HISTAMINE[1,2]

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Henry Dale, in his introductory remarks to the Symposium on Histamine Metabolism at the 22nd International Congress of Physiological Sciences in 1962, reflected: "I suppose that a large part of this remarkably widespread and still prevalent interest in histamine and its actions must have been due to anomalies and difficulties, the paradoxes and conundrums, with which the investigator has found himself called upon to deal, in studies of its distribution in animal organs and tissues, and of its presumptive participation in normal and pathological reactions." The interest in histamine has, indeed, remained prevalent, but the difficulties in elucidating the biological significance of histamine appear less distressing than they did only a few years ago. Hope of progress in this field is entertained by attacking stagnant frontiers with new techniques and new approaches.

At the time of the sumptuous Ciba Foundation Symposium in honour of Sir Henry Dale, in 1956 (1), information on the biological significance of histamine was sought from studies of the histamine content of tissues and body fluids. Schayer in the U.S.A. and workers at the University of Lund, Sweden embarked on the problem in a more dynamic way. Schayer designed isotopic methods for the study of histamine metabolism and applied these methods to fundamental investigations of the biogenesis tissue binding, and catabolism of histamine *in vitro* and *in vivo* (2, 3). The workers in Lund discovered significant connections between changes in the rate of histamine formation (HFC) and physiological phenomena (4, 5, 6, 7, 8, 9). The place of HFC and changes therein in normal physiology will be discussed in an article in *Physiological Reviews* (10). The present review will be chiefly concerned with pharmacological topics related to recent work on the physiology of histamine. For a full and systematic account of the pharmacology of histamine, the reader is referred to the volume on histamine und antihistaminica, edited by Rocha e Silva (11).

Plasma Histamine and Pharmacological Actions

Adam, Hardwick & Spencer (12) established that the histamine equivalent of human plasma obtained from the antecubital vein was less than 1 ng per ml. In the cat, when histamine was infused intravenously at a rate of 330 ng per kg per min, there was no perceptible change in the arterial blood pressure during the infusion, but the plasma histamine rose from <0.3 ng per ml to 3.4 ng per ml. This implies that histamine, like other pharmaco-

[1] The survey of literature pertaining to this review was concluded in June, 1964. References will be mainly confined to the original observations; confirmatory articles will rarely be quoted.

[2] The following abbreviations will be used: DOPA (3,4,-dihydroxy phenylalanine; HFC (histamine-forming capacity = rate of histamine formation); 5-HIAA (5-hydroxyindolyl acetic acid) and ng (nanogram = 0.001 μg).

logically active agents, must be present in the plasma in a certain minimum concentration to exert detectable effects. Obrink (13, 14) suggests that there is no threshold for the stimulation of HCl secretion by histamine, and that any increase in plasma histamine must be presumed to be capable of making some contribution to the gastric secretory response. These latter results are at variance with older observations by Emmelin, Kahlson & Wicksell (15) who found, in dogs provided with a Pavlov pouch and given intravenous infusions of histamine, that 0.5 and 0.6 μg per kg per min was active and 0.2 and 0.4 was inactive in exciting gastric secretion. They also showed, in cats and dogs, that increases in plasma histamine resulting from injections too small to be detected by extraction and biological assay, produced vasodilatation, bronchoconstriction, increased motor activity of the bladder and secretion of gastric juice. These experiments indicated that "normally there may be no active histamine in the plasma." Lindell & Westling (16) infused C^{14}-labelled histamine intravenously in man at a rate of 0.1 to 0.3 μg per kg per min and produced a distinct increase in pulse rate and facial flushing; the resulting increase in plasma histamine was too low to be detected by non-isotopic methods. All these results should be taken to indicate that the absence of a detectable increase in endogenous histamine levels does not rule out histamine as a cause or participant in producing the changes in effector organs suspected to be due to histamine release or elevated HFC.

Characteristics of Histidine Decarboxylase

Mammalian histidine decarboxylase was discovered by Werle in 1936 (17). It was not until much later that interest in this enzyme was revived by investigations of the origin of histamine in the body [for references see Gaddum (18)] and on the distribution of the enzyme in various mammalian tissues and within cells (19).

Mammalian tissues contain at least two enzymes capable of decarboxylating histidine, as shown by Schayer (20). The specific histidine decarboxylase is abundant in mast cells and certain rapidly growing tissues, e.g. foetal rat liver. It is not activated by benzene and is strongly inhibited *in vivo* by α-methyl-histidine but not by α-methyl-DOPA. The nonspecific enzyme designated by Lovenberg, Weissbach & Udenfriend as aromatic L-amino-acid decarboxylase (21), decarboxylates all the naturally-occurring aromatic L-amino-acids. This enzyme is activated by benzene, closely resembles DOPA decarboxylase, and does not appear to play any part in the physiological formation of histamine (22). Håkansson (23) demonstrated *in vitro* that the pH optimum for the specific enzyme is not fixed but depends on the concentration of the substrate, and that the enzyme is more active at acid pH. The non-specific enzyme has been mistaken by some workers for the specific one. Experiments carried out in the presence of benzene led Telford & West (24) to misleading conclusions, among others that "the liver is by far the most potent source of histidine decarboxylase in the rat." They believed that the adult liver was nearly as potent as that of the embryo in this respect

and, further, that the duodenum and kidneys in the rat form histamine at high rates. As a matter of fact, the HFC of these tissues has been found to be very low (2, 25).

Inhibition of Histamine Formation *In Vivo*

Investigations on inhibition of histidine decarboxylase *in vitro* will be fully discussed only in the *Physiological Review* article (10), as space is limited in the present review and *in vivo* studies appear more interesting to pharmacologists. Quantitative studies of the inhibition of histidine decarboxylase *in vivo* became feasible with the introduction of two methods of assessing the rate of endogenous histamine formation in the rat. One method, devised by Schayer, measures the amount of C^{14}-histamine excreted in the urine following the injection of a known amount of C^{14}-histidine (26). The other method depends on the demonstration that, in the female rat, the urinary excretion of free histamine reflects the endogenous formation of this amine (27, 28). The possibility of inhibiting histamine formation to a small fraction of normal was first demonstrated in female rats fed a pyridoxine-deficient histamine-free diet and injected with semicarbazide in doses which by themselves would not be inhibitory (29, 30).

Inhibition by pyridoxine-deficient diet.—*In vitro* studies have shown that pyridoxal phosphate is essential for the activity of various amino acid decarboxylases (31), including mouse mastocytoma histidine decarboxylase (32). This coenzyme function has also been shown *in vivo* by feeding rats on a partly-synthetic histamine-free diet without pyridoxal phosphate, when the formation of histamine can be reduced to about 50 percent within 2 weeks and to about 20 percent in 6 to 7 weeks. The original rate of formation was rapidly restored when pyridoxal phosphate was added to the diet or injected subcutaneously (30).

Inhibition by semicarbazide.—This carbonyl reagent was first shown by Werle & Heitzer (33) to inhibit mammalian histidine decarboxylase *in vitro*. Although this compound also inhibits other pyridoxal-dependent decarboxylases, it may be useful in studies of histamine formation *in vivo* until stronger and more specific compounds have been found. Semicarbazide injected alone does not inhibit *in vivo* histamine formation. However, in rats, when administered in conjunction with a pyridoxine-free diet, its effect was so potent that subcutaneous doses of 2×50 mg per kg daily reduced the whole-body HFC to about 20 percent of normal within 2 days (30). In mice, the HFC cannot be inhibited by this procedure because semicarbazide is highly toxic in this species (7).

Cortisone and prednisolone.—Schayer, Smiley & Davis (34) found that injection of cortisone inhibits histamine formation in the skin, but not in the stomach, of rats; Schayer (2) showed that prednisolone greatly reduces the histidine decarboxylase activity of particle-free extracts of rat lung. The

whole-body HFC of rats, however, was not altered by either three successive daily injections of 1 mg cortisone or by prednisolone in six daily doses of 5 mg (30).

Hydrazine compounds.—Carbonyl reagents, i.e. pyridoxine antagonists, of this group, are known to inhibit amino acid decarboxylase *in vitro* [for references see Clark, (35)]. *In vivo*, isonicotinic hydrazide in 13 successive daily doses of 100 mg per kg caused only a slight reduction in whole-body HFC of rats which subsided during the course of injections (30).

α-methyl-DOPA.—In vitro, this compound strongly inhibits the kidney histidine decarboxylase from guinea pigs, as shown by Mackay & Shepherd (36), Werle (37), and Weissbach, Lovenberg & Udenfriend (38), and from rabbits, as demonstrated by Ganrot, Rosengren & Rosengren (22); but it does not strongly inhibit the histidine decarboxylase from mast-cell tumours (38), from rat foetal liver (22), or from Ehrlich ascites tumor cells (7). *In vivo*, this compound did not significantly reduce the whole-body HFC of rats even in the toxic doses of 4×100 mg per kg administered on two successive days (30, 39).

α-Methyl-histidine.—Robinson & Shepherd (40) published a method which yielded very small amounts of α-methyl-histidine and studied its inhibitory action on histidine decarboxylase from guinea pig kidney and from rat hepatoma *in vitro* (41). This compound was a much weaker inhibitor of the former enzyme than was α-methyl-DOPA, but was about ten times as active in inhibiting the enzyme from rat hepatoma, although in this case, it was much less potent than the hydrazine compounds. Weissbach, Lovenberg & Udenfriend (38) found α-methyl-histidine inactive *in vitro* on histidine decarboxylase of mouse mast cell and guinea pig kidney. However, the workers in Lund recognized α-methyl-histidine as a specific, nontoxic inhibitor of histamine formation (30, 39). In the experiment illustrated in Figure 1, α-methyl-histidine (4×100 mg per kg) was injected subcutaneously on two successive days. As a result, the daily urinary histamine dropped on the first day from 125 to 60 μg, i.e., the whole-body HFC was lowered to half the normal. Doubling the dose of α-methyl-histidine reduced the rate of formation to 30 percent. The smallest dose giving a significant reduction was 4×25 mg per kg daily. The inhibitory influence of α-methyl-histidine disappeared rapidly on discontinuance of treatment. Figure 1 also shows that the excretion of 5-HIAA (5-hydroxyindolyl acetic acid), believed to reflect the rate of endogenous formation of 5-hydroxytryptophan, is not seemingly influenced even in daily doses as large as 4×100 mg per kg; this is taken to indicate that α-methyl-histidine does not inhibit the decarboxylation of 5-hydroxytryptophan. Rats under the influence of α-methyl-histidine, in the dose range employed, did not exhibit discernible psychical or physical ill effects. α-Methyl-histidine was inhibitory even if pyridoxine had been omitted from the diet for 24 days; at this stage, α-methyl-histidine (4×200

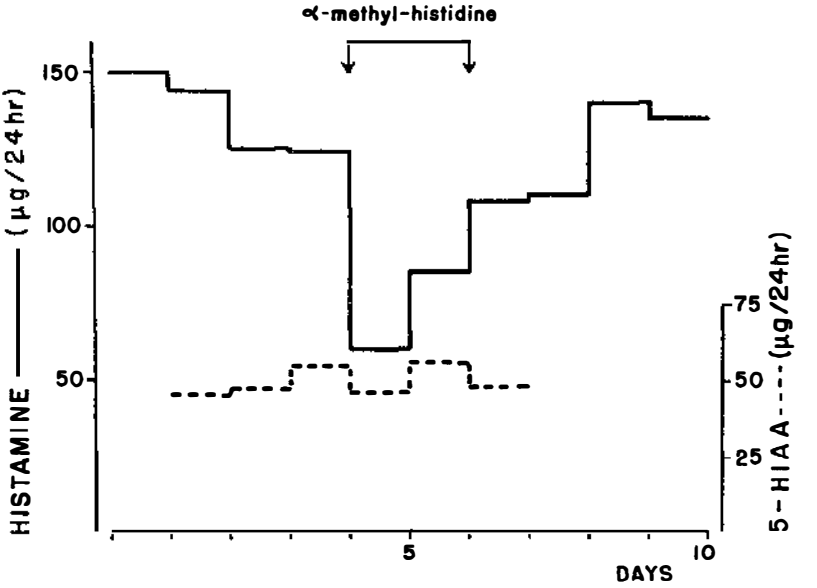

FIG. 1. Excretion of histamine and of 5-HIAA (dotted line) in the urine of a female rat: between the arrows, α-methyl-histidine, 4×100 mg per kg daily, for 2 days. [*J. Physiol.* **169**, 474 (1963)]

mg per kg) on four successive days reduced the whole-body HFC by about 50 percent, which shows that inhibition by this compound is due to interference with the histidine decarboxylase itself, and not merely with the coenzyme pyridoxalphosphate. The mode of action of this inhibitor appears to be by competition with the substrate; α-methyl-histidine is decarboxylated by rat foetal liver histidine decarboxylase. This may in part account for the large doses of the compound required for inhibition *in vivo*. It was not possible to establish the extent to which larger doses of the inhibitor would reduce the HFC *in vivo* because of limited supply of α-methyl-histidine.

FEED-BACK RELATION BETWEEN HISTAMINE CONTENT AND HFC

"Overshoot," in histamine formation, on discontinuing effective inhibition, suggests that a reduction in tissue histamine content causes a concurrent elevation of HFC in the tissue (30). Schayer, Rothschild & Bizoni (26) and Schayer & Ganley (42) have, in fact, demonstrated that depletion of rat skin histamine by 48/80 or by polymyxin B concomitantly activates skin histidine decarboxylase. These circumstances led the workers in Lund to assume the existence of a feed-back relationship and to search for evidence of this. Observations in the rat suggested that flushing the tissues with "long-acting histamine" lowered the whole-body HFC. More definite information

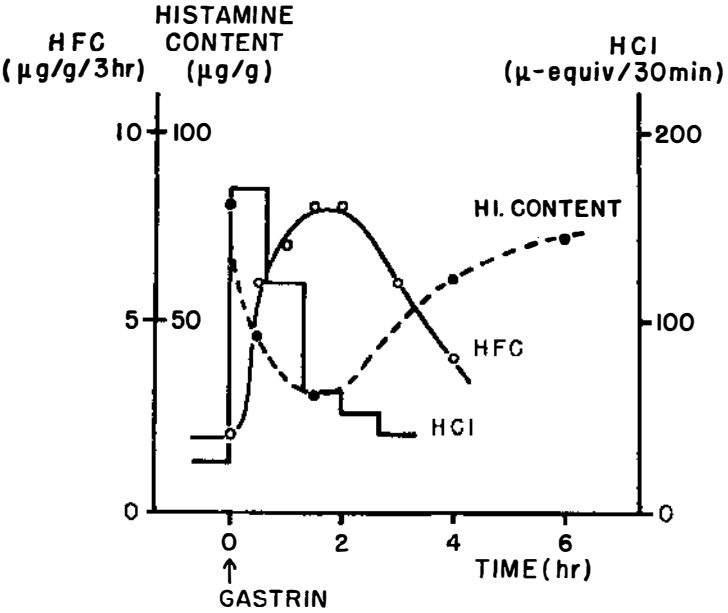

FIG. 2. Changes in HFC and in histamine content of gastric mucosa resulting from an injection of gastrin in fasted rats provided with a whole stomach fistula. [*J. Physiol.* (In press)]

was obtained by observations on the parietal cell-carrying region of the gastric mucosa. The feeding of fasted rats, or the injection of gastrin (Figure 2), brought about a liberation of histamine from preformed mucosal stores and a concomitant elevation of mucosal HFC. By contrast, elevation of the mucosal histamine content by histamine injections was associated with a concurrent fall in mucosal HFC (9).

It has been shown by various authors that none of the tissues investigated can be completely depleted by means of any of the known histamine liberators. This fact has been interpreted to indicate that there are at least two kinds of skin histamine, releasable and nonreleasable, and that nonreleasable histamine has some metabolic function (43). In the light of current knowledge, it seems worth considering the possibility of a feed-back relationship being involved in these phenomena.

Strong evidence has recently been given in favour of the view that HCl secretion is associated with liberation of histamine and elevation of HFC in the gastric mucosa. Nevertheless, the parietal cells gave normal secretory responses even when mucosal histamine content and HFC had been experimentally reduced to very small fractions of their initial values, indicating that normally histamine is available far in excess of the virtual needs (9).

Elevation of HFC

Within the short span of time since the monumental London Symposium on Histamine (1), physiological significance has been ascribed to tissue HFC, and, furthermore, means have been found to elevate HFC; this is a fact interesting in itself, and, in addition, of some promise to medicine. Schayer's pioneer work on the elevation of the HFC of rat skin, resulting from partial depletion of its histamine content, has already been quoted. In this particular instance, mast cells were disrupted, and it is not known to what extent the elevation of HFC was associated with regeneration of these cells. The following account of the "pharmacology of HFC" will describe elevations of HFC produced by factors and circumstances in which concomitant mast cell disruption was not a prominent event.

Thyroid.—Schayer (44) noted that neither thyroidectomy nor hypophysectomy caused significant changes in histidine decarboxylase activity of rat lung. Using Schayer's isotopic methods, Bjurö, Westling & Wetterqvist (45) found that treatment with thyroxine or liothyronine (L-3,5,3-triiodothyronine) increased the urinary excretion of free histamine in male and female rats under the influence of aminoguanidine. It is probable that liothyronine elevated the whole-body HFC since larger amounts of C^{14}-histamine were excreted after subcutaneous injection of C^{14}-histidine, than in untreated controls. Moreover, an increased formation of histamine could be demonstrated isotopically only in the glandular portion of the stomach, where the HFC was approximately doubled, whereas no increase was found in the skin. The histamine content of the skin, by contrast, was found to be high in hyperthyroid states in rats and in man by Gotzl & Dragstedt (46) and Feldberg & Loeser (47). The lack of parallelism between HFC and histamine content is repeatedly referred to in this review.

Epinephrine.—Schayer found that 20 μg epinephrine, injected intramuscularly in mice, produced a substantial increase in histidine decarboxylase activity of skin, lung (48), and muscle (49). In a study of histamine formation in physical exercise and anoxia, the action of epinephrine and related compounds on whole-body and tissue HFC was investigated in the mouse, rat, and cat (8). In mice, 2 μg per mouse, subcutaneously, evoked a twofold elevation of HFC in all tissues studied (lung, skin, hind limb skeletal muscle, and diaphragm) 3 hr after the injection. An increase in the dose of epinephrine to 5, 10, and 20 μg per mouse resulted in graded elevations of tissue HFC with peak values at 4 hr. The elevation of HFC was not accompanied by a detectable release of histamine in these tissues. The whole-body HFC, as reflected in the urinary histamine, was increased by epinephrine in a similar fashion as the tissue HFC.

In the rat, epinephrine, in the dose range 5 to 100 μg per rat subcutaneously, produced a fall in the HFC of the lung and no obvious changes in skin and muscle 3 hr after injection (8).

In kittens, with litter mates being used as controls, 80 μg epinephrine per 100 g body-weight subcutaneously caused no, or only insignificant, alterations in the HFC of lung, skin, skeletal muscle, and kidney at 3 hr (8).

Norepinephrine.—In mice, 20 μg norepinephrine subcutaneously produced elevations of tissue HFC similar to those obtained with epinephrine, but of lower magnitude (8).

DOPA *and* DOPA*mine.*—In mice, 50 mg per kg of either DOPA or DOPAmine given intraperitoneally, induced similar elevations of tissue HFC as produced by 20 μg norepinephrine (8).

Endotoxin.—In a study of histidine decarboxylase and histamine synthesis as related to shock, Schayer (49) demonstrated that injection of endotoxin (*E. coli* endotoxin) in mice caused large increases in HFC of skin, muscle, lung, liver, and spleen with peak elevations 6 hr after injection. In small intestine, brain, heart, and kidney, no definite increase in histidine decarboxylase activity was found. In these experiments, there seemed to be no correlation between elevation of tissue HFC and density of mast cells.

Anaphylaxis.—From the work of Dragstedt and of Feldberg in 1932, and from innumerable confirmations, it is known that preformed histamine is released in anaphylaxis [for references see Feldberg (50)]; it has also been shown that tissues are damaged. Having in mind the feed-back relationship already referred to and knowing that HFC has been found to be elevated in certain damaged tissues during repair (28, 51), it was an obvious step to investigate tissue HFC in anaphylactic shock. Thus far, observations have been made only in rats and mice (52, 53). In rats, histamine liberation in anaphylaxis has been thoroughly studied by Mota (54), who concludes that nearly all the histamine liberated in anaphylaxis in rats comes from the mast cells. In the present authors' experiments, the animals were sensitized with egg white and pertussis vaccine, and the shock dose of egg white was injected 11 to 13 days later. Tissues were excised 3 hr after the last injection and their HFC was determined isotopically. In rats, the HFC was greatly elevated in all tissues examined, except in the skin. In the Sprague-Dawley strain, the main sites of accelerated histamine formation were in the small intestine and in the lung; in these tissues, the HFC was found to be almost 25 times the normal value. In a local strain of rats, the liver and spleen were the main sites of accelerated histamine formation. In mice, in anaphylaxis, the HFC was elevated to about the same extent in lung, liver, spleen, and abdominal skin. These results suggest the following conclusions: (*a*) in the first place, a major enzymic change occurs in anaphylaxis, namely elevation of histidine decarboxylase activity; and (*b*) secondly, on the basis of tissue mast cell figures established by various authors, there is no apparent correlation between mast cell density and elevation of HFC in anaphylaxis in rats and mice. Other species, particularly the guinea pig, should be investigated in this respect.

In so far as histamine is responsible for the manifestations of anaphylaxis in the species studied, participation takes place in two phases: the first is the well-known, very brief phase of histamine release; there is, however, also a subsequent long phase of accelerated formation of histamine. The fact that intracellular histamine formation is accelerated may explain the relative or complete ineffectiveness of histamine antagonists in anaphylaxis. These drugs are not likely to abolish the actions within the cell of histamine resulting from elevated tissue HFC. This histamine should not be confused with preformed histamine intracellularly released. The observations referred to concern histamine newly synthesized, believed to exert actions only during the very process of its formation and, thus, is provisionally referred to as nascent histamine (55).

Anaphylactic manifestations last longer than the brief period of histamine release; this may be explained in part by the long lasting phase of accelerated histamine formation. Recent work and views on anaphylaxis have been reviewed by Mongar & Schild (56).

Histamine and the Nervous System

In an earlier volume of the series, Erspamer (57) remarked, "Histamine in the CNS has been ignored for a long time by several investigators as a second-class amine. But this amine, however annoying the fact may be, has the same citizenship rights in the CNS as catecholamines and 5-HT, whose function in the CNS is approximately as obscure as that of histamine."

The discovery of high concentrations of histamine in cerebral regions related to the hypophysis, by Harris, Jacobsohn & Kahlson (58), brought brain histamine to the fore. Its distribution was thoroughly explored by Adam (59). The fluorometric method, as originally described (60), is not suitable for the determination of brain histamine, although it may well be for some other tissues. The situation was clarified by Carlini & Green (61) who showed that fluorometric measurements can give erroneously high values for brain histamine. The apparent agreement between fluorometry and bioassay reported earlier (60) is absent when certain precautions are taken in the bioassay of histamine in the brain (59, 61). Brain extracts can contain substances other than histamine which give a histamine-like fluororescence and also contract the isolated guinea pig ileum.

The distribution of histamine among different areas of the brain has been mapped out in some detail (59), but less is known about the subcellular structures that contain the histamine. There is reason to assume that the histamine content in the pituitary gland and the hypophyseal stalk is related to their mast cell content (59) but the brain tissue, proper, does not contain mast cells. Recent reports (61, 62, 63) on the subcellular distribution of histamine in brain tissue agree that most of the histamine is particle bound, but the reports are at variance regarding the kind of particle(s) with which the histamine is associated. Thus, bioassay of histamine in subcellular fractions showed that most of the particle-bound histamine was in the small particles

(61), whereas the fluorometric technique demonstrated most of the histamine in the larger particles (63). These differences may arise from the different techniques for assaying histamine, or from differences in fractionating the homogenates, or both. The results obtained by bioassay may suggest that most of the histamine sediments with the synaptic vesicles (61).

Little is known about the effect of drugs on the histamine content of the brain in mammals. This is in sharp contrast to the wealth of information available on the effect of drugs on levels of such compounds as serotonin and catecholamines in the brain. Ungar & Witten (64), using the fluorometric technique, failed to demonstrate that reserpine had any effect on brain histamine in rats. Different results were obtained by Adam & Hye (65), who recently reported on the effects of compound 48/80, reserpine, and chlorpromazine on brain histamine in cats, estimated by bioassay. They showed that 48/80 lowered the histamine concentration in the pituitary and the hypophyseal stalk (i.e. mast-cell-containing tissues), but not in the hypothalamus and thalamus; whereas, reserpine lowered the histamine concentration in the hypothalamus and thalamus, leaving that in the pituitary unaffected. This would place histamine in the same category as serotonin and norepinephrine, these being three amines which are concentrated in the hypothalamus and other parts of the brain stem and which can be depleted by reserpine.

The mammalian brain contains much of the enzyme imidazole-N-methyl transferase (66). The highest concentrations are present in the pituitary gland and the hypothalamus, and lower concentrations are in the cerebellum and the cerebral cortex (67). It is interesting to note that the two former tissues are particularly rich in histamine, whereas the latter ones contain little or no histamine (58, 59). Imidazole-N-methyl transferase, in the presence of S-adenosyl-methionine (66) converts histamine into methylhistamine [(1-methyl-4(β-aminoethyl)-imidazole] (3). Formation of methylhistamine, and its oxidation product, methylimidazoleacetic acid (1-methyl-imidazole-4-acetic acid), from histamine has been demonstrated in feline brain tissue by White, both *in vitro* (68) and *in vivo* (69, 70), and the methylation of histamine can be regarded as the major route of inactivation of histamine in the brain (71). The enzyme diamine oxidase is absent (72), and, consequently, there is no oxidation of histamine to imidazoleacetic acid in the brain (68, 69, 70). Histamine can be formed from histidine in the brain *in vivo* (69, 70). It seems reasonable to assume that the histamine contained in the brain is formed locally, as little or no histamine penetrates the blood-brain barrier (73). This assumption would imply that imidazole-N-methyl transferase in the brain, together with histidine decarboxylase, is concerned with the physiological regulation of the local histamine turn-over, rather than acting as protective devices against histamine reaching the brain from other parts of the body. It would then appear that inhibition of one of these enzymes would change the brain levels of histamine. From this point of view, some observations on the actions of chlorpromazine should be quoted: (*a*) chlor-

promazine inhibits imidazole-N-methyl transferase *in vitro* (66); (*b*) it inhibits *in vivo* the methylation of histamine in whole mice (74) and also in cat brain (75); and (*c*) it increases the concentration of histamine in the brain of rats (64) and cats (65).

Previous reviewers have discussed the various pharmacological actions of histamine on the central and peripheral nervous system (57, 76, 77). In some of the experiments on the brain, it is doubtful if the effects observed are direct effects of histamine on the nervous system. In several cases, it is difficult to eliminate the side effects of histamine on other organs such as blood vessels or bronchi (leading to vasodilatation, hypotension, or asphyxia), or on the adrenal medulla, which may contribute to the phenomena observed on the central nervous system. One way of overcoming this difficulty is intraventricular administration of histamine (71, 78, 79). Further, histamine has been applied to central nervous system neurons by electrophoresis through micropipettes inserted into the tissue, the electrical activity being recorded simultaneously. In such experiments histamine had no effect on spinal neurons (80), nor did it affect synaptic transmission in the lateral geniculate body of cats (81), but it did inhibit neurons in the cerebral cortex of the cat (82). This effect may be related to the earlier finding that intracarotid injection of histamine in the cat inhibits transcallosally evoked potentials (83). The physiological implications of the above-mentioned findings remain to be explained. Finally, reports should be mentioned which indicate that histamine carried by the blood stream stimulates secretion of ACTH by the anterior pituitary gland, suggesting that histamine should be considered in the discussions on the control of the secretion of this gland (84, 85, 86).

Histamine and Micro-Circulation

Schayer (87) has introduced the concept of intracellular histamine formation, at rates determined by the actual tissue requirement for blood, as the principal regulator of the micro-circulation. The evidence for this is indirect and depends on the observations that subjection of experimental animals to procedures, stimuli, or agents which are likely to increase the need for blood in tissues, produced increased histidine decarboxylase activity, which results in the formation of "induced" histamine. In this hypothesis, the local want for blood and oxygen is implicated as a common factor, evoking the activation of the inducible enzyme. This hypothesis represents a revival of ideas originally fostered by Thomas Lewis and by Anrep. The concept is likely to lead to further studies in a field which is at the very core of experimental physiology.

Promotion of Wound Healing by Elevation of HFC

Wound tissue, excised 24 hr after infliction of a skin wound in rats, has a very high HFC, the histidine decarboxylase activity being 50 to 60 times that of undamaged control skin. In granulation tissue, the HFC ascends to the same high levels, and in both kinds of tissue the high activity subsides

during the course of healing. In granulation tissue, the histamine content was much lower (less than 10 percent) than in normal skin, indicating lack of binding sites for nascent histamine. When skin HFC had been elevated by injecting the histamine liberators 48/80 or polymyxin B, the rate of healing, as measured by the tensile strength in the intact animal, was strikingly augmented. Exposure of the wound to extracellular histamine from injected long-acting histamine did not promote healing (6). This work has been confirmed and extended by Sandberg (88, 89) who found that elevation of skin HFC in rats promoted the rate of collagen formation in healing wounds, whereas inhibition of HFC retarded collagen formation. Furthermore, cortisone restrained the normally-occurring elevation of HFC in wound tissue and retarded the rate of wound healing (90, 91). Histamine antagonists did not retard healing (92), in conformity with the view that these antagonists do not interfere with nascent histamine.

High levels of HFC have been found also in human skin wound tissue (93, 94). This fact should encourage efforts to promote healing in man by a search for suitable means to elevate HFC locally.

Boyd & Smith (95) and Fenton & West (96), employing a crude procedure of measuring tensile strength after the wound area had been excised, found that 48/80 and polymyxin B retarded wound healing, whereas Hvidberg et al. (97) and Maslinski (98), using a similar technique to measure tensile strength as the workers in Lund, confirmed the results of this latter group.

Itching is often felt during the healing of wounds of the skin. This phenomenon may, at least in part, be due to increased rate of histamine formation in granulation and wound tissue. The role of histamine in pain and itching has been reviewed by Keele & Armstrong (99).

Histamine in Allergy

Schild et al. (100) demonstrated that isolated bronchial muscle from the lung of an asthmatic patient contracted when in contact for the first time with dilute solutions of the specific antigen to which the patient was clinically sensitive. The authors reflect that there is no essential difference between the phenomenon which they described and the situation in experimental anaphylaxis in animals, and, moreover, that histamine release and contraction of the bronchial muscle play a definite part in allergic asthma. Bouhuys et al. (101), using the clearance of nitrogen from the lungs during oxygen breathing as a criterion, found that asthmatic subjects were more sensitive to inhaled histamine than normal control subjects. This latter finding brings to mind observations by Parrot et al. (102, 103). These workers claim that normal human blood, and more specifically a gamma-globulin fraction, has the capacity to bind histamine and that allergic patients, including asthmatics, are devoid of this "histaminopexic" action of the plasma. This idea is difficult to reconcile with the fact that all human tissues so far investigated form histamine and, accordingly, free histamine is continuously available for the presumed binding in a histaminopexic manner. Nevertheless, human blood

plasma, even after hydrolysis with strong hydrochloric acid does not display significant histamine activity on biological assay (12). The histaminopexic action of human plasma, whatever its significance, is thus not likely to be a factor of considerable magnitude.

Concluding Remarks

So far, the pharmacology of histamine has dealt mainly with the effects of exogenous histamine and of histamine liberators, but now has been broadened in scope by the discovery that the rate of endogenous histamine formation can be lowered and elevated by drugs and by agents normally produced by the body. It has also become evident that the tissue content of histamine is only a vague guide to its physiological significance or to changes in histamine metabolism produced by drugs. By contrast, changes in tissue HFC appear meaningful and of considerable consequence. In depicting and interpreting the actions of compounds, such as the catechol amines and their cognates, we must now consider the complication that these agents alter the tissue HFC. Added to this is the fact that a species difference exists in the response of HFC to drugs. Elevation of tissue HFC may be part of the integrated machinery designed to sustain homeostasis, in that histamine augments local blood supply and endothelial permeability and stimulates the pituitary-adrenocortical and the reticuloendothelial systems which both serve to maintain homeostasis.

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