REVIEW ARTICLE

ADRENERGIC MECHANISMS FOR HISTAMINE H_2-RECEPTOR EFFECTS ON RAT MYOMETRIUM

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Histamine, a naturally occuring autacoid is known to evoke a wide variety of actions. It produces vasodilatation, increase in capillary permeability and contraction of smooth muscles of bronchioles, ileum and spleen (17,18,19). It relaxes the rat myometrium (29). In addition it enhances gastric acid secretion (65) and produces positive inotropic and chronotropic action on heart (78). The effects of histamine such as stimulation of non-vascular smooth muscles, vasodilatation and increase in capillary permeability can be specifically blocked by classical antihistaminics such as diphendramine, tripelennamine, mepyramine etc. (8,33,45,92). The receptors involved in these actions were classified as H_1-receptors by Ash and Schild (5). The other actions of histamine such as gastric acid secretion, inhibition of rat myometrium and positive inotropic and chronotropic action on heart are specifically blocked by burimamide, metiamide and cimetidine. These actions have been described by Black *et al.* (11) as H_2-receptors effects. Structural modifications of the imidazole molecule of histamine have led to the development of specific H_1 and H_2-receptor agonists, (31,32,40,46). Compounds such as 2-methyl histamine, 2-(2-pyridyl) ethylamine and 2(2-thiozolyl) ethylamine show a greater selectivity for H_2-receptors (25), while 4-methyl-histamine, dimaprit and impromidine show a greater selectivity for H_2-receptors (16,26,71). The histamine receptors in various tissues can be identified and characterized by such tools as the specific H_1 and H_2-receptor agonists and antagonists. The present article is concerned with histamine mechanisms in rat uterus and involvement of adenylate cyclase-cyclic adenosine-monophosphate (CAMP) system.

HISTAMINE RECEPTORS IN RAT UTERUS

Histamine has been reported to inhibit the spontaneous contractions of the rat isolated uterus (1,27,29,86). It also inhibits the responses of rat uterus to acetylcholine (28), 5-hydroxytryptamine (4), barium chloride (64) and oxytocin (37). The inhibitory responses and the relaxing effects (16,20,34) of histamine were not antagonized by H_1-

receptor antagonists such as mepyramine, diphenhydramine etc. (5). Black *et al.* (11) could block these effects by new group of drugs called H_2-receptor antagonists like burimamide, metiamide and cimetidine. Histamine inhibitory responses of rat uterus are mediated through H_2-receptors (12,62).

Adrenergic drugs are also known to produce relaxation of rat uterus (3,23,48,72). The adrenoceptors in the rat uterus were classified by Ahlquist (3) as *beta*-adrenoceptors. It was however, postulated by him (2) and other (21,48,72) that the uterus contains both *alpha* excitatory and *beta* inhibitory receptors. The presence of *alpha* adrenoceptor in rat myometrium is not confirmed. Levy and Ahlquist (47) and Jenson and Vennerod (39) showed that phentolamine and tolazoline the *alpha* adrenoceptor blocking agents could reduce the adrenergic effects in rat uterus. However, various authors failed to confirm these results (2,44,49,55,64). Levy and Tozzi (48) suggested that it is possible that reduction of the adrenergic effect observed by Jenson and Vennerod (39) may be due to intrinsic activity of tolazoline. Blockade of the adrenergic response to *beta*-adrenoceptor antagonist is well established (44,75,76,82). Similarity between adrenergic and histamine response of the rat uterus was first indicated by Jensen and Vernnerod (38) who showed that dichloroisoprenaline a *beta* adrenergic antagonist blocked the effect of histamine on the rat isolated uterus. Later Tozzi (83) reported that histamine-induced inhibition of rat uterus was similar to that of tyramine and that it indirectly activates *beta*-adrenoceptor by releasing catecholamines. He found (83) that propranolol, an effective *beta*-adrenoceptor blocking agent produced a significant parallel shift of histamine, tyramine and isoprenaline dose-response curves. Tachyphylaxis to histamine and tyramine on rat uterus has been previously demonstrated (84). It has also been reported that the effects of histamine on the rat uterus are blocked in rats pretreated with reserpine (30). All these evidences tentatively suggest that the action of histamine on the rat uterus is more like that of tyramine.

Data from our laboratory (89,91) also support these findings. We found that propranolol competitively antagonizes the responses to histamine in the dose range required to antagonize the responses to isoprenaline and that histamine fails to relax the depolarized uterus obtained from reserpine pre-treated rats.

HISTAMINE AND ADENYLATE CYCLASE SYSTEM

If histamine works through the release of catecholamines in rat uterus, then it must show some other characteristics of *beta*-adrenoceptors.

In the last two decades much evidence has been accumulated to suggest the correlation between adenylate-cyclase CAMP system and catecholamines in various smooth muscles including myometrium. The *beta*-adrenoceptor stimulation in myometrium by catecholamines results in elevation of CAMP (50,79,85) and a quantitative relationship

has been demonstrated between the increase in CAMP levels and the relaxing effects of catecholamines (6,14,15,23,52,53,68,70,77,80,82). Both relaxation and the increase in CAMP is prevented by *beta*-adrenoceptor blockers (81). These and other findings support the hypothes is that CAMP acts as a second messenger substance responsible for the relaxing effect of *beta*-adrenoceptor agonist in smooth muscle (6,7,9,14,15,52,53,61,68,70,73,74, 78,79,80,81,82,85). However, several laboratories have reported the results which do not support the second messenger hypothesis (10,22,35,36,63,66,67,87,90). It has been shown that compounds like D600 (44,51), aspaminal (85) etc. relax the rat isolated uterus without affecting CAMP levels. PGE_1 which produces contractile response of rat myometrium, elevates CAMP level in this tissue (35,36,87). Diamond and Homles (22), and Verma and McNeill (90) reported that isoprenaline can produce dose-dependent relaxation of rat uterus without concomitant increase in CAMP. In a recent study it was demonstrated (63) that at different levels of CAMP, relaxation responses of the muscle to isoprenaline remained the same.

H_2-receptors in other tissues appear to be associated with adenylate cyclase (60,88). Histamine and its analogues increase the activity of cardiac adenylate cyclase and increase intracellular levels of CAMP. This action precedes the positive inotropic and chronotropic action on the heart (41 56,57,58,59,60,61,69,88). In gastric mucosa, H_2-receptor stimulation leads to increases in CAMP levels along with gastric acid secretion (13,24,42,43). Mitznegs *et al.* (54) reported that histamine depresses the spontaneous motility of the rat isolated uterus as well as increases CAMP levels in this tissue. Both the effects were blocked by metiamide, an H_2-receptor antagonist. From these findings it was strongly suggested that the histamine-induced inhibition of rat uterine motility was mediated through CAMP formed in response to stimulation of H_2-receptors in the rat myometrium.

Verma and McNeill (89) also demonstrated elevation of CAMP levels in rat uterine segments incubated with histamine. However, when *in vitro* studies were carried out using adenylate cyclase prepared from rat uterus, McNeill and Verma (62) failed to demonstrate any stimulation of this enzyme by histamine. Adenylate cyclase prepared from guinea pig heart or rat gastric mucosa is stimulated by histamine and its analogues (60,84). Thus in rat myometrium H_2-receptors do not appear to be associated with adenylate cyclase.

Histamine has indirect relaxant effects on the rat uterus (83,89). This may explain the findings of McNeill and Verma (62) that any indirectly acting drug under normal circumstances would not stimulate the adenylate cyclase particulate. It is possible that adenylate cyclase is involved but that the amount of the enzyme that can be stimulated by histamine is very small relative to the total amount of enzyme in the preparation. Their preparation of the enzyme, which was made from the whole tissue, may not have been

sensitive enough to detect the change. Since histamine receptors appear to be associated with the adrenergic neruonal uptake system it is possible that an examination of adenylate cyclase prepared from neuronal membranes of the uterus may prove fruitful when techniques become available.

In summary, histamine produces inhibition of rat myometrium through the stimulation of H_2-receptors. The evidence cited in this article suggests that H_2-receptor stimulation in rat-myometrium triggers the release of catecholamines which is ultimately responsible for the inhibitory effect on the rat myometrium. The stimulation of adenylate cyclase and increase in CAMP level reported by Mitznegs *et al.* (54) also appears to be a phenomenon mediated due to catecholamine release. McNeill and Verma (62) reported that histamine did not stimulate adenylate cyclase prepared from rat uterus. Their findings very strongly suggest the indirect effects of histamine in the rat uterus.

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