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Mechanisms involved in the vasorelaxing influence of histamine on isolated human subcutaneous resistance arteries

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Abstract

The effects of histamine were analysed on human subcutaneous small arteries. No effect was seen on non-precontracted preparations. After precontraction (norepinephrine 1 μM and K^+ 30 mM) histamine potently relaxed the arteries (EC_{50} = 0.3 μM; max. effect = 95% relaxation). The histamine H_1 receptor antagonist, pyrilamine (10 μM), had only a small, non-significant inhibitory influence on histamine-induced relaxation while the histamine H_2 receptor antagonist, cimetidine (0.1 mM), had a significant inhibitory influence. Relaxation was completely blocked in the presence of both antagonists. Both 2-pyridylethylamine (histamine H_1 receptor agonist) and dimaprit (histamine H_2 receptor agonist) elicited relaxation. Removal of endothelium reduced the relaxation effects of histamine and 2-pyridylethylamine, but not of dimaprit. Inhibition of nitric oxide synthesis by nitro-L-arginine significantly inhibited histamine-induced relaxation and even more clearly the cimetidine-resistant component. We conclude that histamine potently relaxes human subcutaneous arterioles, and that most probably both muscular histamine H_2 receptors and endothelial histamine H_1 receptors, thus activating nitric oxide release, contribute to the relaxation.

Keywords: Histamine; Arteriole, human, subcutaneous; Nitric oxide (NO); Prostanoid; Histamine H_1 receptor; Histamine H_2 receptor

1. Introduction

Histamine is present in high concentrations in the wall of blood vessels, either in a free form or stored in mast cells (El-Ackad and Brody, 1975). While a physiological role for histamine in the regulation of vascular tone is not established, its importance in pathological situations such as anaphylactic shock is well recognized (Babe and Serafin, 1996). The vasomotor effects of histamine have been repeatedly studied in vivo, in situ and on isolated vessel segments. Marked species and regional differences have been reported for the effects elicited by histamine, as well as for the receptor subtypes mediating these effects. The ultimate effect of histamine is actually the resultant of the relative predominance of contractile and relaxing components, originating directly from the smooth muscle cells and indirectly from endothelial cells (Van de Voorde and Leusen, 1983; Leusen and Van de Voorde, 1988; Levi et al., 1991).

In general, intravenous administration of histamine causes a fall in peripheral vascular resistance and a decrease in systemic blood pressure, mediated by both histamine H_1 and H_2 receptors. In contrast, the influence of histamine on specific vascular beds is quite variable: it elicits either vasoconstriction, vasodilatation, or a combination of these responses, depending on the dose, route of administration, animal species, anatomic region, caliber and preexisting tone of the vessel (Levi et al., 1991). Thus, observations made in a certain vascular bed may not be extrapolated to the human circulation. Even within a specific vascular bed of one species, a marked regional heterogeneity can be observed (Van de Voorde et al., 1994).

In the human circulation, histamine elicits a fall in peripheral resistance mediated by both histamine H_1 and H_2 receptors. This action of histamine on isolated human blood vessels has been analysed mainly in large- and medium-caliber conduit arteries (Levi et al., 1991). These vessels do not, however, play a substantial role in the regulation of vascular resistance. The present study aimed to analyse the effects of histamine on an isolated small human artery. Small arteries isolated from subcutaneous fat tissue were studied, and histamine was found to be a

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potent relaxant on this preparation. We investigated the receptor types mediating this relaxation and also the contribution of the endothelial relaxing factors, nitric oxide (NO) and prostanoids.

2. Materials and methods

2.1. Preparations

Blood vessels were dissected under the microscope from abdominal wall subcutaneous fat tissue, resected from women during laparotomy for gynaecological reasons. The study was approved by the Ethical Committee of the Medical Faculty of the University of Gent. After removal, the fat tissue was immediately submerged in a cold Krebs–Ringer bicarbonate solution (composition in mmol/l: NaCl 135; KCl 5; $NaHCO_3$ 20; glucose 10; $CaCl_2$ 2.5; $MgSO_4 \cdot 7$ aq 1.3; KH_2PO_4 1.2; EDTA 0.026).

2.2. Tension measurements

Arterial ring segments were isolated from the tissue and mounted in an automated dual small vessel myograph (model 500 A, J.P. Trading, Aarhus, Denmark) using 40 μm diameter stainless steel wires. After mounting, the vessels were allowed to equilibrate for 30 min in the Krebs–Ringer bicarbonate solution, which was continuously bubbled with 95% O_2–5% CO_2 at 37°C. Afterwards, the relationship between passive wall tension and internal circumference was determined for each vessel by an automated procedure (Mulvany and Halpern, 1977). These characteristics allowed the internal circumference of the vessels to be set at a normalized value, L_0, corresponding to 90% of the internal circumference the vessel would have under a passive transmural pressure of 100 mmHg, in order to obtain optimal conditions for active force development (Aalkjaer et al., 1984). Normalized vessel lumen diameter values were calculated as L_0/π (Mulvany and Halpern, 1977). Results of the present study were obtained using vessels with a normalized lumen diameter ranging from 124 to 670 μm. After a second equilibration period of at least half an hour at optimal length, the vessels were contracted 3 times with Krebs–Ringer bicarbonate solution containing 10 μM norepinephrine and 120 mM K^+ (prepared by appropriate equimolar replacement of NaCl by KCl). Vessels failing to produce an active tension equivalent to a pressure of 100 mmHg in response to this stimulus were excluded from the study.

2.3. Experimental protocols

Concentration–response curves for the agonists were made with relaxed preparations (only for histamine) or with preparations precontracted with 1 μM norepinephrine in Krebs–Ringer bicarbonate solution in which K^+ was increased to 30 mM by replacement of Na^+ on an equimolar base. As found in preliminary experiments, increasing the concentration of K^+ was necessary to obtain reproducible and sustained contractions during repeated application of norepinephrine (and many other contracting agonists). Inclusion of K^+ to prevent tachyphylaxis of this preparation was described by Nielsen et al. (1989).

The relaxing effects of cumulative concentrations of acetylcholine (1 nM–10 μM) on stabilized precontracted preparations were assessed. Preparations showing a weak relaxation in response to acetylcholine, indicating damage to the endothelium (McCarthy et al., 1994; Van de Voorde et al., 1997), were excluded. In some experiments, the endothelium was intentionally removed by bubbling the lumen of the vessel with carbogen gas (Spokas and Folco, 1984; Ralevic et al., 1989). To do this, the tip of an L-shaped glass pipette was advanced with a micromanipulator (under microscopic control) into the lumen of the unstretched vessel and used to apply carbogen gas locally for 2 min. Thereafter, the vessel was again stretched to its original preload level. In experiments using histamine receptor agonists, cumulative concentration–response curves were made with stabilized precontracted (norepinephrine 1 μM and K^+ 30 mM) preparations. Histamine receptor antagonists or blockers of NO or prostanoid synthesis were continuously left in contact with the preparations during the indicated time before precontraction and further during the concentration–response curves.

2.4. Drugs and statistics

Acetylcholine chloride, norepinephrine bitartrate, N^G-nitro-L-arginine, indomethacin crystalline, cimetidine crystalline, pyrilamine maleate were all obtained from Sigma (St. Louis, MO, USA), 2-pyridylethylamine dihydrochloride and dimaprit dihydrochloride were gifts from Smith-Kline Beecham Pharmaceuticals (Genval, Belgium). All concentrations are expressed as final molar concentrations. Concentration–response curves were made by cumulative addition of a small volume (100 μl) into the experimental chamber (10 ml). Stock solutions were made in water except for indomethacin, which was dissolved in ethanol. All solutions were freshly prepared from appropriate stock solutions.

Relaxations are expressed as a percentage of the active wall tension obtained with norepinephrine 1 μM and K^+ 30 mM. The data are expressed as means $\pm$ S.E.M. Statistical significance was evaluated using Student's *t*-test for paired observations. The variable *n* indicates the number of vessels studied.

3. Results

3.1. Effects of histamine

The addition of increasing concentrations of histamine to non-precontracted preparations did not elicit a contrac-

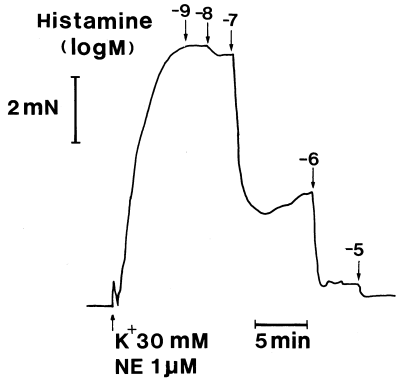

Fig. 1. Original tracing of an experiment in which the influence of increasing molar concentrations of histamine was investigated on an isolated human subcutaneous small artery (normalized diameter 299 μm) precontracted with a mixture of K^+ 30 mM and norepinephrine 1 μM.

tion ($n = 5$). On precontracted preparations, histamine consistently induced a potent concentration-dependent relaxation. An original recording of such an experiment is presented in Fig. 1. In some experiments ($n = 4$), we investigated whether these responses could be reproduced on a second application. It was found that a second application of histamine elicited a concentration–response curve similar to the one obtained with the first application.

3.2. Influence of histamine antagonists

In these experiments, concentration–relaxation effects of histamine were measured on precontracted preparations before and after incubation with the histamine H_1 receptor antagonist, pyrilamine 10 μM ($K_d = 0.4$ nM), the histamine H_2 receptor antagonist, cimetidine 0.1 mM ($K_d = 0.8$ μM), or a combination of both antagonists. The results of these experiments are summarized in Fig. 2. Incubation of the vessels with cimetidine 0.1 mM for 10 min resulted in a significant inhibition of the relaxation effect of histamine (Fig. 2A). On the other hand, after incubation of the vessels with pyrilamine 10 μM for 10 min, the concentration–relaxation curve for histamine was slightly, but not significantly, shifted to the right (Fig. 2B). In the presence of both antagonists together, the relaxation response to histamine was almost completely blocked (Fig. 2C).

3.3. Effects of histamine-agonists

In these experiments, we investigated the effects of increasing concentrations of the histamine H_1 receptor agonist, 2-pyridylethylamine, and the histamine H_2 receptor agonist, dimaprit, on precontracted preparations. The results of these experiments are summarized in Fig. 3. Both agonists clearly elicited a relaxing effect.

3.4. Removal of the endothelium

In these experiments, we investigated the effects of increasing concentrations of histamine, 2-pyridylethylamine and dimaprit on precontracted preparations before and after removal of the endothelium by bubbling the lumen of the preparations for 2 min with carbogen gas. The effectiveness of the procedure was evaluated by measuring the loss of relaxation in response to acetylcholine or bradykinin, two agonists that exert their relaxing effect through endothelium-mediated mechanisms (McCarthy et al., 1994; Knock and Poston, 1996; Van de Voorde et al., 1997). On preparations showing no or almost no relaxation in response to acetylcholine or bradykinin, histamine still elicited a strong relaxation that was, however, significantly less pronounced than on control preparations with endothelium (Fig. 3A). The relaxing effect of the histamine H_1 receptor agonist, 2-pyridylethylamine, but not that of the histamine H_2 receptor agonist, dimaprit, was impaired after removal of the endothelium (Fig. 3B,C).

3.5. Influence of inhibition of NO and prostanoid synthesis

In one series of experiments, concentration–relaxation effects of histamine were measured on precontracted

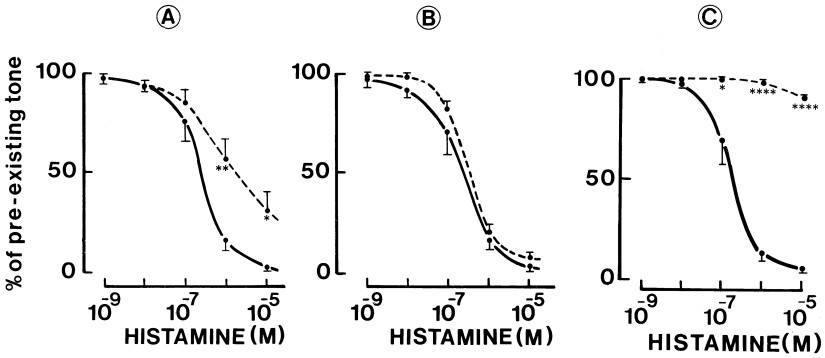

Fig. 2. Relaxation effects (in percentage of active tension with norepinephrine 1 μM and K^+ 30 μM) of increasing molar concentrations of histamine on human subcutaneous arteries in the absence (●—●) or presence (●- - -●) of cimetidine 0.1 mM ($n = 6$) (A), pyrilamine 10 μM ($n = 8$) (B), or a mixture of cimetidine 0.1 mM and pyrilamine 10 μM ($n = 4$) (C) ($* P < 0.05$; $** P < 0.02$; $*** P < 0.001$).

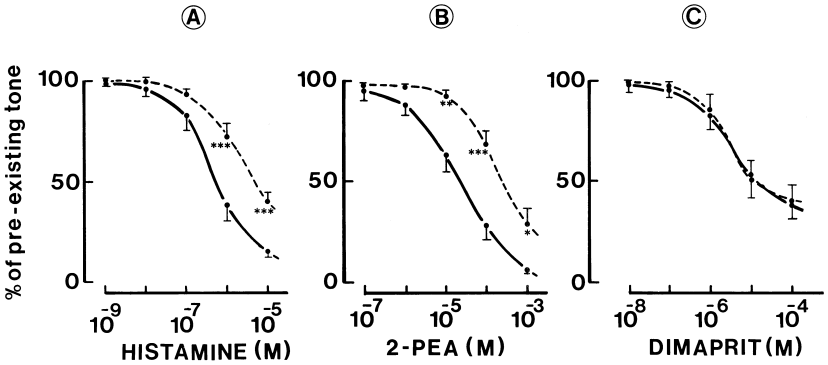

Fig. 3. Relaxation effects (in percentage of active tension with norepinephrine 1 μM and K^+ 30 μM) of increasing molar concentrations of histamine ($n = 11$) (A), 2-pyridylethylamine ($n = 9$) (B) and dimaprit ($n = 8$) (C) on human subcutaneous arteries before (●—●) and after (●- - -●) removal of the endothelium. ($* P < 0.05$; $* * P < 0.02$; $* * * P < 0.01$).

preparations before and after incubation (10 min) with the NO synthase inhibitor, nitro-L-arginine 0.1 mM, for 10 min. At this concentration, nitro-L-arginine significantly inhibited the response to histamine (Fig. 4A).

In another series of experiments, concentration–relaxation curves for 2-pyridylethylamine and dimaprit were made before and after incubation of the preparations with nitro-L-arginine 0.1 mM (10 min) and thereafter with both nitro-L-arginine and indomethacin (10 μM, 20 min). The concentration–response curve of 2-pyridylethylamine was shifted slightly to the right by nitro-L-arginine. Additional blockade of prostanoid synthesis with indomethacin did not further influence the response (Fig. 4B). The concentration–response curve of dimaprit was not shifted to the right by nitro-L-arginine and indomethacin, but to the left instead (Fig. 4C).

Concentration–response curves for histamine were made in a separate series of experiments, first after incubation of the preparations with cimetidine 100 μM (10 min), thereafter with cimetidine and nitro-L-arginine (0.1 mM, 10 min) and finally with a combination of cimetidine, nitro-L-arginine and indomethacin (10 μM, 20 min). The results are presented in Fig. 4D. The cimetidine-resistant relaxation induced by histamine was found to be significantly inhibited by nitro-L-arginine. No further inhibition was obtained with indomethacin.

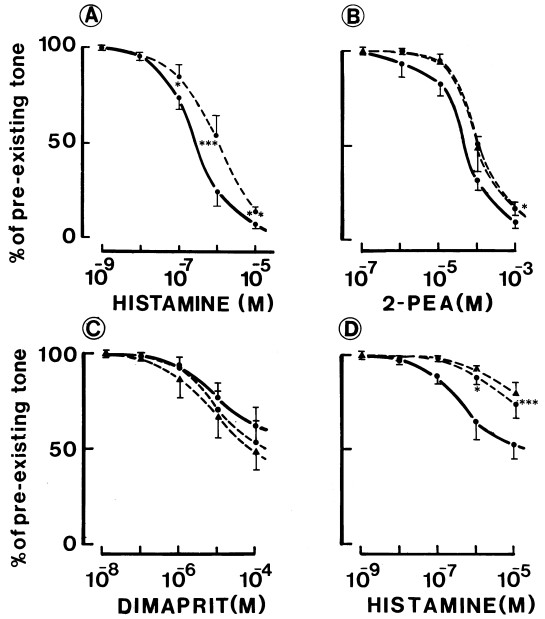

Fig. 4. Relaxation effects (in percentage of active tension with norepinephrine 1 μM and K^+ 30 μM) of increasing molar concentrations of (A) histamine in the absence (● ——— ●) and presence (●- - -●) of nitro-L-arginine (100 μM) ($n = 6$) (B) 2-pyridylethylamine in the absence of any blocker (● ——— ●), in the presence of nitro-L-arginine (100 μM) (●- - -●) and in the presence of nitro-L-arginine (100 μM) and indomethacin (10 μM) (▲ - - - ▲) ($n = 5$) (C) dimaprit in the absence of any blocker (● ——— ●), in the presence of nitro-L-arginine (100 μM) (●- - -●) and in the presence of nitro-L-arginine (100 μM) and indomethacin (10 μM) (▲- - -▲) ($n = 5$) (D) histamine in the presence of cimetidine (100 μM) (●—●), in the presence of cimetidine (100 μM) and nitro-L-arginine (100 μM) (●- - -●) and in the presence of cimetidine (100 μM), nitro-L-arginine (100 μM) and indomethacin (10 μM) (▲- - -▲) ($n = 6$) ($* P < 0.05$; $* * P < 0.02$; $* * * P < 0.01$).

4. Discussion

Histamine is an autacoid with an established physiological role in the regulation of gastric acid secretion and as neurotransmitter in the central nervous system (Babe and Serafin, 1996). In the cardiovascular system, histamine might also have a role in the regulation of microcirculatory homeostasis (Schayer, 1965). The physiological role of histamine in the regulation of vascular tone, however, remains to be fully established. On the other hand, its role in pathological situations, such as the 'triple response' in the skin and anaphylactic shock, is well accepted (Babe and Serafin, 1996) and so is the rationale for the use of histamine receptor antagonists as drugs in the treatment of these vascular disturbances.

The present study aimed to analyse the influence of histamine on small arteries isolated from human subcutaneous fat tissue. On these small blood vessels, histamine

behaves as a very potent relaxant, eliciting almost complete relaxation. Histamine elicits a relaxation that is much more pronounced than the relaxations we found with acetylcholine and bradykinin on the same preparation (Van de Voorde et al., 1997).

In general, histamine relaxes vascular smooth muscle cells through activation of both histamine H_1 and H_2 receptors. To reveal the receptor type(s) involved in the histamine-induced relaxation of human subcutaneous small arteries, experiments were performed using histamine receptor agonists and antagonists. The data provide evidence that both receptor types are involved.

The involvement of histamine H_2 receptors is the most evident since the histamine H_2 receptor antagonist, cimetidine, significantly inhibited the histamine-induced relaxation. The involvement of histamine H_2 receptors is further substantiated by the observation that the selective histamine H_2-receptor agonist, dimaprit, elicited relaxation of precontracted preparations.

Demonstration of the involvement of histamine H_1 receptors in histamine-induced relaxation was more difficult. The histamine H_1 receptor antagonist, pyrilamine, was found to have only a slight inhibitory influence on histamine-induced relaxation. However, a potent relaxation caused by activation of the remaining histamine H_2 receptors may have masked the presence of histamine H_1 receptors in this preparation. That histamine H_1 receptors are involved is evidenced by the observation that the histamine H_1 receptor agonist, 2-pyridylethylamine, elicited relaxation of precontracted preparations. It should, however, be mentioned that 2-pyridylethylamine is not very selective as a histamine H_1 receptor agonist. As yet, no potent and selective histamine H_1 receptor agonists are available (Hill et al., 1997). The involvement of histamine H_1 receptors is more convincingly substantiated by the observation that the relaxation remaining after blockade of the histamine H_2 receptors with cimetidine is completely blocked by the histamine H_1 receptor antagonist, pyrilamine.

The biological actions of histamine result, not only from activation of histamine H_1 and H_2 receptors, but also from activation of histamine H_3 receptors (Leurs et al., 1995). Histamine H_3 receptors are mainly found on neuronal tissue, but some observations suggest that they are also present on vascular tissue (Ishikawa and Sperelakis, 1987; Ea-Kim et al., 1992). Considering the total block of histamine-induced relaxation by the combination of a histamine H_1 and a H_2 receptor antagonist, the involvement of histamine H_3 receptors in this effect is unlikely.

Changes in vascular tone elicited by histamine result from interaction with histamine receptors, which are located on smooth muscle and/or endothelial cells (Van de Voorde and Leusen, 1983; Leusen and Van de Voorde, 1988; Levi et al., 1991). To determine whether endothelial cells contribute to the relaxing effect of histamine on human subcutaneous vessels, the effects of histamine were compared before and after removal of the endothelium. While removal of the endothelium results in almost complete loss of the relaxation in response to acetylcholine and bradykinin (Van de Voorde et al., 1997), the relaxing effect of histamine is only slightly diminished. This indicates that the major relaxing effect is due to direct activation of receptors on the smooth muscle cells. These receptors are histamine H_2 receptors. This can be concluded from the results obtained with the receptor agonists. The histamine H_2 receptor agonist, dimaprit, elicited a similar relaxation effect on preparations both with and without endothelium. The histamine H_2 receptor mediated component of histamine-induced relaxation thus relies on a direct action on the smooth muscle cells. Such an effect is known to be coupled to adenylate cyclase activation (Leurs et al., 1995). In contrast to the histamine H_2 receptor-mediated effect, the histamine H_1 receptor-mediated relaxation elicited by 2-pyridylethylamine was significantly less in preparations without endothelial cells. This indicates that the histamine H_1 receptor-induced effect is mediated by the endothelium. This fits with the concept that endothelial modulation of vascular tone is mostly mediated by histamine H_1 receptors (Levi et al., 1991). The rather slight influence of endothelial removal on histamine-induced relaxation is also in line with the limited influence of histamine H_1 receptor antagonism and indicates a predominant relaxing influence of histamine H_2 receptor activation.

The relaxing influence of endothelial cells on the underlying smooth muscle cells relies on the release of various relaxing factors. Nitric oxide, formed through enzymatic conversion of L-arginine by NO synthase, is considered as the most important of these factors. Besides nitric oxide, prostanoids and an endothelium-derived hyperpolarizing factor, the chemical nature of which is still unknown, are also known as endothelial relaxing factors modulating vascular tone (Vane et al., 1990; Cohen and Vanhoutte, 1995).

Nitric oxide (Akar et al., 1994), prostanoids (Alhencgelas et al., 1982) and the endothelium-derived hyperpolarizing factor (Chen and Suzuki, 1989) are all known to be released from endothelial cells in response to histamine. Under our experimental conditions, the potential involvement of the endothelium-derived hyperpolarizing factor was masked since our preparations were contracted with 30 mM K^+. This was in our hands essential to obtain a stable and reproducible level of contraction of the human subcutaneous arteries, but this blocks the action of the endothelium-derived hyperpolarizing factor (Chen and Suzuki, 1989). Nitric oxide seems to be responsible for the histamine H_1 receptor-mediated endothelial relaxing influence seen in our experiments. This conclusion is based on the observations that the 2-pyridylethylamine-induced relaxation rather than the dimaprit-induced relaxation is blocked by the NO synthase inhibitor, nitro-L-arginine, and that the cimetidine-resistant relaxation in response to histamine, thus representing the histamine H_1 receptor-in-

duced relaxation, is impaired in the presence of nitro-L-arginine. Additional inhibition of prostanoid synthesis with indomethacin did not further impair the response, indicating that prostanoids do not contribute to the endothelial relaxing influence.

The relaxation obtained with 2-pyridylethylamine on endothelium-denuded preparations might suggest that histamine H_1 receptors inducing relaxation are present on vascular smooth muscle cells. However, as already mentioned, 2-pyridylethylamine is not very selective as a histamine H_1 receptor agonist. Moreover, histamine H_1 receptors on vascular smooth muscle cells are known to mediate only contraction (Levi et al., 1991; Hill et al., 1997).

The presence of a histamine H_1 receptor on the smooth muscle cells mediating contraction is unlikely. Histamine does not elicit contraction of relaxed preparations. More convincingly, no further contraction is seen with histamine on precontracted preparations in which the relaxing histamine H_2 receptors are blocked, and in which the release of endothelial relaxing factors is blocked.

5. Conclusion

We can conclude from the present study that histamine elicits a potent relaxing influence on isolated human subcutaneous small arteries, and that most probably, both a direct activation of muscular histamine H_2 receptors and activation of endothelial histamine H_1 receptors, leading to the release of nitric oxide, contribute to the relaxation.

Acknowledgements

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