CHAPTER 5

Catabolism of Histamine

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A. Introduction

The role of histamine in the control of general and local homeostasis is a recent discovery which is undergoing further investigation. The physiological significance of histamine-degrading enzymes as well as possible functions of histamine metabolites are also being reconsidered. The function of histamine-degrading enzymes in the elimination of histamine from its receptor-binding sites remains a topic for further study.

The functional role of the various products of histamine metabolism so far has not been recognized, although some have been shown to possess biological activity. Imidazoleacetic acid (ImAA), the product of oxidative deamination of histamine – but not t-methylimidazole acetic acid, the product of methylation – has behavioural effects in mice and rats (Roberts and Simonsen 1966) and acts as a potent neural inhibitor in cortical neurones (Phillis et al. 1968). There is growing evidence that ImAA can mimic certain actions of gamma-aminobutyric acid (GABA) (Benton et al. 1974; Bowery and Jones 1976) and inhibit specific release of diamine oxidase (DAO) from human neutrophils (Herman et al. 1979). Though there are no data concerning the biological activity of intermediary metabolites of oxidative deamination of histamine or N\(^{-}\)-methylhistamine (t-MH) – imidazoleacetaldehyde and t-methylimidazoleacetaldehyde, respectively – several aminoaldehydes are known to influence cell proliferation and viability (Perin et al. 1978; Gaugas and Dewey 1981). The target cells for histamine metabolites do not need to be connected with histamine-binding sites.

The biological significance of histamine catabolism remains to be elucidated. It seems quite likely that the level of histaminosis is directly linked to the intensity of histamine catabolic activity. The higher the histamine-degrading capacity, the lower the histamine level in blood serum becomes. Histamine once released is rapidly cleared from the circulation (Lorenz et al. 1981). Radiolabelled histamine injected intravenously appears in tissues within minutes (Reilley and Schayer 1971) and is excreted in urine as metabolites, free histamine representing only a small fraction. An intestinal barrier prevents more than 99% of the histamine in the digestive system from reaching the circulation. When histamine is given to guinea pig by stomach tube, the DL\(_{100}\) is approximately 1300 times higher than when it is adminis-
tered intravenously (Naranjo 1966). In some tissues, e.g. liver and intestine of guinea pig and chick, the degrading capacity enormously exceeds the synthetic capacity (Fogel 1988).

The contribution of the two main routes of histamine catabolism, oxidative deamination and ring methylation, varies not only from species to species but from tissue to tissue and even between various parts of the same organ. Inhibition of one route can switch the degradation to another pathway. Nevertheless, some patterns can be distinguished. In most tissues of the rat (Schayer 1959) and herbivores (Eliassen 1971a,b), as well as in intestine and blood vessels of omnivores and carnivores, oxidative deamination prevails (Kapeller-Adler 1970; Holcslaw et al. 1985). On the other hand, ring methylation seems to be the most important route of histamine metabolism in mammalian brain (Green 1970; Schayer and Reilly 1973; Schwartz et al. 1974).

Histamine N-methyltransferase is widely and ubiquitously distributed among animal tissues, whereas the distribution of DAO is restricted to the tissues which transport large quantities of materials (intestine, kidney, plasma).

Although the fate of exogenous histamine has been elucidated in some species, the metabolism of endogenous histamine remains obscure. The levels of urinary histamine and its metabolites are greatly influenced by food intake and foodstuffs containing histamine, and by the presence of bacteria in the alimentary tract or even in the vagina (Keyzer et al. 1983). Thus, the metabolism of exogenous histamine may not quantitatively or even qualitatively reflect the normal catabolism of endogenous histamine. Histamine delivered into the bloodstream is distributed to the tissues according to blood flow, while endogenous histamine is metabolized at its catabolic sites. This is well illustrated by data presented by Granerus et al. (1968). Healthy subjects were given $[^{14}\text{C}]-\text{histamine}$ intravenously for over 12 h. In the urine collected during this period the proportions of radioactive histamine: t-MH: methylimidazole acetic acid (MImAA) were 1:1.4:7.6, whereas the proportions of endogenous histamine and its metabolites were 1:8.5:132, respectively (Granerus et al. 1968).

At this point it should be mentioned that the fate of parenterally administered histamine differs from that taken orally. N$^1$-methylimidazole acetic acid (t-MImAA) was the major urinary metabolite of parenterally administered histamine and accounted for 60% of the sum of three main metabolites, while ImAA represented 13.5% and ribosylimidazole acetic acid (ImAA-rib) 26.5% (Schayer and Cooper 1956). Orally administered histamine was catabolized most via oxidative deamination, the corresponding values being 50% for ImAA-rib, 6% for ImAA and 44% for t-MImAA (Sjaastad and Sjaastad 1974). There is still a need for quantitation of all histamine metabolites formed in natural physiological conditions and in disease.