



THE DISPOSITION AND FATE OF
HISTAMINE IN ARTERIES

A THESIS SUBMITTED FOR THE DEGREE OF

Master of Science

by

Michael John Stacey B.Sc. (Hons.), B.D.S.

Department of Clinical and Experimental Pharmacology
The University of Adelaide
South Australia

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BIBLIOGRAPHY

D E C L A R A T I O N

I declare that this thesis contains no material which has been accepted for the award of any other degree or diploma in any university, and to the best of my knowledge contains no material previously published by another person, except where due reference is made in the text. I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Michael John Stacey

S U M M A R Y

Although histamine is present in mast cells in most species, in many tissues histamine is also contained in cells other than mast cells and its cellular distribution, metabolism, and function is unknown. This thesis is concerned with two questions:

- (1) Is histamine present in nerves which innervate small blood vessels?

This question relates to the distribution of endogenous histamine and its possible neurotransmitter role.

- (2) What is the fate of exogenous histamine in the blood vessel wall?

This relates to the mechanisms of uptake and catabolism of exogenous histamine in the smooth muscle cells and nerves of arteries.

Much of the study on endogenous histamine was carried out on the rabbit ear artery (REA). This tissue is more representative of small resistance vessels than the more commonly employed aorta. Furthermore, it is readily denervated and its vascular pharmacology has been extensively studied. In this study it was shown to contain large amounts of histamine. However, neither chronic sympathetic denervation nor chronic afferent denervation caused significant decreases in the histamine content. It was concluded that the major proportion of the endogenous histamine in the artery was not contained in nervous tissue.

The presence and distribution of mast cells was studied in the REA, rabbit aorta, central ear vein and the great auricular nerve. Mast cells were detected in the distal portions of the REA and in the connective tissue around the rabbit ear vein and auricular nerve (distal segments only). Mast cells were not found in the rabbit aorta. Since all the above vessels contained histamine, it is concluded that mast cells may represent a source of histamine in the REA and rabbit ear vein. This could account for the finding that histamine content in the distal region of the REA (10.2 $\mu\text{g/g}$ tissue) is approximately twice that in the proximal region (4.9 $\mu\text{g/g}$ tissue).

The studies on exogenous histamine catabolism required the development of analytical techniques for separating histamine and its catabolites. The results indicated that the rabbit aorta, REA and guinea pig aorta, when

incubated with ^{14}C -histamine, accumulated ^{14}C material against a concentration gradient. The above tissues converted histamine to catabolites, whose distribution suggested that both oxidative deamination and N-methylation were significant pathways of catabolism. This study found no evidence that procedures which disrupt catecholamine uptake and storage in sympathetic nerves affected histamine uptake and metabolism. These procedures comprised the inhibition of neuronal uptake by cocaine in the rabbit aorta, and chronic sympathetic denervation of the REA by removal of the superior cervical ganglion.

The above studies provided no evidence to suggest that the intramural nerves were either a site of storage or catabolism in the REA or aorta. In this respect the results do not support a neurotransmitter role for histamine in the peripheral arteries. However, the results do not exclude the possibility that there may be interaction at the post synaptic level between the distributions of histamine and noradrenaline. This possibility emerges because in the rabbit aorta, corticosterone, an inhibitor of extraneuronal uptake of noradrenaline, also inhibited the uptake and accumulation of ^{14}C -histamine in this tissue.

A I M

The aim of this thesis was to study the disposition and fate of histamine in arteries. This study is presented in two parts. Firstly, the localization of endogenous histamine in the vessel wall was investigated by comparing selectively denervated blood vessels with untreated controls. In addition the qualitative distribution of mast cells was studied in three rabbit blood vessels by histochemical techniques. Secondly, the possible role of sympathetic nerves for the uptake and catabolism of exogenous histamine was studied in rabbit blood vessels.

The study arose out of an investigation of the endogenous histamine content and catabolism of exogenous histamine in the rabbit aorta by Dr. Foldes. Most of the candidate's research has been on the rabbit ear artery but some comparative catabolic studies were carried out on the guinea pig aorta. The thesis commences with a brief survey of the disposition and metabolism of histamine in blood vessels (Chapter 1) and of the methods of analysing histamine in biological fluids. Chapters 2 and 3 deal with the effects of denervation on the content of endogenous histamine in the rabbit ear artery. Chapter 4 discusses the comparative distribution of mast cells in the rabbit ear artery, ear vein, great auricular nerve and aorta.

The last chapter (5) describes the comparative catabolism of exogenous histamine in the rabbit ear artery with that in the rabbit aorta and the aorta of the guinea pig. In both the studies of endogenous and exogenous histamine, emphasis is placed on the possible neurotransmitter role of histamine.

PUBLICATIONS

Part of the material contained within this thesis has already been published as follows.

FOLDES, A., STACEY, M. and de la LANDE, I.S. (1976):

Evidence for the extraneuronal localisation of histamine in the rabbit aorta.

Proc. Aust. Physiol. Pharmacol. Soc., 7/2:147P.

FOLDES, A., STACEY, M.J. and de la LANDE, I.S. (1978):

Histamine metabolism in aortae of two histamine sensitive species.

(From Proceedings of Aust. Soc. Clin. Exp. Pharmacol. 10th meeting Nov. 1976).

Clin. Exp. Pharmacol. Physiol., 5:239.

STACEY, M.J., FOLDES, A. and de la LANDE, I.S. (1978):

Localisation of histamine in rabbit central ear artery.

(From Proceedings of Aust. Soc. Clin. Exp. Pharmacol. 10th meeting Nov. 1976).

Clin. Exp. Pharmacol. Physiol., 5:240.

FOLDES, A. and STACEY, M.J. (1977):

The metabolism of exogenous histamine by aortic tissues.

Aust. J. Exp. Biol. Med. Sci., 55:441.

These are reproduced for reference within this thesis (see Appendix).

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