Vascular Effects of Histamine

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Summary: Four subtypes of receptors (H₁, H₂, H₃ and H₄) mediate the actions of histamine. In the vascular wall, the effects of histamine are mediated via H₁ and H₂ receptors and the actions are modulated by H₃ 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 histamine 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, neurotransmission in the central nervous system and cardiovascular function. Four subclasses of receptors (H₁, H₂, H₃ and H₄) mediate the actions of histamine (Black et al, 1972; Arrang et al, 1983; Leurs et al, 1995; Rangachari, 1998). In general, activation of H₁ receptors (Ash and Schild, 1966) results in vasoconstriction while H₂-receptor activation (Black et al, 1972) mediates vasodilation. H₃ receptors (Arrang et al,1983) are described as modulators of histamine synthesis and release in the CNS, therefore, primarily function in modulation of neurotransmitter. H₄ receptors possess a limited expression; they are expressed in haemopoietic cells, involved in immune 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 H₁ and H₂ receptors elicits (respectively) vasoconstriction and vasodilatation (Black et al, 1972; Ebeigbe et al, 1989); vasodilatation is, by far, the more predominant effect of histamine in humans. The H₁ and H₂ receptors mediating vasodilation are distributed throughout the resistance vessels in most vascular beds. Activation of either H₁ or H₂ 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).

H₃ receptors are located mainly on vascular smooth muscle cells and the vasodilator effects produced by their stimulation are mediated by cyclic Adenosine monophosphate (cAMP); H₁ 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 cyclase, 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).

**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 H₃-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 Ca²⁺ 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 Ca²⁺-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 some 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 H₂ receptor blockade (Ebeigbe and Cabanie, 1991; 1992).
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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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.


