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HISTAMINERGIC MECHANISMS IN BRAIN

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Jean-Charles Schwartz
Unité de Neurobiologie, Centre Paul Broca de l'INSERM, 2tr, rue d'Alésia, 75014 Paris, France

Since the initial findings by Sir Henry Dale at the beginning of this century that the imidazoleethylamine histamine (HA) was a potent agonist on a variety of biological systems as well as a normal constituent of many tissues, it was hypothesized that the amine acts as a messenger between the cells in which it is stored and those responding to its application. To characterize precisely the messages delivered by a candidate transmitter substance, i.e. to attribute to it a precise physiological role, requires that the cells from which this substance emanates should be identified and that its actions on the target cells as well as the circumstances of its release should be known. During recent years, significant progress has been made in this direction and HA has been identified as one of a dozen of probable neurotransmitters in the brain. As expected, this evidence has been derived from two kinds of complementary studies that are reviewed here: the first concerns HA localization and metabolism ("HA in the brain") while the second concerns its action on various target systems ("HA on the brain"). Several reviews (1–5) and a symposium (6) have recently been devoted to this matter.

HISTAMINE IN THE BRAIN: LOCALIZATION AND METABOLISM

Occurrence and Distribution

In 1943, Kwiatowski (7) found with a bioassay procedure that HA was present in mammalian brain, more in gray than in white matter. The same procedure was used by Adam (8) to establish in detail the distribution of HA between regions of the dog brain. Large regional differences in amine levels were reported and later confirmed in other species like the cat (9), the rat (10, 11), the mouse (12, 13), the monkey (14), or man (15).

In these studies HA was assayed either with fluorometry following purification by ion-exchange chromatography (16) or with the more sensitive radioenzymatic assay (11), both procedures yielding similar results. The mean cerebral level of HA in most species is around 50 ng/g, about one tenth of noradrenaline or serotonin

levels, but its relative distribution is more or less parallel to that of these monoamines: the highest concentration is in the hypothalamus while the lowest is in the cerebellum or in the medulla-pons, and the intermediate levels are in the mesencephalon and telencephalon.

Recently the biochemical mapping of HA in discrete nuclei of rat hypothalamus (17, 18) or rat mesencephalon (19) has confirmed that HA is unevenly distributed even within brain regions. Such observations are compatible with the view that different densities of putative histaminergic neurons occur in various parts of the CNS. However, before interpreting these data in such a way, one must consider that the amine is probably also stored in non-neuronal cells.

Biosynthesis

Labeled HA does not diffuse readily from blood to brain (20–22, 25), indicating that the cerebral stores depend on local biosynthesis. White (24, 25) showed that this was the case in cat brain but did not characterize the enzyme responsible for the decarboxylation of ^{14}C-histidine. In 1970 Schwartz et al (26) studied the kinetics of the enzyme in homogenates from rat hypothalamus and the effects of selective inhibitors and concluded that the "specific" L-histidine decarboxylase (EC 4.1.1.22) was involved rather than the aromatic L-amino acid decarboxylase (EC 4.1.1.26), suggesting that HA synthesis does not take place in catecholaminergic or serotoninergic neurons containing the latter enzyme. Indeed, after chemical degeneration of monoaminergic neurons elicited by 6-hydroxydopamine or 5,7-dihydroxytryptamine, brain L-histidine decarboxylase (HD) is left unaltered (27). The inhibition of HA synthesis in brain slices (28) as well as in vivo (29, 30) by compounds like α-hydrazinohistidine, but not by α-methyldopa, an inhibitor of aromatic-L-amino acid decarboxylase, confirms that the latter enzyme is not involved.

The regional distribution of HD activity in the brains of rats (26, 31) or mice (30, 12) grossly parallels that of HA. However this does not always hold true: in the median eminence of rat hypothalamus an extremely high HA level is associated with an almost undetectable HD activity (18). In fact, the ratio of HA level/HD activity (which is expressed in units of time) appears well correlated with the half-life of the amine in various regions of mouse brain (12, 32).

Subcellular fractionation of homogenates from rat cortex shows that a major portion of HD activity is associated with synaptosomes from which it can be released in soluble form by osmotic shock, indicating that HD is, like other enzymes, responsible for the synthesis of putative transmitters present in the cytoplasm of nerve endings (33). This view is confirmed by the observation that, in vivo, synthesis of ^{3}H-HA from its ^{3}H-precursor takes place predominantly in the nerve-ending fraction (34). In rat hypothalamus, the picture is not so clear because HD activity appears associated to a lesser extent with synaptosomes from which it is only partially releasable in soluble form (35), but this relative discrepancy might be due to technical differences in homogenization or fractionation.

The developmental pattern of HD activity in rat brain is comparable to that of enzymes responsible for the synthesis of other putative neurotransmitters: at birth, when synapses are still few, HD activity is low and predominantly found in the

supernatant fraction of homogenates; then its activity increases several fold during synaptogenesis while its subcellular localization is progressively shifted into the fraction rich in nerve endings (23, 36).

Although the rate of ^{3}H-HA synthesis can be rapidly modified, the biochemical mechanisms by which such changes occur are not entirely clear. While HD activity does not appear to be regulated by a feedback mechanism, the rate-limiting step might be the availability of the precursor amino acid (28). In fact the apparent K_m of HD is about 3.10^{-4}M (26, 28), whereas the mean concentrations of L-histidine (L-His) in plasma and brain tissues ($\sim 6.10^{-5}$M) are not sufficient to normally saturate the enzyme. Thus brain HA is increased when the levels of L-His in plasma are elevated either following administration of loads of the amino acid (29, 30, 37) or as a consequence of a genetic defect in histidase (38). Conversely, cerebral HA rapidly decreases when L-His uptake is diminished in a competitive manner in mice loaded with other amino acids (39).

Storage

In peripheral tissues, mast cells constitute a major site of storage of HA in which it is held in large granules also containing heparin (40). The importance of these cells in brain has been overlooked for a long time because they were only rarely encountered upon histological examination (1). However mast cells have been recently identified in different brain regions of various animal species (41–44), even at the electron microscopic level (45). Moreover, in a preliminary report Rönnberg et al (46) have been able to reveal HA in mast cells from rat brain after its condensation with *o*-phtalaldehyde into a fluorescent product. However, using the same procedure, El-Ackad & Brody (47) did not reach a clear-cut conclusion in this respect. Although particularly abundant in the meninges, mast cells are also encountered in the brain parenchyma and are, in all cases, closely associated with blood vessels. Their number and morphology vary during brain maturation (44, 45).

No suitable histochemical method is available to visualize HA-containing neurons, but the subcellular fractionation approach used in several laboratories (35, 48–51) strongly indicates that such neurons occur in mammalian brain. Although in some studies there was evidence for a bimodal distribution of HA-storing particles, in all cases it was reported that a significant percentage of the amine is recovered in fractions containing synaptosomes. Furthermore, when synaptosomes are subjected to an hypoosmotic treatment, a substantial fraction of HA is recovered attached to synaptic vesicles (49, 51). This finding, together with the observation that HD is highly localized in the cytoplasm of nerve endings, suggests that both synthesis and storage of neuronal HA takes place in the same subcellular structures as other putative neurotransmitters.

Recently, the respective sizes of the neuronal and non-neuronal compartments, the latter probably corresponding to mast cells, have been evaluated in the cerebral cortex of rat (27) and cat (52) by combining data from deafferentation and subcellular studies. Approximately 50% of HA (but almost all HD activity) in cortex appears to be neuronal, while this percentage might be higher in other regions like rat hippocampus (53).

In the neonatal rat brain, i.e. before formation of most synapses, a paradoxically high level of HA (10, 23, 36, 54, 55), predominantly found in the crude nuclear fraction (36, 55), contrasts with a low HD activity (23, 36). These observations, previously attributed to a nuclear localization of HA (55), have been explained by Martres et al (36) on the assumption that mast-cell granules constitute the major store for HA during this period. This latter interpretation is confirmed by the observations that a large number of mast cells occur in the neonatal rat brain (44) and that, upon subfractionation of the crude nuclear pellet, HA-storing particles sediment like mast-cell granules but differently from nuclei (56).

Release

HA has not yet been reported to be released from any brain area following stimulation of corresponding afferent fibers. However, the axotomy of HA-containing pathways afferent to the cortex (27) or the hippocampus (53) is immediately followed by a strong but transient elevation of the amine content in these structures, which precedes the degeneration processes and could be attributed to a diminished release from nerve endings in which the impulse flow is interrupted. In vitro endogenous HA (57, 58), as well as endogenously synthesized ^{3}H-Ha (28) and exogenous ^{3}H-HA (59), is released from brain slices by K^+-evoked depolarization, and the efflux is both temperature- and calcium-dependent. The released amine appears to emanate predominantly from a rapidly turning-over compartment and because this release is accompanied by increased uptake of ^{3}H-L-His and increased ^{3}H-HA formation, there is evidence for a compensatory mechanism adjusting the rate of synthesis to the rate of release (28).

Reserpine releases both endogenous HA and endogenously synthesized ^{3}H-HA from hypothalamic slices (58, 60) and, in vivo, accelerates the disappearance of ^{3}H-HA from rat brain (61). However, there is no extensive depletion, as in the case of monoamines, in the content of endogenous HA in the brain of treated animals (62), except perhaps in cat hypothalamus (9).

Compound 48/80, a mast-cell degranulator, elicits an increased release of HA from slices from neonatal (36) and adult (28) rat brain, but the amine emanates from a slowly turning-over compartment. After systemic injection, this drug elicits a 40% depletion of HA from rat median eminence without affecting other hypothalamic structures inside the blood-brain barrier (18); significant depletion of whole brain HA also follows the intracerebral administration of compound 48/80 to newborn rats (63).

Hence, the data on HA release by various agents are also consistent with the view that the brain amine is stored both in a neuronal and in a mast-cell compartment.

Inactivation

There is apparently no high affinity uptake process to terminate rapidly the actions of HA in brain (2, 59, 64). The catabolism of HA in peripheral organs (65) involves two pathways: (*a*) direct oxidative deamination catalyzed by diamine oxidase and resulting in the formation of imidazoleacetic acid, (*b*) N-methylation into 3-methyl-

histamine (MHA) which is then converted by monoamine oxidase (MAO) into 3-methylimidazoleacetic acid. The first pathway is not operating in mammalian brain since diamine oxidase is absent (66) and, in contradiction with earlier reports (11, 67) labeled imidazoleacetic acid could not be detected after intracerebral administration of labeled HA (31, 68). On the contrary, high levels of labeled MHA appear soon after the administration of labeled HA (24, 31, 68, 69) or labeled L-His (31, 34, 70), especially in the brain of animals treated with MAO inhibitors. Indeed, methylation is an inactivation process since MHA lacks the characteristic activities of HA on brain tissues (71, 72). Methylation probably follows HA release since this conversion is reduced when the turnover of HA is reduced by anesthesia (34, 73). Minor quantities of MHA might also be formed by decarboxylation of the natural amino acid L-3-methylhistidine (39).

The enzyme responsible for this transformation, histamine-N-methyltransferase, is found in high activity in all regions of mammalian brain (69, 74, 75). It utilizes the methyl-donor S-adenosylmethionine which is, then, converted into S-adenosylhomocysteine, a potent competitive inhibitor of the reaction (76). This mechanism accounts for the interrelationships between the reactions of transmethylation of several amines in brain (69). The enzyme is evenly distributed in neurons and glial cells as indicated by its presence in clones derived from glioma or neuroblastoma (77) as well as by regional (75), subcellular (51), and developmental (36) studies.

Peptido amines are formed when HA and various amino acids are incubated with brain homogenates, but the function of these compounds is as yet obscure (78).

Turnover

Pollard et al (34) and Dismukes et al (70) have determined the turnover of HA in rat brain by examining the fluctuations with time of the specific activity of the amine in relationships with that of ^{3}H-L-His, after intraventricular administration of the latter. While the analytical data were in good agreement in both studies, because of the utilization of different mathematical models, the values for the half-life of cerebral HA were 46 min (34) and 30 sec (70), respectively.

A similar approach used in mice receiving ^{3}H-L-His by i.v. infusion (12, 13, 32) indicated that the half-life of HA in a rapidly turning-over compartment in brain, i.e. about 20 min, was much shorter than in any peripheral organ. Derived from kinetic data, there was also evidence for a second, slowly turning-over compartment (probably held in mast cells), a finding that might account for the partial, although rapid depletion of cerebral HA in animals treated with HD inhibitors (29, 30, 79). In the neonatal rat brain, the half-life of HA is, like in typical mast cells, in the order of several days (36).

The turnover of HA was reported to be accelerated and its endogenous level decreased in the brain of rats stressed by restraint (79) but this result could not be duplicated (80). Actually, in mice, restraint elicits an almost instantaneous decrease in turnover which is not secondary to adrenal stimulation (13). The turnover of HA is also decreased immediately after anesthesia (34, 73) and is higher during periods of arousal of a 24-hr cycle (81–84). Hence, a fraction of HA in brain turns over at

a rapid rate which can be modified almost instantaneously, as could be expected for a neurotransmitter.

Anatomical Disposition of Histaminergic Neuron Pathways

In the absence of a suitable histochemical technique, the anatomical disposition of histaminergic neurons in brain has been investigated by following the neurochemical changes elicited by specific lesions. The first attempts were not successful probably because HA level (and not HD activity) was selected as the marker for degenerative changes (85, 86).

In 1974, starting from the similar regional distribution of HA and the monoamines, Garbarg et al (87) lesioned the medial forebrain bundle (MFB) unilaterally in the hypothalamus and presented evidence for an ascending histaminergic pathway in rat brain: after 1 week HD activity is lowered ipsilaterally by 30–50% in all telencephalic areas, while caudal regions are unaffected. The time for half-decline of HD, i.e. 2 days, is consistent with anterograde degeneration of nerve tracts. Shortly after the lesion, i.e. in the period preceding degenerative changes, the reduced ^{3}H-HA synthesis and the progressive enhancement of endogenous HA in cortex indicates that the turnover of HA depends on impulse traffic in terminals of this tract (27). That HD in telencephalic areas is contained in terminals from extrinsic neurons is confirmed by the almost complete disappearance of enzyme activity after surgical isolation of an area of cat cortex (52) or complete deafferentation of rat hippocampus (53). In addition, selective lesions of afferents to the hippocampus demonstrate that histaminergic neurons enter this region, like the monoaminergic ones (88), partly through a dorsal route comprising the fornix and partly via fibers emanating from the amygdaloid area (53). After the various kinds of lesions, the decreases in HA levels, although significant, were less pronounced than those of HD, an observation consistent with the presence of the amine in non-neuronal cells, whereas the enzyme should be almost entirely confined to neurons.

Recently the existence of these histaminergic fibers has received strong support from the electrophysiological work of Haas et al (89) showing that inhibitions recorded in cortex after stimulation of the MFB, or on hippocampal pyramidal cells after stimulation of the fornix, are not only mimicked by HA but also prevented by metiamide, an HA antagonist.

While the precise localization of HA cell bodies remains to be established, recent lesion studies suggest that the ascending fibers emanate from the posterior hypothalamus or upper midbrain (32). There is also evidence for a descending system innervating the brain stem, especially the periventricular gray (19), a feature constituting an additional similarity with the anatomical disposition of noradrenergic and serotoninergic systems.

HISTAMINE ON THE BRAIN: ACTIONS ON TARGET SYSTEMS

The actions of HA have been studied either at the cellular level, i.e. on electrophysiological and biochemical parameters, or on behavior. While the former studies are

obviously easier to interpret, the latter might be more informative about the functions in which putative HA neurons are implicated.

Histamine and cAMP

The original finding by Kakiuchi & Rall (90) that HA was one of the most powerful agents in increasing the cyclic adenosine 3',5'-monophosphate (cAMP) level in slices from rabbit cerebellum has been repeatedly confirmed in a variety of regions and species like the chick (91), rabbit (90, 92, 93), guinea pig (72, 94–96), pig (97), rat (98), mouse (98, 99) and man (100). In addition, HA stimulates cAMP accumulation in cultured glioma cells (101). As in the case of other systems, there is no apparent correlation between the HA content of brain regions and their responsiveness: for instance, the hippocampus, which contains a low density of HA nerve endings, is the most responsive structure in the guinea pig (95). The action of HA appears mediated by receptors distinct from those mediating the responses to catecholamines, as indicated by large differences in responsiveness to the two classes of biogenic amines during brain maturation (92) or in various brain regions and, finally, by the lack of effect of adrenergic receptor blockers (95).

The discovery by Black et al (102) of specific agonists and antagonists of the two classes of HA receptors, i.e. H_1 and H_2, has allowed the identification of those mediating the cAMP response in brain. Baudry et al (96) demonstrated that, on slices of guinea pig cortex, HA stimulation is partially inhibited by either a H_1-antagonist (mepyramine) or a H_2-antagonist (metiamide) and totally blocked in the presence of both agents. While these data were essentially confirmed on slices from hippocampus (103), Hegstrand et al (104) found evidence for H_2-receptors only on homogenates from the same region, but the latter result is difficult to interpret since the responsiveness to HA is largely lost upon homogenization of the tissue. In chick brain the stimulation of cAMP formation is exclusively mediated by H_2-receptors (91).

Clonidine, an imidazoline derivative, is a relatively potent agonist of H_2-receptors on slices from guinea pig hippocampus (105) while its hypotensive action is blocked by intraventricular metiamide (106).

The cellular localization and functional roles of the two kinds of HA receptors mediating the stimulation of cAMP synthesis remains to be established. However, the observations that HA acts on isolated nerve endings (107) and that HA and cAMP exert similar actions when iontophoretically applied (71) are consistent with a possible role of the nucleotide as "second messenger" in histaminergic neurotransmission, as postulated in the case of noradrenergic synapses (108).

Electrophysiological Actions

Although few systematic studies have been undertaken, it appears that the actions of HA applied by iontophoresis on individual brain neurons result from the activation of specific receptors since they are generally not affected by antagonists of other putative CNS transmitters. HA elicits variable actions depending on the brain area where it is applied. On most neurons from the cerebral cortex of anesthetized cats or rats (109–111) HA has, like catecholamines and indoleamines, a weak depressant

action evidenced by a reduction of spontaneous or glutamate- and acetylcholine-induced firing, without depression of spike amplitude. Excitation is recorded only on a few cortical neurons and might be produced by higher doses of HA.

In contrast, Haas et al (75, 112, 113) have recently demonstrated that HA increased the discharge frequency of a great proportion of hypothalamic neurons including identified neurosecretory cells in the supraoptic nucleus. HA also excites neurons in the ventromedial hypothalamic nucleus (114).

Scarcer are the data on other brain regions. While excitatory actions are observed on neurons from the thalamus and the central gray of midbrain (71) depression is more frequent in the medulla oblongata (115), on neurons of the reticular formation of the brain stem, on the cerebellar Purkinje cells (116), on cells from cuneate nucleus (117), or on the spinal motoneurons (118). The ionic mechanisms responsible for both of the actions of HA on mammalian brain are not known but, in Aplysia, excitation results from an increase in Na^+ conductance while an increase in K^+ conductance might cause slow hyperpolarization (119).

It is tempting to hypothesize that the two opposite actions of HA are mediated by distinct receptors, i.e. excitation by H_1-receptors and inhibition by H_2-receptors. Indeed, this appears to be the case for the opposite actions of HA both on cerebral ganglia of the Aplysia (119) and on the superior cervical ganglion of the rabbit (120). In mammalian brain also, the depressant effects of HA on cerebral cortex, hippocampus, midbrain, or hypothalamus are reduced or blocked by metiamide, while this H_2-receptor antagonist has no specific effect on excitations. The important observation that inhibitions elicited by stimulations of the MFB or the fornix can be selectively reduced by metiamide (89) suggests that H_2-receptors might also be involved in the postsynaptic actions of the endogenous transmitter released from these fiber systems.

However, it must be stressed that these identifications of receptors mediating the various electrophysiological actions of HA remain to be confirmed, inasmuch as they lie mainly on the effects of H_2-antagonists. The actions of specific H_1- and H_2-agonists have not yet been reported and the data derived from the use of H_1-antagonists (the classical antihistamines) are doubtful in view of the nonspecific membrane stabilization elicited by these compounds.

Effects on Vegetative Functions and Behaviors

Intraventricular HA elicits a tachycardia and a rise in blood pressure via stimulation of sympathetic centers, which appears to involve H_1-receptors (121–124). On the other hand, the hypotensive activity of clonidine, a H_2-receptor agonist (105), was reported to be blocked by metiamide (106); however, the finding could not be confirmed by others (H. Schmitt, personal communication).

Intraventricular (125) or intrahypothalamic (126) administration of HA elicits a dose-related hypothermia which appears to involve both H_1- and H_2-receptors (127–129).

Emesis is observed in dogs receiving HA either systemically or intracerebrally (130) and results from a stimulation both of H_1- and H_2-receptors, at the level of the area postrema (131).

The effects of HA in the control of water metabolism have received relatively large attention. Intraventricular HA elicits an increase in water intake in satiated rats (132), an effect which is blocked by H_1-antagonists, and can be reproduced by microinjections of the amine into restricted hypothalamic areas known to be involved in the control of body water homeostasis (133). Following intraventricular HA, there is also a marked antidiuresis (134–136) which is accompanied by a rise in blood ADH (131) and prevented by lesioning the median eminence (136). That this action probably involves a stimulation of neurosecretory cells in the supraoptic nucleus is confirmed by the observation that the firing of these cells is increased by iontophoretically applied HA (113). Since this effect of HA is independent of cholinergic receptors and since both the supraoptic and the paraventricular nuclei of the hypothalamus contain rather high levels of HA and HD activity (17, 18), the hypothesis that histaminergic neurons in the hypothalamus might participate in the control of ADH release deserves consideration.

The actions of HA on complex behaviors is, as yet, poorly substantiated. Increased levels of brain HA elicited by L-His loads do not result in dramatic behavioral changes, except a slight motor depression (37) but this kind of experiment might be misleading in view of the direct pharmacological actions of the amino acid or of imidazoleacetic acid, its main metabolite. Intrahypothalamic administration of HA or L-His causes a dose-related elevation of self-stimulation thresholds, an effect prevented by prior treatment with H_1-receptor antagonists (137).

Desynchronization of electroencephalogram (EEG) patterns is recorded after the intraventricular administration of HA (138). Although this effect might be due to nonspecific (for instance vascular) actions of HA, it might also indicate that histaminergic neurons are involved in the control of arousal mechanisms. This idea is supported by several kinds of observations, i.e. by the anatomical disposition of the ascending pathway diffusely projecting in the whole telencephalon, by the effects of hypnotics on HA turnover (73), by the well-known sedative properties of H_1-receptor antagonists, and by the circadian fluctuations in brain HA levels (82–84) and in rates of HA synthesis (M. Verdière, C. Rose, and J. C. Schwartz, in preparation).

CONCLUSION

When the data concerning the localization and the metabolism of HA in the brain are considered together with those concerning its actions on brain tissues, it appears likely that the amine functions as a messenger in cell-to-cell communications in the CNS.

One of the main difficulties currently encountered in identifying the HA-mediated communications lies in the duality of the histaminergic cells in mammalian brain.

Mast cells have been characterized histologically but, in view of the probably very low turnover of the amine therein, it is doubtful that mast-cell HA participates in physiological regulations under normal conditions. Nevertheless, the close association of cerebral mast cells with blood vessels suggests that HA might be involved in vascular control, at least in the course of immune or inflammatory reactions.

On the other hand, while due to technical shortcomings characterization and localization of histaminergic neurons have been restricted to indirect approaches (mainly neurochemical and not histochemical), there is little reasonable doubt about their occurrence in mammalian brain. Indeed a fraction of brain HA appears to be synthesized at a rapid rate in a distinct population of neurons, to be released in conjunction with nerve activity, to affect selectively the firing of other neurons, possibly through cAMP formation, and then to be enzymatically inactivated.

At this time, the functions of these putative histaminergic neurons are not entirely clear, in spite of preliminary indications that they might be implicated in the control of water metabolism, of wakefulness, or of emotional behaviors. While the functional roles of other aminergic systems in brain has been better unraveled during the recent years, it appears that such a delay in the case of HA rests on a lack of several investigative tools. Undoubtedly, the discovery of a sensitive histochemical method to map out precisely the histaminergic neurons, as well as the development of chemical agents to modify selectively the metabolism and the actions of HA, will lead us in the coming years to a better understanding of the messages that the imidazoleamine delivers in our brain.

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