 1985; Ericson et al., 1987; Reiner and McGeer, 1987). A descending pathway reaches the brain stem and spinal cord (Wahlestedt et al., 1985; Takada et al., 1987). By and large histamine receptor density correlates with the target regions of histaminergic fibers (see Chapter 9, this volume).

Spinal cord. Histamine was applied to motoneurones and interneurones in the lumbar cord by microionophoresis. Phillis et al. (1968a) found depression due to hyperpolar-

ization and a reduction of synaptic potentials. Engberg et al. (1976) tested histamine along with other biogenic amines on cat motoneurons: they found hyperpolarizations, sometimes followed by longer lasting depolarizations and a reduction of afterhyperpolarizations following action potentials. These effects were produced by all amines and by protons as well as a number of other substances and were considered unspecific. In the hemisected frog spinal cord, Tebécis (1970) observed negative d.c. potentials (depolarizations) when recording from the dorsal root and positive or negative potentials when recording from the ventral root. No information on the receptors involved in these responses of spinal neurons is available.

Brainstem. Ionophoresis was also employed in early investigations of histamine actions in the medullary reticular formation. Neuronal firing rates were depressed by histamine and its metabolites. The N-tele-methyl compounds, the natural metabolites, were less active, in keeping with the idea that histamines action as a transmitter is terminated by metabolism—a high affinity uptake has not been described. Imidazole-acetic acid, probably not a significant natural metabolite, caused a strong depression of firing, an effect taking place on GABA- but not on histamine-receptors (Anderson et al., 1973; Haas et al., 1973). Most vestibular neurones are also depressed by locally administered histamine, through activation of H_2-receptors, some cells are excited (Satayavivad and Kirsten, 1977). Serotonergic cells in the dorsal raphe nucleus are also depressed via H_2-receptors, an effect which may ultimately take place on the GABA-benzodiazepine receptor complex (Lakoski et al., 1984). A similar H_2-receptor dependent depression of firing was found in the nucleus accumbens (Chronister et al., 1982). In all microelectrophoretic (ionophoretic) studies indirect actions are difficult to exclude, a good reason for studying in vitro preparations which allow the necessary manipulations for a more rigorous investigation.

Brainstem in vitro. Intracellular recordings from neurones in the medial pontine reticular formation which are responsible for physiological phenomena accompanying REM (rapid eye movement) sleep have revealed a strong excitatory action mediated via H_1-receptors. Histamine causes an inward current in voltage clamp experiments but little change in membrane resistance. This could indicate a remote location of the receptors on dendrites. The effects were often long outlasting (20-30 min) brief exposure times. As REM sleep occurs also in the presence of lesions of the tuberomammillary-reticular fibers, the histaminergic projection to this nucleus is likely to play a modulatory role on behavioural state control (Greene et al., 1989; Gerber et al., 1990).

The majority of medial vestibular neurones were depolarized by histamine and impromidine (50-100 μM), some displayed hyperpolarization or biphasic effects when histamine was superfused (Phelan et al., 1990). Increases in excitability were observed in locus coeruleus neurones (unpublished observation of the author) but the neighbouring neurones in the mesencephalic nucleus of the trigeminal nerve which have been shown to receive substantial innervation from the tuberomammillary nucleus were unresponsive to histamine and adenosine (Regenold et al., 1988). This pathway has been advocated as purinergic (Nagy et al., 1986).

Hypothalamus. Several response patterns occur on hypothalamic neurones when histamine is ionophoretically ejected from micropipettes into their immediate environment (see review by Roberts and Calcutt, 1983). Rapid, brief and longer lasting excitations are blocked by mepyramine, while inhibition of firing is mimicked by H_2-agonists and blocked by H_2-antagonists (Haas, 1974; Haas and Wolf, 1977). Preoptic neurones which project to the tuberomammillary region (Carette, 1978; Wouterlood and Gaykema, 1988), rostral hypothalamic neurones involved in thermoregulation (Sweat-

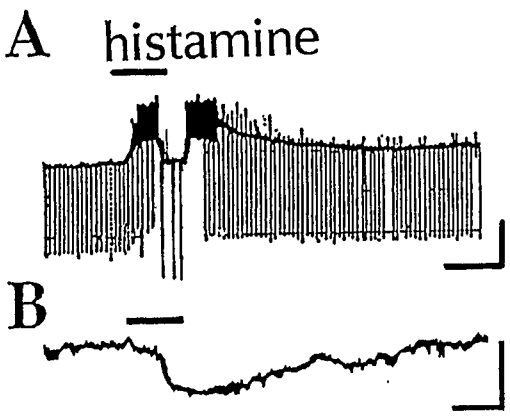

Fig. 2. Histamine causes depolarization (A: bath perfusion during time indicated by bar, H_1-effect) of a neurone from the medial pontine reticular formation and hyperpolarization (B: ionophoretic application, H_2-effect) of a granule cell from the dentate area of the hippocampus. During the depolarization in A, membrane potential was returned to its resting value by current injection (manual clamp). Downstrokes are voltage responses to negative current pulses which indicate an increase of input resistance, probably a block of potassium conductance, during histamine action. Slice preparations, Calibrations 10mv, 2min.

man and Jell, 1977), suprachiasmatic neurones (Liou et al., 1983) and ventromedial neurones (Renaud, 1976) display similar responses in rat and cat.

Supraoptic neurones are recipients of a strong histaminergic innervation and are excited through activation of H_1-receptors (Haas et al., 1975; Haas and Wolf, 1977; Haas and Geller, 1982; Armstrong and Sladek, 1985; Weiss et al., 1989). This action explains the increased vasopressin release and antidiuresis following local injections of histamine in the supraoptic region (Bennett and Pert, 1974; Dogterom et al., 1976; Tuomisto et al., 1980).

Cultured hypothalamic neurones respond to histamine, about half of them with a depression of firing mediated by H_2-receptors and a quarter with an H_1-receptor mediated excitation (Geller, 1976, 1979, 1981). The inhibitory effect (H_2) is postsynaptic and potentiated by phosphodiesterase inhibitors, indicating mediation by cyclic AMP. An H_2-receptor dependent depression arises in organotypic co-cultures of the tuberomammillary region and the hippocampus in the latter if the former is electrically stimulated (Reiner et al., 1988; Blüsselberg et al., 1990).

The histaminergic neurones in the tuberomammillary nucleus display a set of typical electrophysiological properties (Haas and Reiner, 1988; Haas et al., 1989; Greene et al., 1990). They are sensitive to histamine themselves. The histamine H_3-receptor agonist R-methylhistamine inhibits their firing, sometimes through a hyperpolarization of several millivolts which is accompanied by an increased input resistance. This action could naturally occur as a self-restricting inhibition of the histamine cells through dendritic release (Reiner and Haas, 1987; Schönrock et al., 1990). A possible mechanism is inhibition of an inward (Ca^{++}) current; such an action could occur at the histaminergic endings as well, where H_3-receptor activation has been shown to inhibit Ca^{++}-dependent release of histamine (see Chapter 7, this volume). The Ca^{++}-channel involved in this action is probably of the N-, not the L-type (Takemura et al., 1989) and coupled to a G-Protein (Arrang et al., 1990).

Cerebral cortex. Cortical neurones have been studied extensively with microionoophoretic techniques (Phillis et al., 1968b; Haas and Bucher, 1975; Phillis et al., 1975; Sastry and Phillis, 1976a; Haas and Wolf, 1977; Haas et al., 1978). Most cells are depressed by histamine through an H_2-receptor-activation but H_1-receptors may also be involved. Amitryptiline which binds to H_1 and H_2 receptors (Green and Maayani, 1977) could block both, the depressant actions of histamine and noradrenaline (Haas, 1979). Pyramidal cells projecting to the brainstem or spinal cord behave in the same way as unidentified deep cortical neurones. Impromidine and 4-methylhistamine, the H_2-agonists, mimic the depression, metiamide and cimetidine, the H_2-antagonists, block it. Electrical stimulation of the medial forebrain bundle, in which the histaminergic fibers ascend, evokes a metiamide sensitive inhibition on cortical neurones. This indicates an inhibitory influence of histaminergic afferents, mediated by H_2-receptors (Sastry and Phillis, 1976b; Haas and Wolf, 1977). The sensitivity of cortical neurones to ionophoretically evoked depressions by histamine increases after lesions of the median forebrain bundle. This denervation supersensitivity is not paralleled by a change in the sensitivity of the H_2-receptor mediated adenylate cyclase stimulation indicating that this response is independent of cyclic AMP (Haas et al., 1978). A cyclic AMP and H_2-receptor dependent response, as described below in detail in the hippocampus, which is excitatory or rather excitation-potentiating, has been observed in the entorhinal cortex (Haas et al., 1990). Excitatory effects, probably dependent on H_1-receptor activation, are seen less frequently in the cortex with microionophoretic application.

Hippocampus in vitro. Local application of histamine by ionophoresis depresses the firing of most neurones, as in vivo, in the hippocampal slice preparation. This inhibition is usually associated with a hyperpolarization and sometimes a conductance increase and can be mimicked by impromidine. It is a postsynaptic effect as it is seen in synaptic isolation too (Haas, 1981a,b). Histamine microdrop application to the slice surface can also cause slow depolarization and enhancement of epsps, an effect believed to be presynaptic and H_1-receptor mediated (Segal, 1980, 1981; Tagami et al., 1984). Bath application of histamine causes no consistent changes of synaptic potentials in the CA1 area of the rat but an increased response to ionophoretic excitatory amino acid application (Haas, 1984; Haas and Greene, 1986).

Pyramidal and granule cells in the hippocampus are moderately depolarized by histamine and this effect is also present in Ca^{++} deficient, tetrodotoxin or cadmium containing medium when synaptic interactions are abolished (Haas and Konnerth, 1983; Haas et al., 1984; Haas and Greene, 1986; Greene and Haas, 1990). It is mimicked by impromidine at about equal concentrations and blocked by cimetidine but not mepyramine and mediated by cyclic AMP (Haas, 1985a,b). Buffering the intracellular Ca^{++} to very low levels with EGTA (given through the microelectrode) blocks this action suggesting that H_2-receptor activation reduces a tonic Ca^{++}-dependent outward current. A bursting activity which develops in hippocampal neurones in low Ca^{++}, high Mg^{++} medium, when synaptic contacts are out of function (Haas and Jefferys, 1984) is much enhanced by histamine H_2-receptor activation and stimulation of adenylate cyclase. This histamine effect is potentiated by phosphodiesterase block. H_1-receptor activation has a slight inhibitory effect on low Ca^{++} firing (Haas et al., 1984).

A Ca^{++} activated potassium conductance (gK(Ca)) is, to a larger or lesser extent, present in all principal hippocampal neurones and plays an important role in the regulation of their responsiveness. It is responsible for the accommodation of firing (adaptation to a depolarizing stimulus) and a

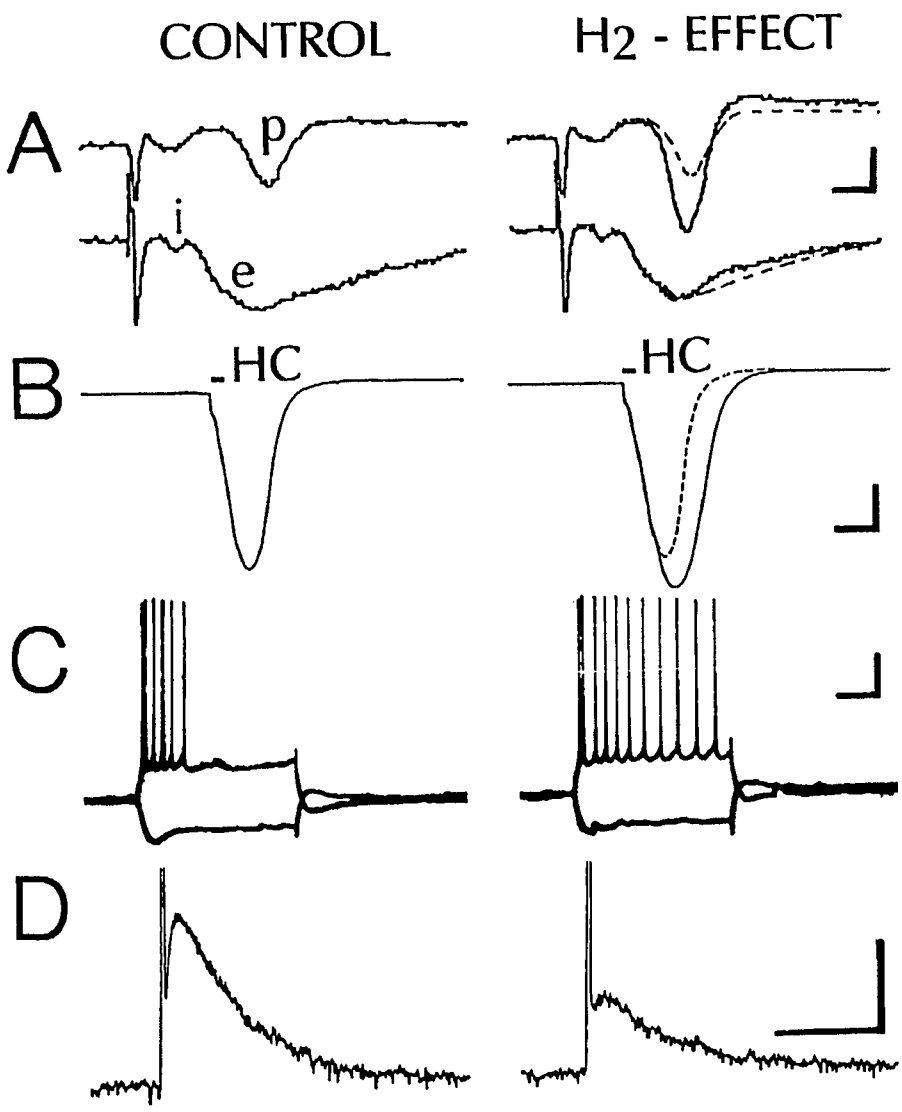

Fig. 3. H_2-receptor mediated potentiation of excitation in hippocampus. A: Pyramidal population spike (p) but not input volley (i) and extracellularly registered epsp (e) is increased by impromidine (H_2-agonist, 1μM). B: DC potential evoked by ionophoretically administered homocysteate (HC, during time indicated by small bar) is enhanced by 10 μM histamine. C: Accommodation of firing is blocked by 1μM histamine; responses to ±-current injection are shown superimposed. D: Long lasting tail current (I_{ahp}, following a brief Ca^{++} inward current is reduced by 10 μM histamine (I_{Ca} is unchanged, not visible in this record). A,B: broken lines in right records are controls. A,B,C from CA1, D from a dentate granule cell, single electrode voltage clamp. Calibrations: A 1mV, 2ms; B 2mV, 10s; C 20mV, 200ms; D 50 pA,4s.

long lasting afterhyperpolarization (ahp) following action potentials. Histamine specifically blocks this conductance and, as measured in voltage clamp, the slow component of the Ca^{++}-dependent potassium current (Iahp) by activating the H_2-receptor. This action is not secondary to a block of Ca^{++}-inward current and is most probably mediated by cyclic AMP. It is mimicked by impromidine but not thiazolethylamine, an H_1-agonist, and blocked by cimetidine but not mepyramine. Other agents that stimulate adenylate cyclase have the same effect: noradrenaline (trough β-receptor-activation), vasointestinal peptide (VIP), forskolin and 8-bromo-cyclic AMP itself (Madison and Nicoll, 1982; Haas and Konnerth, 1983; Haas, 1985; Haas and Greene, 1986; Pellmar, 1986; Haas and Rose, 1987; Greene and Haas, 1990). It occurs in slices from human hippocampus too (Haas et al., 1988a).

Endogenous adenosine exerts effects on hippocampal neurones at A_1-receptors which are almost exactly opposite to those produced by histamine H_2-receptor activation: hyperpolarization, induction of a potassium current, increase of gK(Ca) (Haas and Greene, 1984, 1988; Greene and Haas, 1985, 1990). The latter action probably reflects, opposite to the H_2-receptor mediated effect, the negative coupling of A1-receptors to adenylate cyclase.

Synaptic potentials in the hippocampus can be registered with intracellular or with extracellular recording. Field potentials registered in the dendritic areas reflect synaptic current (extracellular epsps). In the dentate area, an H_2-receptor mediated increase and an H_1-receptor mediated decrease of those potentials was found (Greene and Haas, 1990). Interneurones in the hippocampus have not been recorded with sufficient stability to test for drug effects directly, but their activity is reflected in spontaneous inhibitory (GABA-mediated) synaptic potentials registered in the principal neurones. The number of these potentials always increases markedly when histamine is added to the bath: thus the interneurones are also excited by an H_2-dependent mechanism or the transmission of inhibitory signals to the principal neurones is enhanced by histamine. The synchronous discharge of principal neurones in response to afferent fiber stimulation can be registered as a sharp negative population spike. This summed action potential is enhanced by histamine (H_2-receptor mediated), sometimes for prolonged periods (long-term potentiation) (Haas, 1984; Kostopoulos et al., 1988). Paired-pulse inhibition of population spikes is attenuated in an H_2-receptor dependent manner (Springfield and Geller, 1988). This effect can be explained by the observation that a small late component of the ipsp is due to a Ca^{++} dependent K^+-conductance and cyclic AMP sensitive (blocked by histamine and VIP, Haas and Gähwiler, 1987).

Activating Effect of Histamine on the Central Nervous System

Intraventricularly applied histamine causes several behavioural changes including centrally mediated arousal. Monnier et al. (1970) ascribed it to direct stimulation of ascending reticular, hippocampal and hypothalamic activating systems (but see Wolf and Monnier, 1973). This is strongly supported and enlarged by recent work from Jouvet's laboratory (Lin et al., 1988, 1989) describing EEG desynchronization (increased wakefulness) after local injection of histamine into the ventrolateral posterior hypothalamus. The effect was suppressed by mepyramine and this H_1-receptor antagonist had opposite actions to histamine, namely decreased wakefulness and increased slow wave sleep (high voltage, low frequency EEG). The sedative side-effect of H_1-receptor antagonists has long stirred interest in the connection between the histamine-system and sleep-waking regulation (see Tasaka et al., 1989). The strong H_1-receptor mediated excitation found on single neurones in the pons and the hypothalamus is in keeping with these results and their inter-

TABLE 1. Synopsis of Electrophysiological Histamine Effects

Species preparation	Effect		Receptor	Ion	Messenger	Authors
Glia)	dep		H1			Hösli and Hösli
Culture)	hyp		H2			Hösli et al.
Aplysia	dep		H1	Na+		Carpenter and Gaubatz
	epsp	f				
	epsp	s				
	hyp			Cl-		Gruol and Weinreich
	ipsp	f		Cl-		Gruol and Weinreich
	hyp	s	H2	K+	Gi	Sasaki and Sato
	ipsp	s	H2	K+		
Helix	exc		H1			Kerkut et al.
Achatina	exc,	dep	H1,H2			Takeuchi et al.
Onchidium	dep		H1	Na+		Gotow et al.
	hyp		H2	Na-Ca		Gotow et al.
Insect Photoreceptor	hyp			Cl-		Hardie
Vegetative Ganglia	facil		H1			Trendelenburg
						Brimble and Wallis
Tasaka et al.						
	ACh	+	H1			Brezenoff and Gertner
	ACh	-	H2			Snow and Weinreich
	ahp	-	H1	K+		Christian and Weinreich
Myenteric Neurones	dep		H2	K	cAMP	
	rel	-	H2			Tokimasa and Akasu
	rel	-	H3			Tamura et al.
						Ishikawa and
Spinal cord	hyp					Phillis et al.
	depr					Engberg et al.
Brain stem	depr		H2			Haas et al.
					not cAMP	Anderson et al.
Vestibular	depr		H2			Satayavivad and
	dep		H2			Phelan et al.
Raphe	depr					Lakoski et al.
Pons	dep		H1			Gerber et al.
N. accumbens	depr		H2			Chronister et al.
Hypothalamus	dep,	exc	H1			Haas and Wolf
Hypothalamus culture	exc		H1			Geller
	depr		H2			Geller
Hypothalamus TM	hyp		H3	Ca++		Reiner et al.
Hypothalamus SON	dep,	exc	H1			Haas et al.
						Armstrong and
Hypothalamus SCN	exc		H1			Liou et al.
Cerebral cortex	depr		H2		not cAMP	Phillis et al.
	depr		H2		not cAMP	Haas et al.
	depr		H2 (H1)			Sastry and Phillis
	exc		H1			Haas and Wolf
Hippocampus	dep	)	H2	gK(Ca)	cAMP	Haas and Konnerth
CA1, dentate	ahp	-)	H2	gK(Ca)	cAMP	Haas and Greene
CA1,	pop	+)	H2			Kostopoulos et al.
CA1	PPI	-	H2			Springfield and
	hyp		H2	K		Haas
	Iahp		H2	K(Ca)		Pellmar
CA1 low Ca	exc		H2		cAMP	Haas et al.
Dentate	psp	-	H1			
	psp	+	H2			
	Iahp		H2	K(Ca)		Greene and Haas
CA1, CA3	epsp		H1			Segal

ACh: acetylcholine, ahp: afterhyperpolarization, dep: depolarization, depr: depression, exc: excitation, (e,i)psp: excitatory or inhibitory postsynaptic potential, f: fast, facil: facilitation of transmission, hyp: hyperpolarization, pop: synaptically evoked population spike, PPI: paired pulse inhibition, rel: release, s: slow, SCN: suprachiasmatic nucleus, SON: supraoptic nucleus, TM: tuberomammillary nucleus -: decrease, +: increase.

pretation (Haas, 1974; Gerber et al., 1990). At cortical recording sites H_1-receptor mediated excitations are also encountered but seem to be superseded usually by H_2-receptor mediated depression. The more intriguing activation of the cortex occurs through H_2-receptors and block of the accommodation of firing—an effect which is potentiated by H_1-receptors (Baudry et al., 1975). An enhancement of hippocampal excitability by activating the tuberomammillary nucleus has been described in preliminary form (Haas et al., 1988b, Mizumori et al., 1988). Histamine levels and turnover have also been shown to be high during waking in rats (Friedman and Walker, 1968; Orr and Quay, 1975; Schwartz et al., 1976). Histamine and prostaglandin D2 modulate Ca^{++}-current in sensory neurones (Docherty et al. 1989). The receptors involved are not yet known. This action, if occurring on histamine release sites, could explain the sleep inducing effect of PGD2 (Ueno et al., 1983) as a suppression of the histaminergic activation.

CONCLUSIONS

The spectrum of histamine as a biological messenger seems to be wide, reaching from hormone to classical transmitter. The latter function is most clearly evident in invertebrates. In concert with other ascending aminergic pathways the histaminergic neurones fulfill mainly a typical modulating function in vertebrate nervous systems. A small number of large cells with multifold arborizing axons can influence the functional state of the whole brain. Histamine is released from the many varicosities of their axons in the target areas in a relatively diffuse manner and reaches receptors in the vicinity, the exact site of action is determined by the location of the receptors. In keeping with this disposition the repertoire of electrophysiological parameters influenced by histamine receptor activation allows the setting, regulation, or switching of behavioral states.

The position of histamine neurones at the ventral surface of the brain and close to the inner surface at the mammillary recess of the third ventricle makes them sensors for the cerebrospinal fluid which would signal its composition by this way to widespread but not indiscriminate target areas. Histamine and companion transmitters from the dendrites of tuberomammillary neurones might, in addition to an autoreceptor function and regulation of transmitter release from afferent terminals, gain access to the cerebrospinal fluid. Histamine and other hormones released from mast cells which are abundant near the median eminence at least in some species would also profoundly affect histamine neurones and their hypothalamic targets.

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