

The possible involvement of hyperpolarizing mechanisms in histamine-induced relaxation of the rat portal vein

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Abstract

The present study evaluated the effects of histamine 10^{-2} M on longitudinal preparations of rat portal vein. It was observed that histamine 10^{-2} M induced relaxation of rat portal vein preparations pre-contracted with phenylephrine 10^{-4} M. On the other hand, no pharmacological effects were observed in preparations not pre-contracted. The observed histamine-induced relaxing effect was absent in preparations pre-contracted with KCl (120 mM) or in the presence of depolarizing nutritive solution. However, the histamine-induced relaxation was still present in the endothelium-removed preparations. The histamine-induced relaxation also was not prevented by astemizole (10^{-6} M, 10^{-5} M and 10^{-4} M), cimetidine (10^{-5} M, 10^{-4} M and 10^{-3} M) or thioperamide (10^{-6} M, 10^{-5} M and 10^{-4} M), selective antagonists H_1 , H_2 and H_3 , respectively. The presence of L-NAME 10^{-4} M or L-NAME 10^{-4} M plus indomethacin 10^{-5} M also did not prevent the histamine-induced relaxation observed in rat portal vein. Thus, the histamine-induced relaxation observed in rat portal vein appears to involve a non-endothelial hyperpolarizing mechanism independent of H_1 , H_2 and H_3 receptors.

Key words: endothelium, histamine, hyperpolarizing mechanism, portal vein, relaxation

Introduction

Histamine may present different vascular responses depending on the vascular territory. Such pharmacological features result from its action upon different receptor subtypes, located either in smooth muscle or in endothelial cells (Hill *et al.*, 1997). Several studies have suggested that histamine induces endothelium-dependent relaxation by stimulation of H_1

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receptors in many arterial beds of different animal species such as rat thoracic aorta (Van de Voorde and Leusen, 1983) and mesenteric arterial bed (Adeagbo and Oriowo, 1998; Jin *et al.*, 2006), guinea-pig pulmonary artery (Abacioglu *et al.*, 1987) and gastrointestinal arterioles (Beyak and Vanner, 1995), isolated monkey and dog coronary arteries (Toda, 1986) and bovine retinal arteries (Benedito *et al.*, 1991). Stimulation of H_1 receptor also evoked endothelium-dependent relaxation in human cranial (Jansen-Olesen, 1997) and subcutaneous resistance arteries (Van de Voorde *et al.*, 1998). In addition, H_2 -mediated nitric oxide release was described in a culture of pig endothelial cells (Kishi *et al.*, 1998). Endothelium nitric oxide (NO)-dependent relaxation induced by histamine through the stimulation of the receptor H_1/H_2 has also been suggested in guinea-pig coronary arteries (Pierpaoli *et al.*, 2003). Moreover, endothelium-mediated relaxation induced by stimulation of H_3 receptors has been suggested in rabbit cerebral arteries (Ea Kim *et al.*, 1992) and cat hind-limb vascular bed (Champion and Kadowitz, 1997).

Moreover, histamine may induce vasoconstriction through stimulation of H_1 located in the vascular smooth muscle cells of monkey coronary arteries (Toda, 1986) and human cranial arteries (Jansen-Olesen, 1997). On the other hand, endothelium-independent vascular relaxation following stimulation of H_2 receptor located in vascular smooth muscle cells has been suggested in isolated monkey and dog coronary (Toda, 1986) and mesenteric arteries (Okamura *et al.*, 1994), guinea-pig pulmonary artery (Abacioglu *et al.*, 1987) and human cranial (Jansen-Olesen *et al.*, 1997) and subcutaneous resistance arteries (Van de Voorde *et al.*, 1998).

Most studies on cardiovascular actions of histamine, like these previously cited, have been done in arterial beds. However, histamine also evokes equivalent vascular actions in the venous bed (Matsuki and Ohhashi, 1990; Dachman *et al.*, 1994; Okamura *et al.*, 1994). On the other hand, it has been described that histamine at concentrations up to 10^{-4} M induces only a minimal contraction of rat Wistar isolated portal vein (Cohen and Wiley, 1977; Högestätt *et al.*, 1986), which may indicate the absence of functional histamine receptors in this preparation as suggested in rat hepatic vascular smooth muscle (Shibamoto *et al.*, 2004).

In another manner, in a preliminary experiment, we have occasionally observed that high concentrations of histamine (10^{-3} to $\geq 10^{-1}$ M) induce relaxation of isolated longitudinal rat portal vein pre-contracted with phenylephrine 10^{-4} M. Although this effect occurred at high concentrations, we decided to study it, since unknown histamine-activated mechanisms, perhaps non-receptor-mediated, may be disclosed. Such knowledge may help us to interpret the concentration-response curves obtained in isolated vascular preparations challenged with histamine, especially at its upper points. Moreover, a massive release of histamine may be involved in circulatory collapses that may be observed in individuals with mastocytosis, a group of disorders characterized by pathologic increase of mast cells in tissues including skin, bone marrow, liver, spleen, and lymph nodes (Longley *et al.*, 1995; Droogendijk *et al.*, 2006; Escribano *et al.*, 2006) and anaphylaxis (Ogawa and Grant, 2007). Such circulatory collapses may be more severe in individuals with impaired enzymatic histamine degradation (Maintz and Novak, 2007). The circulatory collapses consequent to a massive histamine release may also aggravate the local accumulation of histamine since it may reduce the movement of molecules following the blood flow. Thus, in vascular territories where such vascular disturbances occur,

excessive histamine concentration may induce pharmacological effects similar to those observed in our experiments.

Thus, the present study aimed to investigate the histamine induced-relaxation of rat portal vein focusing on the histamine receptors involved in local regulatory mechanisms.

Methods

Animals

Male Wistar rats weighing 350–400 g were used according to instructions of the Guide for the Care and Use of Laboratory Animals, National Academy of Sciences (1996). This study was also approved by the Research Ethics Committee of the Faculty of Medicine of Marília. Rats were housed in groups of five animals per cage and received food and water *ad libitum*. Animals were kept under a 12 h light-dark cycle and at 25°C room temperature.

Organ bath studies

The animals were anesthetized with tribromoethanol (250 mg/kg, *i.p.*) and exsanguinated. Next, portal veins were carefully removed and cleared of all connective tissues. These portal veins were cut into strips (10–15 mm) and set longitudinally in 10 ml organ baths, fixed to a lower stainless steel hook attached to a stationary support and to an upper one connected to an isometric force recording transducer. Each organ bath contained Krebs-Henseleit solution of the following composition (mM): NaCl 130; KCl 4.7; CaCl₂ 1.6; KH₂PO₄ 1.2; MgSO₄ 1.2; NaHCO₃ 15 and glucose 11.1. The nutritive solution, pH 7.4, was kept at 37°C and continuously bubbled with a 95% CO₂ and 5% O₂ mixture. Contractions were recorded using a polygraph (Ugo Basile, Italy). Prior to the addition of drugs, preparations were equilibrated for 60 min under a resting tension of 0.5 g. To investigate the histamine-induced relaxation in the absence of vascular endothelium, some preparations were perfused sequentially with Krebs-Henseleit solution (1 ml), sodium deoxycolate 1% (2.5 ml) and Krebs-Henseleit solution (1 ml). The effectiveness of this procedure was confirmed by histological analysis. The actions of histamine were also studied in preparations treated for 20 min with L-NAME 10⁻⁴ M and indomethacin 10⁻⁵ M (added in the organ bath), inhibitors of nitric oxide synthase (NOS) and cyclooxygenase (COX), respectively. Similarly, preparations were studied in the presence of astemizole (10⁻⁶ M, 10⁻⁵ M and 10⁻⁴ M), cimetidine (10⁻⁵ M, 10⁻⁴ M and 10⁻³ M) and thioperamide (10⁻⁶ M, 10⁻⁵ M and 10⁻⁴ M), antagonists H₁, H₂ and H₃, respectively (Janssen and Sims, 1993; Monge *et al.*, 1997; Adeagbo and Oriowo, 1998). Some preparations were also studied in depolarizing nutritive solution (Krebs-Henseleit solution containing KCl 60 mM offset by an equimolar NaCl reduction) to verify the participation of hyperpolarizing mechanisms in the responses of the rat portal vein preparations to histamine.

In preliminary experiments it was observed that longitudinal preparations of rat portal veins stimulated with phenylephrine 10⁻⁴ M present a somewhat unstable plateau, presenting a small spontaneous relaxation across the time period. The administration of high histamine concentrations (10⁻³ to $\geq$ 10⁻¹ M) during this plateau induces a concentration-dependent relaxation. But despite administering histamine on an exponential scale, the obtained

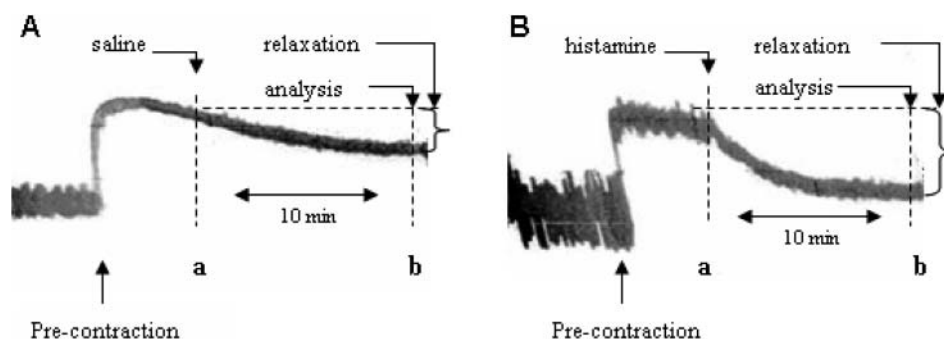


Fig. 1. Typical register obtained in preparations of rat portal vein challenged with vehicle (A) or histamine 10^{-2} M (B) 4 min after the pre-contractile stimulus (phenylephrine 10^{-4} M). Point "a" represents the moment when the drug or vehicle were administrated and point "b" represents the moment when the relaxation was analyzed. } indicates the relaxation, calculated by the difference of vascular tonus detected between the moment of histamine or saline administration and 10 min later.

concentration-response curve did not present a sigmoidal form, which probably indicates that the histamine relaxing effect is superposed to the spontaneous relaxation. Based on these observations, 10^{-2} M was chosen as a concentration of histamine that produces the typical histamine-induced relaxation to be investigated in the present study. In this manner, the data were collected according to the following scheme of drug administration: the preparations were pre-contracted with phenylephrine 10^{-4} M or KCl 120 mM. After 4 min if a characteristic plateau was evident, the preparations were challenged with histamine at 10^{-2} M. The difference in vascular tonus detected between the moment of histamine administration and 10 min later, expressed as the percentage of phenylephrine or KCl-induced pre-contraction (histamine-induced relaxation) was compared with the difference in vascular tonus detected between the moment of saline administration and 10 min later (spontaneous relaxation). Points representing the moment when the drug or saline were administrated (point "a") and when the relaxation were analyzed (point "b") are schematically shown in the Fig. 1.

Experimental design

First of all, the effects of histamine 10^{-2} M were characterized in preparations pre-contracted or not with phenylephrine 10^{-4} M. The second step consisted of verifying whether either the agent chosen to induce pre-contraction or the presence of endothelium influence the histamine-induced relaxation. In the third step the involvement of H_1 , H_2 and H_3 receptors in histamine-induced relaxation was investigated in preparations of rat portal vein. Finally, the fourth step studied participation of NO, prostanoids or hyperpolarizing mechanisms in histamine-induced relaxation.

Chemicals

The following drugs were used: N^G-monomethyl-L-arginine (L-NAME), L-phenylephrine hydrochloride, 1-[p-chlorobenzoyl]-5-methoxy-2-methylindole-3-acetic acid (indomethacin), 1-(4-

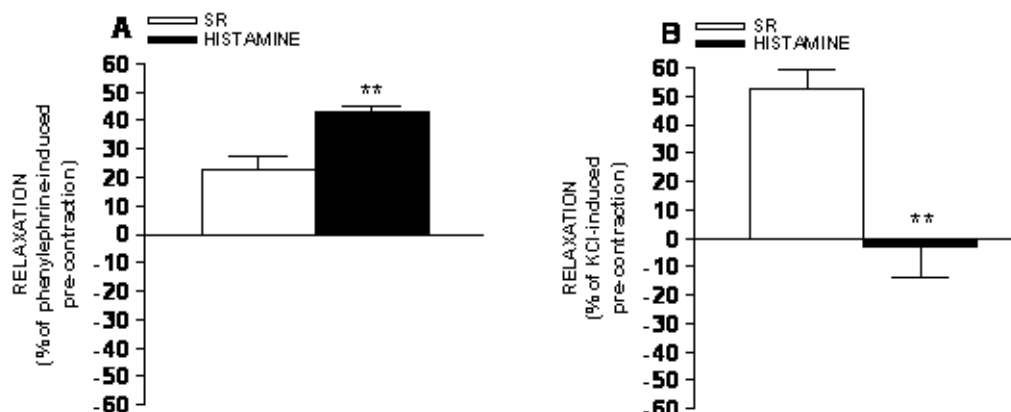


Fig. 2. Relaxation observed in longitudinal preparations of rat portal vein pre-contracted with phenylephrine 10^{-4} M (A) and KCl 120 mM (B) not challenged (spontaneous relaxation - SR; open bar) or challenged with histamine 10^{-2} M (filled bar). Bars represent the mean $\pm$ SEM of 6 independent determinations. **, $P < 0.01$ (Student's *t*-test).

Fluorobenzyl)-2-(1-[4-methoxyphenethyl]piperidin-4-yl) aminobenzimidazole (astemizole), histamine dihydrochloride and thioperamide maleate, purchased from Sigma Chemical Co. (USA) and 2,2,2-tribromoethanol purchased from Acros Organics (USA) and cimetidine (free base) purchased from Galena Química e Farmacêutica Ltda.

Statistical analysis

Data are reported as mean $\pm$ standard error of the mean (SEM). The relaxations induced by histamine 10^{-2} M, expressed as pre-contraction percentage, were evaluated by Student's *t* test for comparison between 2 groups or Analysis of Variance (one way or two ways ANOVA followed by Bonferroni as post-test) for comparisons among more than 3 groups. *P* values less than 0.05 were considered statistically significant.

Results

Longitudinal preparations of rat portal vein stimulated with phenylephrine 10^{-4} M showed a somewhat unstable plateau, presenting a small spontaneous relaxation across the time period (Fig. 1A). Histamine at 10^{-2} M administered during this plateau induced a significant relaxation (Figs. 1B and 2A). However, in preparations pre-contracted with KCl 120 mM, histamine 10^{-2} M did not produce significant relaxation. Moreover, in the preparations pre-contracted with KCl 120 mM, histamine 10^{-2} M reversed the spontaneous relaxation (Fig. 2B). Histamine 10^{-2} M administered in rat portal vein set in depolarizing nutritive solution, instead of relaxation (Fig. 3A), produced a significant contraction expressed as negative relaxation in Fig. 3B. On the other hand, histamine 10^{-2} M induced relaxation significantly greater than the spontaneous relaxation in either intact or removed endothelium of rat portal vein preparations (Fig. 4).

The treatment of rat portal vein with astemizole 10^{-6} M and 10^{-5} M was not effective in preventing histamine-induced relaxation. In preparations treated with astemizole 10^{-4} M the

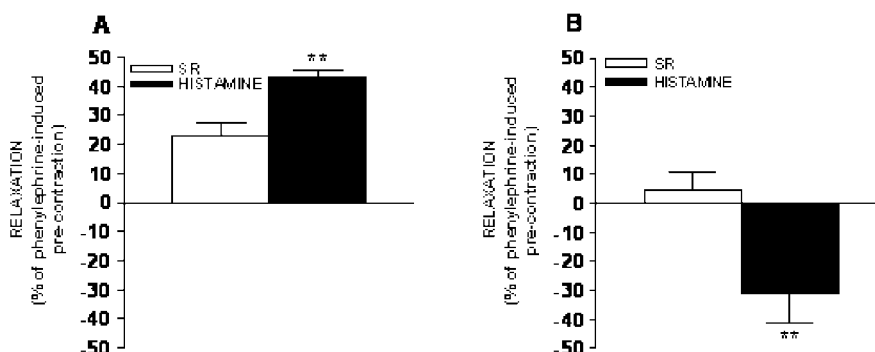


Fig. 3. Relaxation observed in longitudinal preparations of rat portal vein pre-contracted with phenylephrine 10^{-4} M, in presence of standard nutritive solution (A) or depolarizing nutritive solution (Krebs-Henseleit containing KCl 60 mM) (B), not challenged (spontaneous relaxation (SR), open bar) or challenged with histamine 10^{-2} M (filled bar). Bars represent the mean $\pm$ SEM of 6 independent determinations. **, $P < 0.01$ (Student *t* test).

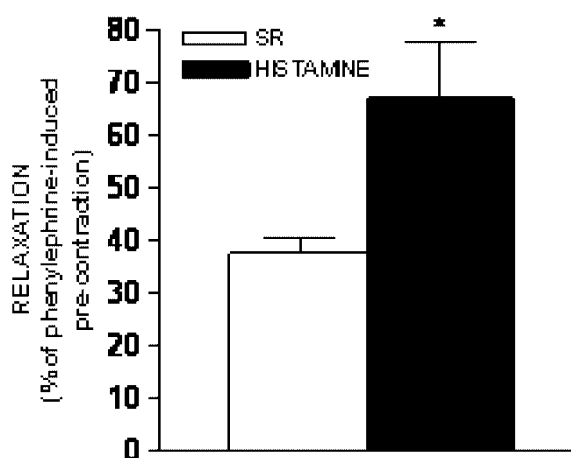


Fig. 4. Relaxation observed in endothelium removed longitudinal preparations of rat portal vein pre-contracted with phenylephrine 10^{-4} M, not challenged (spontaneous relaxation (SR), open bar) or challenged with histamine 10^{-2} M (filled bar). Bars represent the mean $\pm$ SEM of 6 independent determinations. *, $P < 0.05$ (Student *t* test).

histamine-induced relaxation was increased even more (Fig. 5A). Moreover, the histamine-induced relaxation was observed also in preparations treated with cimetidine (10^{-5} M, 10^{-4} M and 10^{-3} M; Fig. 5B) and thioperamide (10^{-6} M, 10^{-5} M and 10^{-4} M; Fig. 5C). This histamine-induced relaxation also occurred in the presence of L-NAME 10^{-4} M or L-NAME 10^{-4} M plus indomethacin 10^{-5} M (Fig. 6).

Discussion

The present study demonstrates that a high concentration of histamine relaxes longitudinal

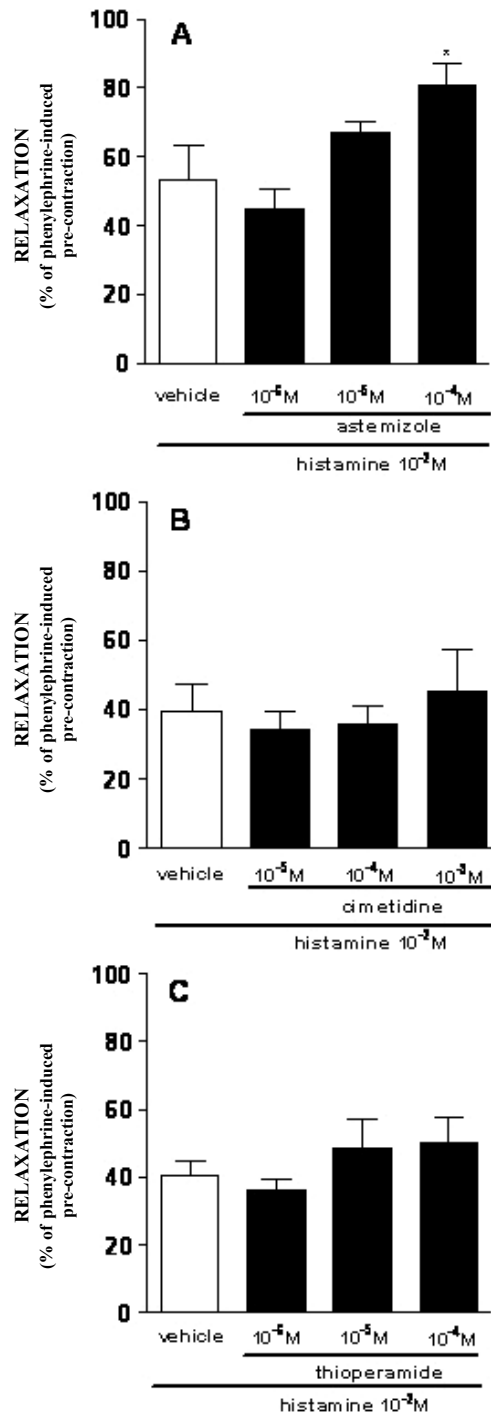


Fig. 5. Relaxation induced by histamine 10^{-2} M in longitudinal preparations of rat portal vein pre-contracted with phenylephrine 10^{-4} M, in absence (open bar) or in presence (filled bars) of different concentrations of astemizole (A), cimetidine (B) or thioperamide (C). Bars represent the mean $\pm$ SEM of 6 independent determinations. *, $P < 0.05$ (one way ANOVA followed by Bonferroni as post test).

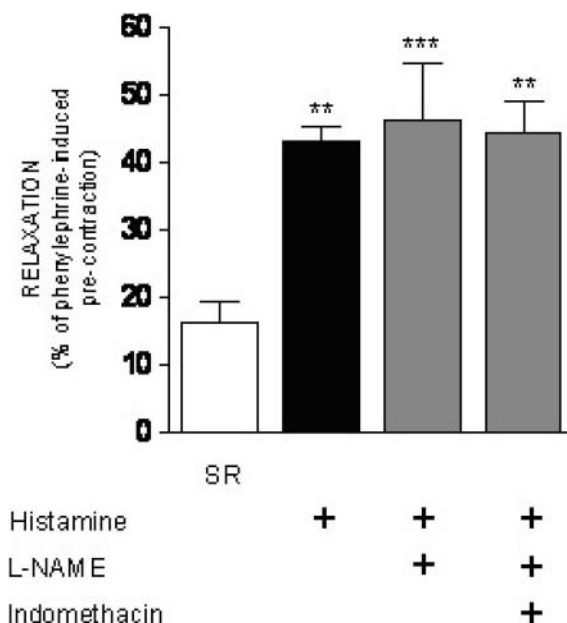


Fig. 6. Spontaneous relaxation (SR) and relaxation induced by histamine 10^{-2} M in longitudinal preparations of rat portal vein pre-contracted with phenylephrine 10^{-4} M, in absence or in presence of L-NAME 10^{-4} M and L-NAME 10^{-4} M plus indomethacin 10^{-5} M. Bars represent the mean $\pm$ SEM of 6 independent determinations. **, $P < 0.01$; ***, $P < 0.001$, related to the SR (one way ANOVA followed by Bonferroni as post test).

preparations of rat portal vein pre-contracted with phenylephrine. Preliminary results suggest that this histamine-induced relaxation is concentration-dependent. However, according to the reasons previously shown, a single intermediate dose of histamine was chosen to make all the comparisons. On the other hand, in the absence of pre-contraction, no pharmacological effects were detected in such preparations (data not shown), which suggests that this range of histamine concentrations produces relaxation but not contraction in longitudinal preparations of rat portal vein. No pharmacological effects were also observed in preparations, either pre-contracted or not pre-contracted, challenged with histamine under 10^{-3} M (data not shown). Thus, this histamine-induced relaxation observed in longitudinal preparations of rat portal vein occurs only in high concentrations. Moreover, the observed histamine-induced relaxation was reversible. Preparations challenged with histamine 10^{-2} M, after nutritive solution substitution, exhibited the same pattern of either phenylephrine-induced pre-contraction or histamine 10^{-2} M-induced relaxation if challenged again.

The interpretation of these results obtained in functional studies of isolated vascular preparations implies the description of pharmacological mechanisms involved in the observed vasomotor response. Frequently, an observed functional response involves several pharmacological mechanisms that interact reciprocally, resulting in synergisms and/or antagonisms. This problem is even more frequent in preparations treated with high concentrations of pharmacological agents. Given that the rat portal vein apparently does not

respond to histamine at lower concentrations, it was possible to show evidence that its actions are related to high concentrations. Such knowledge may help the interpretations of the concentration-response curves, especially at the upper points, obtained from vascular preparations.

In the literature reviewed by Hirasuna *et al.* (1979) it is suggested that unusual levels of histamine may be reached in the blood of patients with myeloproliferative diseases. According to these authors, it can be found reports of more than 0.1 mg per dl and as high as 2 mg of histamine expressed as free base per dl of whole blood. The relaxation observed in the present study occurred in concentrations up to 10^{-3} M or 18.4 mg of histamine per dl of Krebs-Henseleit. Considering that Hirasuna *et al.* (1979) reported concentrations of histamine determined in the blood, it may be lower relatively to the concentration of histamine reached in the tissues where it was produced. In this way, we suppose that the concentration of histamine in these proliferated tissues may be as high as the histamine accumulated in the longitudinal preparations of rat portal vein assessed in the presented experiments. Moreover, a massive release of histamine may be involved in the circulatory collapses that may be observed in individuals with mastocytosis, a group of disorders characterized by pathologic increase of mast cells in tissues including skin, bone marrow, liver, spleen, and lymph nodes (Longley *et al.*, 1995; Droogendijk *et al.*, 2006; Escribano *et al.*, 2006) and by anaphylaxis (Ogawa and Grant, 2007). Such circulatory collapses may be more severe in individuals with impaired enzymatic histamine degradation (Maintz and Novak, 2007). The local accumulation of histamine may also be aggravated by the histamine-induced circulatory collapses since its transference to the adjacent tissues following the blood flow may be interrupted by such collapses. In these extreme situations, the vasomotor actions of histamine may involve mechanisms similar to those observed in the present study. Indeed, the mechanisms investigated in the present study may also be useful in the therapeutic management of these conditions.

In this way, the particularities of histamine actions in rat portal vein were explored. In preparations pre-contracted with KCl, histamine did not induce relaxation. This observation indicates that the histamine-induced relaxation observed in rat portal vein is dependent on the pre-contraction agent utilized, in agreement with previous studies showing that the type of pre-contraction may influence the agonist-induced relaxation of rat mesenteric artery (Plane and Garland, 1996) and rat aorta (Streefkerk *et al.*, 2002).

The absence of histamine-induced relaxation in preparations pre-contracted with KCl also suggests the involvement of hyperpolarizing mechanisms. Furthermore, the absence of relaxation observed in preparations set in depolarizing nutritive solution corroborates the involvement of hyperpolarizing mechanisms in the histamine actions upon the rat portal vein. In fact, it has been proposed that hyperpolarizing mechanisms are suppressed in the presence of a high K^+ concentration (Zygmunt *et al.*, 1994; Gerber *et al.*, 1998; Yousif *et al.*, 2003). Interestingly, in the presence of depolarizing nutritive solution, a small histamine-induced contraction was observed, which suggests the coexistence of other histamine-activated contractile mechanisms, supplanted by the hyperpolarizing ones in the presence of high concentrations of histamine. These supposed histamine-activated contractile mechanisms appear to be also evident in preparations pre-contracted with KCl which present marked

spontaneous relaxations. In these preparations pre-contracted with KCl, we observed not only a reversion of the histamine-induced relaxation to the control spontaneous relaxations level but also a slight histamine-induced contraction.

The involvement of hyperpolarizing mechanisms in histamine-induced relaxation also has been observed in pulmonary (Hasunuma *et al.*, 1991), mesenteric (Yousif *et al.*, 2003) and renal (Yousif, 2005) arterial bed, pulmonary artery (Chen and Suzuki, 1989a, 1989b; Torok, 2000) and rat thoracic aorta (Chen and Suzuki, 1989b) and human mesenteric arteries (Tottrup and Kraglund, 2004). These authors suggest the involvement of an endothelium-derived hyperpolarizing factor (EDHF). The present study, however, suggests a non-endothelium-mediated hyperpolarizing mechanism since histamine-induced relaxation was also observed in endothelium-removed preparations. A direct action of histamine in vascular smooth muscle cells was proposed in cat hind-limb vascular bed (Champion and Kadowitz, 1997) and rat mesenteric arterial bed (Adeagbo and Oriowo, 1998).

The results presented here have shown that high concentrations of histamine display relaxing but not contractile actions in longitudinal muscle fibers of rat portal vein. This information complements previous studies reporting only a minimal contraction induced by histamine concentrations up to 10^{-4} M in isolated Wistar rat portal vein (Cohen and Wiley, 1977; Högestätt *et al.*, 1986). In turn, the absence of important effects of histamine in rat portal vein may indicate lack of functional receptors for histamine, as suggested by Shibamoto *et al.* (2004).

The absence of functional receptors was reinforced in the present study because the histamine induced-relaxation was not prevented in the presence of astemizole, cimetidine or thioperamide. Thus, the presented data also suggest that the histamine-induced relaxation is not mediated by H_1 , H_2 or H_3 receptors. Considering the elevated histamine concentrations that produce the observed relaxation, the antagonists were used at the usual concentration (Janssen and Sims, 1993; Monge *et al.*, 1997; Adeagbo and Oriowo, 1998), and at others ten and a hundred times higher. Astemizole 10^{-4} M enhanced, instead of preventing, the histamine-induced relaxation. It suggests that the histamine-induced relaxation may be counterbalanced by H_1 receptor mediated vasoconstriction. In this way, the above proposed contractile mechanism that counterbalances the histamine-induced relaxation may involve H_1 receptors activation. Histamine-induced vasoconstriction involving H_1 receptors stimulation has been described by several authors in different vascular territories (Konishi *et al.*, 1981; Obi *et al.*, 1991; Takagi *et al.*, 1993; Martinez *et al.*, 2006). However, this enhancement of histamine-induced relaxation occurred in presence of astemizole in a concentration a hundred times higher than the usual. In this way, we can not discard astemizole effects not related to the receptor H_1 inhibition upon the histamine-induced relaxation observed in rat portal vein. Other experimental approaches, however, would be necessary to confirm the participation of H_1 receptors in this enhancement of the histamine-induced relaxation.

The involvement of NO has been proposed in the histamine-induced relaxation in mesenteric arterial bed (Jin *et al.*, 2006), mesenteric artery (Adeagbo and Triggle, 1993; Yousif *et al.*, 2003) and pulmonary arteries (Hasunuma *et al.*, 1991) of the rat and coronary arterial bed of the guinea pig (Pierpaoli *et al.*, 2003). In parallel, both NO and prostanoids are involved in the histamine-induced relaxation of bovine retinal arteries (Benedito *et al.*, 1991). Prostanoids

are also involved in the histamine-induced relaxation in dog mesenteric and gastro-epiploic arteries (Toda *et al.*, 1982). However, the involvement of NO as well as prostanoids in the histamine-induced relaxation was discarded in the present study since it is not inhibited in presence of L-NAME or L-NAME plus indomethacin.

In conclusion, the present study suggests that high histamine concentrations induce relaxation of longitudinal preparation of rat portal vein. Such relaxation appears to involve a non-endothelial hyperpolarizing mechanism.

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