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Review

Vascular Effects of Histamine

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Summary: Four subtypes of receptors (H_1, H_2, H_3 and H_4) mediate the actions of histamine. In the vascular wall, the effects of histamine are mediated via H_1 and H_2 receptors and the actions are modulated by H_3 receptor subtype located on presynaptic neurones. Alterations in vascular responses to histamine are associated with experimental as well as a human form of hypertension, suggesting a role for histanine in cardiovascular regulation.

Keywords*:* Histamine, Vascular smooth muscle, Endothelium

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INTRODUCTION

Histamine or β-aminoethylimidazole is a chemical mediator that was first detected as uterine stimulant in extracts of ergot. It was also observed to stimulate a host of smooth muscles and to possess vasodepressor action (Dale and Laidlaw (1910). Histamine which is a diamine derivative of histidine is produced by the action of the enzyme histidine decarboxylase (Smuda and Bryce, 2011).

Endogenous histamine is a classical inflammatory and immunological mediator mainly produced by mast cells and basophils and plays a role in allergic response, regulation of gastric-acid secretion, neurotransmittion in the central nervous system and cardiovascular function. Four subclasses of receptors (H_1, H_2, H_3 and H_4) mediate the actions of histamine (Black et al, 1972; Arrang et al, 1983; Leurs et al, 1995; Rangachari, 1998). In general, activation of H_1 receptors (Ash and Schild, 1966) results in vasoconstriction while H_2-receptor activation (Black et al, 1972) mediates vasodilation. H_3 receptors (Arrang et al,1983) are described as modulators of histamine synthesis and release in the CNS, therefore, primarily function in modulation of neurotransmitter. H_4 receptors possess a limited expression; they are expressed in haemopoetic cells, involved in immunne response and are targets of particular interest in immunomodulatory therapies (Smuda and Bryce, 2011).

VASCULAR HISTAMINE

The vascular walls of various animal species have been reported to contain large amounts of histamine located in mast cell and non-mast cell stores (El Ackad and Brody, 1975). Also, coronary arteries of some patients with coronary artery disease have been reported to be hyperresponsive to histamine and to contain significantly higher concentrations of histamine (Kalsner and Richards, 1984). Mast cells present in post capillary venules also secrete histamine which induce protein leakage and edema formation

ACTIVATION OF HISTAMINE RECEPTORS

The actions of histamine are mediated via specific receptors on the cell embrane. The four subtypes of histamine receptors are typical G protein-coupled receptors (Rangachari, 1998). In general, activation of vascular H_1 and H_2 receptors elicits (respectively) vasoconstriction and vasodilatation (Black et al, 1972; Ebeigbe et al, 1989); vasodilation is, by far, the more predominant effect of histamine in humans. The H_1 and H_2 receptors mediating vasodilation are distributed throughout the resistance vessels in most vascular beds. Activation of either H_1 or H_2 subtype of histamine receptor can elicit maximal vasodilation, but the responses differ in their sensitivity to histamine, in duration of the effect, and in the mechanism of their production (Hudgins and Weiss, 1968; Ebeigbe et al, 1989; Leurs et al, 1995).

H_2 receptors are located mainly on vasuclar smooth muscle cells and the vasodilator effects produced by their stimulation are mediated by cyclic Adenosine monophosphate (cAMP); H_1 receptors reside mainly on endothelial cells, and their stimulation lead to the formation of local vasodilator substance called

Endothelium derived relaxing factor (EDRF) which has been identified as Nitric Oxide (NO). The EDRF diffuses from endothelial cells to vascular smooth muscle cells and therein activates the enzyme guanylate cyelase, which increases the level of cyclic guanosine monophosphate (cGMP) that leads subsequently, to the relaxation of the vascular smooth muscle (Furchgott and Zawadzki, 1980; Moncada et al, 1989).

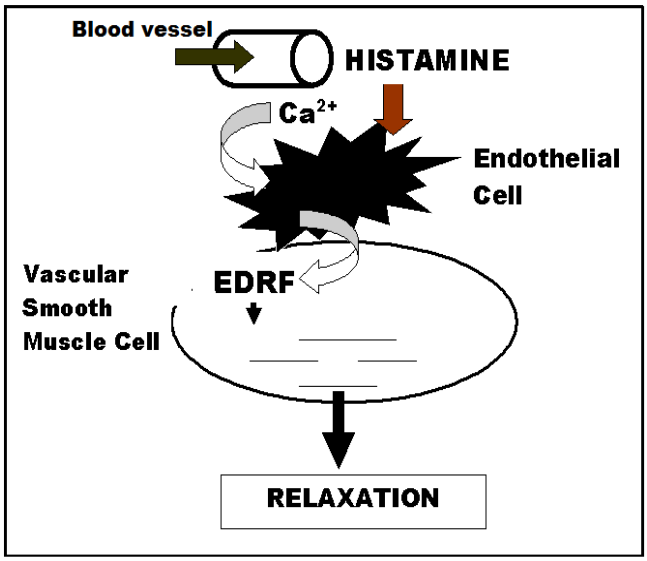

Fig. 1. Schematic representation of endothelium-derived relaxant factor (EDRF)-induced vascular smooth muscle relaxation in response to histamine (released from vascular wall) action on the endothelial cell.

The basal formation of nitric oxide maintains a moderate but significant vasodilation in the systemic resistance vessels. When blood flow in the conduit arteries is increased, there is an augemented endothelial formation of nitric oxide, eliciting flow-dependent vasodilation. Histamine has been widely reported to stimulate endothelial nitric oxide formation in a number of vascular beds (Van De Voorde and Leusen, 1983; Schoeffter and Godfraind, 1988).

Presynaptic H_3 receptors play a role in pathophysiology of cardiac ischemia. H_3 receptors in the heart become activated in the early phase of myocardial ischemia characterized by an increased histamine spillover (Gothert et al 1995). H_3 receptor in the central nervous system appear to be of importance in the control of vascular functions (Schlicker et al 1994). It is found either on histaminergic neurons of the CNS (Autoreceptors) or on the non-histaminergic neurons of the CNS (heteroreceptors). The vascular H_3 receptors appear to play some yet unidentified role in hypertension (Schlicker et al 1994).

H_4 receptor which has recently been characterised as the immune system histamine receptor (Zampeli and Tiligada, 2009) has a regulatory role in the immune system, is involved in dendritic cell activation and T cell differentiation.

VASOACTIVE EFFECTS OF HISTAMINE

The vascular effects of histamine are routinely studied *in vitro*, on ring preparations of isolated blood vessels (Ebeigbe et al, 1983; Schoeffter and Godfraind, 1988; Obiefuna et al, 1991). In the absence of active tone, histamine elicits contraction of vascular smooth muscles (Van de Voorde and Leusen, 1983; Ebeigbe and Cabanie, 1992). The relaxant effect of histamine, however, is usually observed in precontracted blood vessels and is more marked in the presence of an H_1-receptor antagonist (Van de Voorde and Leusen, 1983; Schoeffter and Godfraind, 1988; Ebeigbe and Cabanie, 1992).

At the capillary level, histamine distends the vessel wall to exert inflammatory reactions such as extravasation of blood content. In contrast, the muscular arteries, such as the coronary and mesenteric arteries are constricted by histamine. In addition to the vasomotor action, histamine has been shown to promote gene expression in smooth muscle cells. (Sasaguri and Tanimoto, 2004). Hudgins and Weiss (1968) demonstrated that the histamine-induced contraction of rabbit aorta is dependent to a large extent upon Ca^{2+} entry from the extracellular space.

TRANSMURAL NERVE STIMULATION

In many isolated blood vessels, transmural nerve stimulation elicits contractile responses due to release of noradrenaline from adrenergic nerve terminals (Vanhoutte et al, 1981). However when a vessel is precontracted using various agonists (e.g. noradrenaline, 5-HT, Angiotensin II), transmural nerve stimulation results in frequency-dependent relaxation responses. This Ca^{2+}-dependent relaxation response is presumed to be mediated, at least in part, by the release of histamine (Ebeigbe et al, 1983; Gantzos et al, 1983).

HISTAMINE AND VASCULAR DISEASE

Histamine has been reported to play some role in mediating some cardiovascular diseases: the coronary arteries of come cardiac patients are hyperreactive and contain large stores of histamine (Kalsner and Richards,1984). Contractile responses to histamine are enhanced in vessels from atherosclerotic humans (Ginsburg et al, 1981); reduced endothelium-dependent relaxation responses to histamine have been reported in various animal (Fig. 2) hypertensive models (Lockette et al, 1986; Obiefuna et al, 1991), as well as a human form of hypertension (Ebeigbe and Cabanie, 1991; 1992). Also, rings of isolated human epigastric arteries from pregnancy-induced hypertensive women display modest but significantly greater sensitivity to histamine (Fig. 3) and are more susceptible to H_1 receptor blockade (Ebeigbe and Cabanie, 1991; 1992).

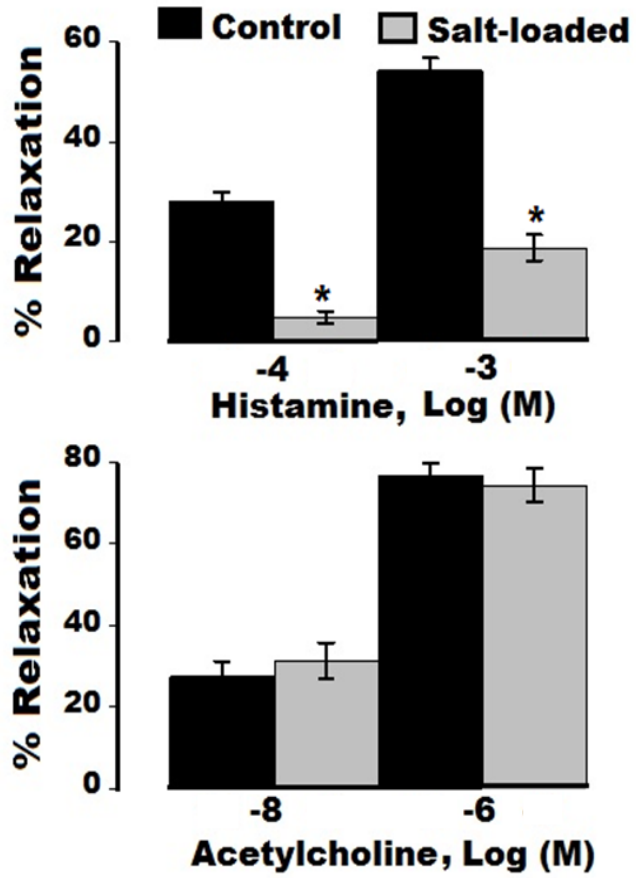

Fig. 2. Relaxation responses of isolated aortae from control and salt-loaded rats to histamine and acetylcholine. The relaxation responses to histamine, but not those to acetylcholine, were significantly (*p<0.05) diminished following salt-loading. (Adapted from Obiefuna, Sofola & Ebeigbe, 1991).

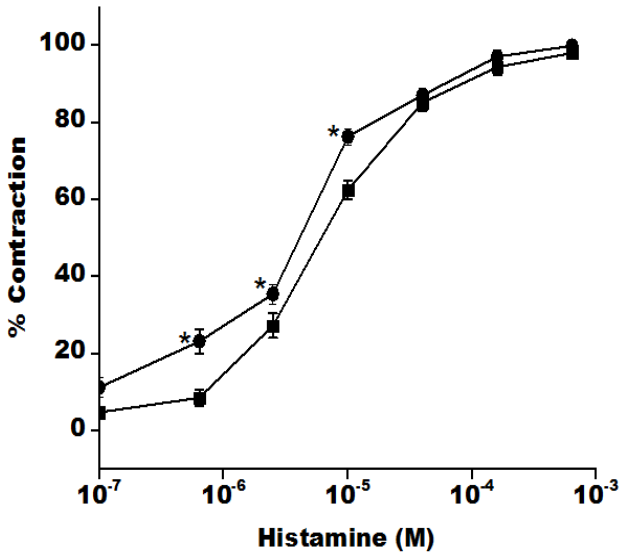

Fig. 3. Dose-response curves to histamine in epigastric arterial rings from control (n = 6, square) and pregnancy-induced hypertensive (n = 5, circle) patients. Asterisks denote significant difference from control values.

In conclusion, histamine, released from blood vessel wall or mast cells, influences vascular smooth muscle reactivity either directly or indirectly via stimulating endothelial cells. Alterations in histamine actions have implication for some cardiovascular disorders.

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REFERENCES

Arrang J.M., Garbarg M., Schwartz J.C. (1983): Autoinhibition of brain histamine release mediated by a novel class (H_3) of histamine receptor. *Nature (lond.)* **302:**832-837

Ash A.S and Schild H.O. (1966): Receptors mediating some actions of histamine. *Br. J. Pharmacol. Chemother*. **27(2):** 427-439

Black J.W., Duncan W.A.M., Durant C.J., Ganellin C.R. and Parsons M.E. (1972): Definition and antagonism of histamine H_1 receptors. *Nature* **236:** 385-390

Dale H.H. and Laidlaw P.P. (1910). The physiological action of beta-iminazolylethylamine. *J. Physiol.* **41:**318-344.

Ebeigbe A.B. and Cabanie M. (1991): In vitro vascular effects of cicletanine in pregnancy-induced hypertension. *Brit. J. Pharmacol.* **103:** 1992-1996

Ebeigbe A.B. and Cabanie M. (1992). Responses of isolated human epigastric arteries to histamine. J *Auton Nerv Syst*. **39**: 201-210.

Ebeigbe A.B., Cabanie M. and Godfraind T. (1989): Effects of Cicletanine on histamine-induced contractions of isolated rabbit mesenteric arteries. *Fundam. Clin. Pharmacol.* **3:** 223-235

Ebeigbe A.B., Gantzos R.D. and Webb R.C. (1983): Relaxation of rat tail artery to electrical stimulation. *Life Sci.* **33:** 303-309

El-Ackad T.M and Brody M.J. (1975): Evidence for non-mast cell histamine in the vascular wall. *Blood Vessels* **12:** 181-191

Furchgott R.F. and Zawadzki J.V. (1980). The Obligatory Role of Endothelial cell in the relaxation of Arterial Smooth Muscle by acetylcholine. *Nature*. **288**: 273-276

Gantzos R.D., Ebeigbe, A.B. and Webb R.C. (1983). Ca^{2+}, histamine antagonists and relaxation to electrical impulses in dog coronary artery. *Eur. J. Pharmacol*. 89: 287-291.

Ginsburg R., Bristow M.R., Kantrowitz N., Baim D.S. and Harrison D.C. (1981): Histamine provocation of clinical coronary artery spasm: implications concerning pathogenesis of variant angina pectoris. *Am. Heart. J.* **102:**819

Hudgins P.M. and Weiss G.B. (1968): Differential effects of calcium removal upon vascular smooth muscle contraction induced by norepinephrine, histamine and potassium. *J Pharmacol Exp Ther.* **159:** 91-97

Kalsner S. and Richards R. (1984): Coronary arteries of cardiac patients are hyperactive and contain

stores of amines: a mechanism for coronary spasm. *Science* **233:** 1435

Leurs R., Smit M.J., and Timmerman H. (1995): Molecular pharmacological aspects of histamine receptors. *Pharmacol. Ther.* **66:** 413-463

Lockette W., Otsuha Y. and Carretero O. (1986): The loss of endothelium-dependent relaxation in hypertension. *Hypertension* **8(2):** 61-66

Moncada S, Palmer R.M. and Higgs E.A. (1989). *Biochem. Pharmacol.* **38**:1709-15. Biosynthesis of nitric oxide from L-arginine. A pathway for the regulation of cell function and communication.

Obiefuna P.C.M., Sofola O.A. and Ebeigbe A.B. (1991): Dietary Salt-loading attenuates endothelium-dependent relaxation in responses to histamine but not to acetylcholine in rat aortic rings. *Exper. Physiol.* **76:** 135-138

Rangachari P.K. (1998). The fate of released histamine: reception, response and termination. *Yale Journal of Biol. Med.* **71**: 173-182.

Sasaguri Y. and Tanimoto A. (2004): Role of Macrophage-derived Histamine in Atherosclerosis-chronic participation in the inflammatory response. *Journal of atherosclerosis and thrombosis.* **11(3):** 122-130

Schlicker E., Malinowska B., Kathmann M. and Gothert M. (1994): Modulation of neurotransmitter release via histamine H_3 heteroreceptors. *Fundam. Clin. Pharmacol.* **8(2):** 128-137

Schoeffter P. and Godfraind T. (1988): Antihistaminic property of cicletanine in human isolated coronary arteries. *Drugs Exp. Clin. Res.* **14:** 159-165

Smuda C. And Bryce P.J. (2011): New Developments in the Use of Histamine and Histamine Receptors. *Curr. Allergy Asthma Rep*. **11(2):** 94–100.

Van de Voorde J. and Leusen I. (1983): Role of the endothelium in the vascular response of rat thoracic aorta to histamine. *Eur. J. Pharmacol.* **87:** 113-120

Vanhoutte P.M., Verbeuren T.J. and Webb R.C. (1981): Local modulation of the adrenergic neuroeffector interaction in the blood vessel wall. *Physiol. Rev.* **61:**151-247

Zampeli E. and Tiligada E. (2009): The role of histamine H_4 receptor in immune and inflammatory disorders. *Br. J. Pharmacol.* **157(1):** 24–33.