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Modified histamine-induced NO-mediated relaxation in resistance arteries in pre-eclampsia

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Abstract

We investigated the characteristic changes in histamine-induced, endothelium-derived nitric oxide (NO)-mediated relaxation in human omental resistance arteries seen in pre-eclampsia. Isometric contraction was provoked by a stable analogue of thromboxane A_2 in endothelium-intact strips from both pre-eclamptic and normotensive pregnant women. Histamine (0.3 nM–10 μM) produced a concentration-dependent relaxation of this contraction in both groups. The magnitude of the relaxation induced by histamine (1 μM) was significantly smaller in pre-eclampsia both in the presence and absence of famotidine (H_2-receptor blocker). In the presence of famotidine, L-N^G-nitroarginine significantly attenuated the histamine-induced relaxation in strips from normotensive pregnant women but not in those from pre-eclamptic women. The relaxation induced by human atrial natriuretic peptide (0.1 nM–1 μM) was also significantly smaller in the pre-eclamptic group. It is concluded that the histamine-induced, endothelium-derived NO-mediated relaxation (mediated via H_1-receptors) is down-regulated in resistance arteries in pre-eclampsia and we suggest that this is due, at least in part, to an attenuation of the action of cyclic GMP in smooth muscle cells.

Keywords: Histamine; Pre-eclampsia; Nitric oxide (NO); Endothelium; ANP (atrial natriuretic peptide); (Human)

1. Introduction

Vascular endothelial cells release vasorelaxing factors, such as nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factor (EDHF), and these play an important role in the regulation of vascular tone, vascular permeability and blood coagulation, thus helping to maintain circulatory homeostasis (Moncada et al., 1991; Garland et al., 1995; Kuriyama et al., 1998). Pre-eclampsia is a common complication in pregnancy, characterized by increases in peripheral vascular resistance and vascular permeability, together with a disturbance of blood coagulation (Lenfant et al., 1990). It has been suggested that an abnormality of endothelial function may be involved in the pathogenesis and/or development of pre-eclampsia (Poston et al., 1995; Sladek et al., 1997). In fact, using isolated human resistance arteries, it has been found that the endothelium derived, NO-dependent relaxation induced by bradykinin and that induced by substance P are both reduced in pre-eclampsia (compared with the response in normotensive pregnant women) (Knock and Poston, 1996; Suzuki et al., 2000a). However, it was recently suggested that whether or not a down-regulation of endothelium-dependent relaxation in resistance vessels is seen in pre-eclampsia depends on the type of receptor responsible for the agonist-induced endothelial cell stimulation (Pascoal et al., 1998). Thus, it remains to be clarified whether the endothelium-dependent relaxations induced by other well-known endothelial stimulants are or are not modified in resistance arteries in pre-eclampsia.

Histamine is present in high concentrations in placental tissues and in the perfused placental vasculature, either in a free form or stored in mast cells (Kohler et al., 1988). Histamine is also released from basophils, whose number increases during pregnancy and returns to within the normal range after delivery (Wasmoen et al., 1987). It has been found that significant changes in histamine concentration occur during physiological reproductive processes and,

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moreover, that mast cells are abundant in female reproductive tissues (Rudolph et al., 1993). Furthermore, it is suggested that endothelial cells produce not only synthesized NO but also histamine (Schayer, 1965). In human arterial preparations, histamine produces a relaxation via H_1-receptors located on endothelial cells (causing them to release endothelium-derived relaxing factors) and via H_2-receptors on smooth muscle cells (Hill et al., 1997; Van de Voorde et al., 1998). Thus, it is possible that histamine plays some important roles in maintaining pregnancy. We recently found that in omental resistance arteries, the histamine-induced smooth muscle relaxation mediated by H_2-receptors was down-regulated in pre-eclampsia (Suzuki et al., 2000b). However, it is unknown whether or not the same is true of the endothelium-dependent relaxation induced by histamine via H_1-receptors.

To try to answer this question, we investigated the effect of histamine on the contraction induced by 9,11-epithio-11,12-methano-thromboxane A_2 (STA_2, a stable thromboxane analogue; Kanmura et al., 1987) in the presence of diclofenac (to prevent the production of prostanoids) in endothelium-intact strips of omental resistance arteries obtained from normotensive pregnant and pre-eclamptic women. Using mepyramine (an inhibitor of H_1-receptors) and famotidine (an inhibitor of H_2-receptors), we first characterized the receptor responsible for the histamine-induced relaxation of the STA_2-induced contraction in these two groups of women. The effect of L-N^G-nitroarginine (L-NNA, an inhibitor of NO synthase) was then examined on the histamine-induced response in the presence and absence of famotidine in strips from both groups. It is well known that NO increases the cellular concentration of guanosine-3′,5′-cyclic monophosphate (cyclic GMP) via an activation of soluble guanylyl cyclase [(Moncada et al., 1991; Kuriyama et al., 1998)], while human atrial natriuretic peptide (hANP) increases cyclic GMP via an activation of ANP-receptor-coupled particulate guanylyl cyclase (Kuriyama et al., 1998). Finally, to investigate whether or not functional changes in the action of cyclic GMP occur in resistance arteries in pre-eclampsia, the effect of hANP on the STA_2-induced contraction was investigated in endothelium-intact, L-NNA-treated strips from both groups of women.

2. Materials and methods

2.1. Preparations

Muscle strips were cut from omental resistance arteries (o.d., 0.1–0.3 mm) obtained from 15 normotensive pregnant women and 12 pre-eclamptic women at the time of caesarean section. Informed consent was obtained from all patients. The procedures used in this study were approved by the institutional review boards of Nagoya City University Medical School. Pre-eclampsia was diagnosed according to the criteria suggested by the working group of the National High Blood Pressure Education Program (Lenfant et al., 1990). These criteria were: (i) the presence of a blood pressure greater than 140/90 mm Hg or a rise of more than 30 mm Hg in systolic blood pressure or of more than 15 mm Hg in diastolic blood pressure from the first trimester value (in a sitting position, measured twice, 6 h apart) and (ii) a significant proteinuria of 30 mg/dl or more after 20 weeks of gestation. Patients were matched for both maternal and gestational age (31 ± 1 vs. 30 ± 2 years and 39 ± 1 vs. 37 ± 2 weeks for normotensive pregnant women and pre-eclamptic women, respectively).

The tissue specimens were immediately placed in Krebs solution and transported to the laboratory. Omental artery segments (3 cm in length) were excised and the connective tissue carefully removed in Krebs solution. The artery was then cut along its long axis using small scissors, care being taken not to damage the endothelium. Small circularly cut muscle strips with intact endothelium (0.1–0.3 mm in width, 0.05–0.08 mm in thickness, 0.3–0.4 mm in length) were then prepared, as described previously (Itoh et al., 1992; Yamakawa et al., 1997; Suzuki et al., 2000a). The usefulness of this preparation in investigations of endothelium-dependent responses in small resistance arteries has been reported previously following studies involving measurements of isometric tension (Suzuki et al., 2000a), membrane potential changes (Yamakawa et al., 1997) or the production of prostanoids (Yamashita et al., 1999).

2.2. Recording of mechanical responses

An endothelium-intact strip of omental artery was placed in a chamber with a capacity of 0.3 ml and superfused with Krebs solution at flow rate of about 2 ml/min. Both ends of the preparation were fixed using fine silk threads and isometric tension was recorded using a strain-gauge transducer (AE801; SensoNor, Horten, Norway). The length, width and thickness and the cross-sectional area of the preparation were measured with the aid of an invert-microscope, as described previously (Itoh et al., 1992).

A resting tension of 2–3 mg was applied so as to obtain a maximum contraction to 128 mM K^+. Each preparation was allowed to equilibrate for 1 to 2 h before the start of the experiment. Diclofenac sodium (3 μM, to inhibit the synthesis of prostanoids) and 5 μM guanethidine (to prevent noradrenaline-outflow from sympathetic nerves) were present throughout each experiment. Diclofenac itself had no effect on the contractions induced by 128 mM K^+ or 1–3 nM STA_2.

2.3. Experimental protocols

In previous experiments on endothelium-intact strips of omental resistance arteries, we found that while STA_2 (0.03–10 nM) produced a concentration-dependent contraction in both groups of women, the sensitivity to STA_2

was higher in strips from pre-eclamptic women than in those from normotensive pregnant women (EC_{50} values were 0.6 ± 0.2 nM for pre-eclamptic women and 3.1 ± 1.0 nM for normotensive pregnant women, Suzuki et al., 2000a). Furthermore, we also found that L-NNA (0.3 mM) enhanced the STA_2-induced contraction in strips from normotensive pregnant women but not in those from pre-eclamptic women (Suzuki et al., 2000a). For that reason, in the present experiments STA_2 was used at 1 nM for the pre-eclamptic group before and after application of L-NNA and at 3 and 1 nM for the normotensive pregnant group before and after the application of L-NNA, respectively, so as to make the amplitude of contraction approximately equal in all cases. Under these conditions, the absolute levels of the STA_2-induced contraction were for pre-eclamptic women, 48.5 ± 7.8 and 51.4 ± 8.3 mg before and after application of L-NNA, respectively, and for normotensive pregnant women, 51.8 ± 5.4 and 50.3 ± 4.2 mg before and after application of L-NNA, respectively.

The preparations were first contracted with STA_2 and, after a steady-state contraction had been attained, histamine was then applied during the on-going STA_2-induced contraction. To obtain a concentration–response relationship for histamine, it (0.01–10 μM) was applied cumulatively from low to high concentration during the STA_2-induced, maintained contraction. When the effects of famotidine (3 μM, an inhibitor of H_2-receptor) and/or mepyramine (3 μM, an inhibitor of H_1-receptor) on the histamine-induced relaxation were to be examined, the strips were first contracted with STA_2. Histamine was then applied during the STA_2-induced contraction (to record the control response), followed by a washout of all of these agents. After a 60-min intermission, famotidine and/or mepyramine was pre-treated for 10 min and the same protocol (described above) was repeated in the presence of famotidine and/or mepyramine. To examine the effect of L-NNA on the histamine-induced relaxation of the STA_2-induced contraction, STA_2 was first applied in the presence or absence of famotidine (3 μM). Histamine (1 μM) was then applied during the STA_2-induced, maintained contraction in the presence or absence of famotidine, followed by a washout of all of these agents. Next, L-NNA (0.3 mM) was applied for 45 min, and the above protocol was repeated in the presence of L-NNA (as before, with or without famotidine).

A concentration–response relationship for hANP (0.1 nM–1 μM) was obtained by its cumulative application during the steady-state contraction induced by STA_2 in endothelium-intact, L-NNA-treated strips.

2.4. Solutions and chemicals

The ionic composition of the Krebs solution was as follows (mM): Na^+ 137.4; K^+ 5.9; Mg^{2+} 1.2; Ca^{2+} 2.6; HCO_3^- 15.5; $H_2PO_4^-$ 1.2; Cl^- 134; and glucose 11.5. All the solutions used in the present experiments contained diclofenac sodium (3 μM, to prevent the production of cyclo-oxygenase products) and guanethidine (5 μM, to prevent effects due to the release of sympathetic transmitters). The solutions were bubbled with 95% oxygen and 5% carbon dioxide and the pH was adjusted to 7.3–7.4.

The drugs used in the current experiments were as follows: histamine–HCl, mepyramine maleate and diclofenac sodium (Sigma, St. Louis, MO, USA), L-NNA (Peptide Institute , Minoo, Japan) and guanethidine (Tokyo Kasei, Tokyo, Japan). STA_2 was kindly provided by Ono Pharmaceutical (Osaka, Japan), famotidine by Yamanouchi Pharmaceutical (Tokyo, Japan) and hANP by Suntory (Osaka, Japan).

2.5. Data analysis

The EC_{50} value (the concentration producing 50% of the maximal effect) for the relaxant action of histamine or hANP on the STA_2-induced contraction was obtained by fitting the data points for each strip by a non-linear least-squares method using software (Kaleida graph; Synergy Software, PA, USA) written for Macintosh Computer (Apple), as described previously (Suzuki et al., 2000a,b). E_{max} represents the maximum response induced by these agents. All results are expressed as the mean ± S.E.M. The n values represent the number of subjects. A two-way repeated-measures ANOVA followed by a post hoc Scheffé's F test was used for the statistical analysis, or unpaired t-tests were used. Probabilities less than 5% ($P < 0.05$) were considered significant.

3. Results

3.1. Effects of histamine on STA_2-induced contraction

In strips from normotensive pregnant women, histamine (0.03–3 μM) produced a concentration-dependent relaxation during the contraction induced by 3 nM STA_2. The maximum relaxation (E_{max}) was by $84.2 \pm 2.0\%$ and the EC_{50} value was 0.134 ± 0.049 μM ($n = 10$). In strips from pre-eclamptic women, histamine again produced a relaxation (this time, on the contraction induced by 1 nM STA_2) but the EC_{50} value (0.355 ± 0.079 μM, $n = 9$; $P < 0.05$) was significantly larger and the maximum relaxation ($E_{max} = 47.9 \pm 3.0\%$, $P < 0.001$) was significantly smaller than those seen in normotensive pregnant women (Fig. 1).

3.2. Effects of H_1- and H_2-receptor antagonists on the relaxation induced by histamine

In strips from normotensive pregnant women, famotidine (3 μM) shifted the concentration–response relation-

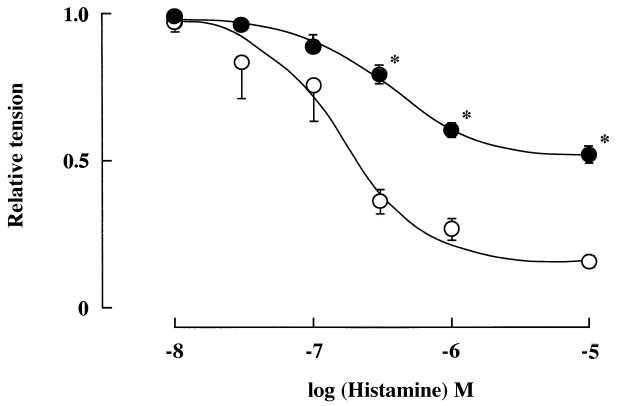

Fig. 1. Concentration-dependent relaxing effect of histamine on contraction induced by STA_2 in endothelium-intact strips from human omental resistance arteries. The concentration of STA_2 was 1 and 3 nM in strips from normotensive pregnant women (○, $n = 10$) and pre-eclamptic women (●, $n = 9$), respectively. Histamine was applied in a step-wise fashion from low to high concentration during the maintained contraction seen in the presence of STA_2. Means, with S.E.M. shown by vertical line. $^{*}P < 0.01$, significantly different from corresponding value in normotensive pregnant group (two-way repeated-measures ANOVA and Scheffé's F test).

ship for histamine to the right ($EC_{50} = 0.335 \pm 0.125$ μM, $n = 10$; $P < 0.05$) with a reduction in the maximum response ($E_{max} = 56.9 \pm 2.0\%$, $P < 0.001$) (Fig. 2A). In strips from pre-eclamptic women, this agent (3 μM) also shifted the concentration–response relationship for histamine to the right ($EC_{50} = 0.673 \pm 0.200$ μM, $n = 6$; $P < 0.03$) with a reduction in the maximum response ($E_{max} = 23.8 \pm 4.1\%$, $P < 0.001$) (Fig. 2B).

Similarly, mepyramine (3 μM) shifted the concentration–response relationship for histamine to the right ($EC_{50} = 0.386 \pm 0.102$ μM, $P < 0.05$) with a reduction in the maximum response ($E_{max} = 55.4 \pm 6.0\%$, $P < 0.001$) in strips from normotensive pregnant women (Fig. 2A). A combined application of mepyramine (3 μM) and famotidine (3 μM) completely blocked the relaxation induced by any given concentration of histamine (0.03–3 μM) in strips from either group of women (Fig. 2A,B).

3.3. Effects of L-NNA on the relaxation-induced by histamine

In the presence of famotidine (3 μM), the relaxation induced by 1 μM histamine in strips from pre-eclamptic women (relaxation, $23.8 \pm 4.8\%$, $n = 9$) was significantly smaller than that obtained from normotensive pregnant women (relaxation, $59.7 \pm 2.1\%$, $n = 10$; $P < 0.02$). In the presence of famotidine (3 μM), L-NNA significantly attenuated the relaxation induced by histamine (1 μM) in strips from normotensive pregnant women (relaxation, $21.9 \pm 3.1\%$, $n = 10$; $P < 0.003$ vs. before the application of L-NNA) but not in those from pre-eclamptic women (relaxation, $18.8 \pm 6.6\%$, $n = 9$; $P > 0.3$ vs. before the application of L-NNA) (Fig. 3).

3.4. Effect of hANP on STA_2-induced contraction

In both groups, hANP (0.003–10 μM) produced a concentration-dependent relaxation in the presence of 1 nM STA_2 in endothelium-intact strips treated with L-NNA (0.3 mM). Although the EC_{50} value for normotensive pregnant women (3.37 ± 3.01 nM, $n = 8$) was not significantly different from that for pre-eclamptic women (10.0 ± 8.0 nM, $n = 4$; $P > 0.1$), the maximum relaxation in-

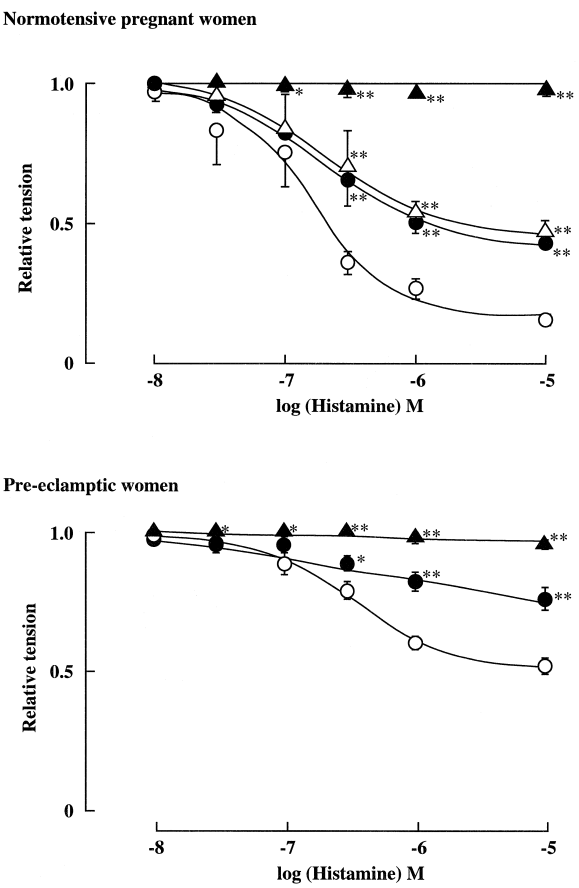

Fig. 2. (A) Effects of famotidine (3 μM) and mepyramine (3 μM) on histamine-induced relaxation in the presence of 3 μM STA_2 in strips from normotensive pregnant women ($n = 10$). (B) Effect of famotidine (3 μM) on histamine-induced relaxation in the presence of 1 nM STA_2 in endothelium-intact strips from pre-eclamptic women ($n = 6$). Histamine was applied in a step-wise fashion from low to high concentration during the maintained contraction seen in the presence of STA_2. Concentration-dependent effects of histamine in the presence of famotidine (●), mepyramine (△) or famotidine plus mepyramine (▲) and in the absence of these drugs (○). Means, with S.E.M. shown by vertical line. $^{*}P < 0.05$, $^{**}P < 0.01$, significantly different from corresponding value in the absence of histamine-receptor blockers (two-way repeated-measures ANOVA and Scheffé's F test).

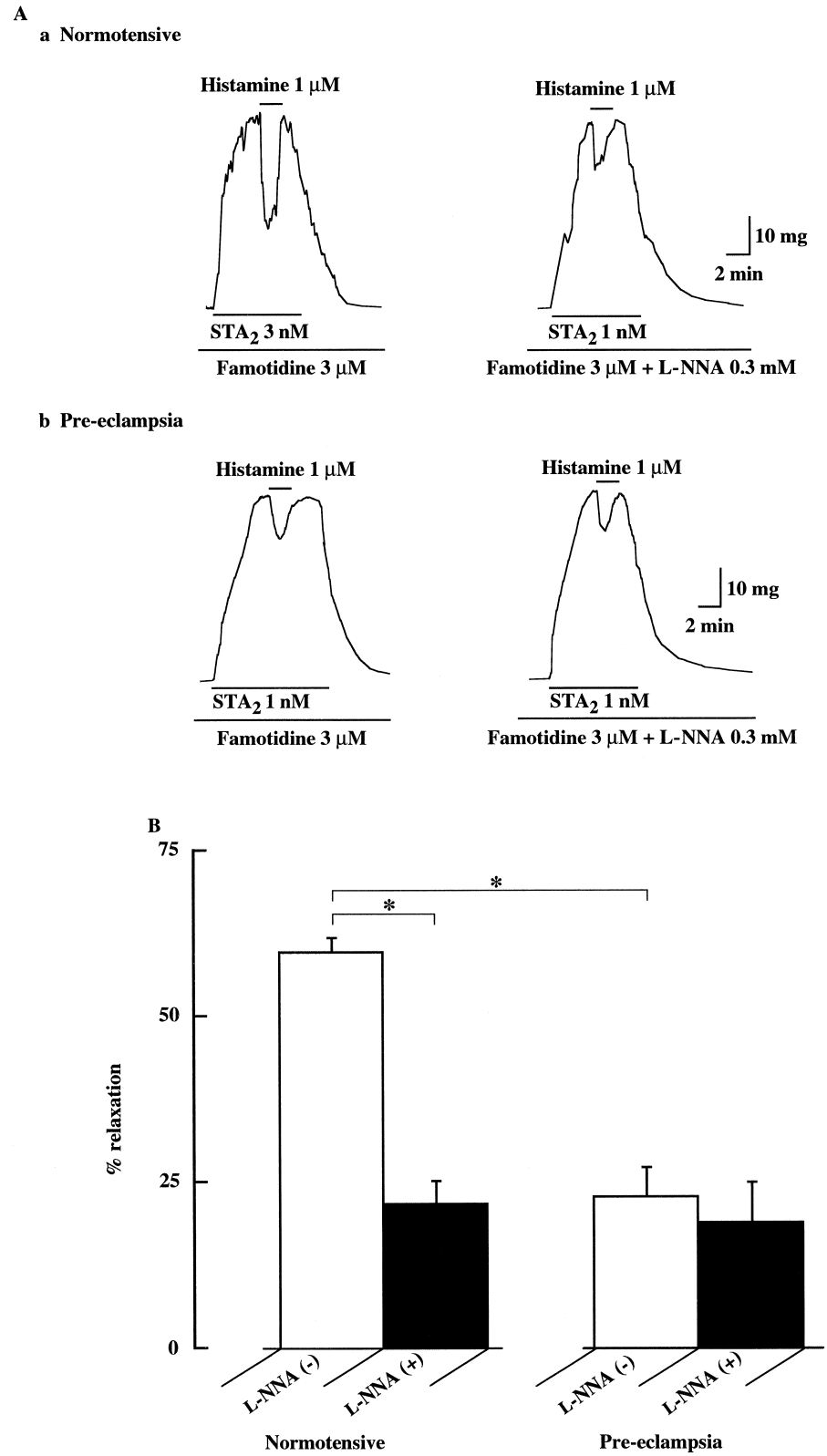

Fig. 3. The effect of L-NNA on histamine-induced relaxation of STA_2-induced contraction in the presence of famotidine (3 μM). (A) Actual traces of the histamine-induced relaxation. Histamine (1 μM) was applied for 2 min during the STA_2-induced contraction. The concentrations of STA_2 are indicated. In the presence of famotidine, L-NNA (0.3 mM) was applied for 45 min and was present throughout the experiment. (B) Summary of the histamine-induced relaxations recorded in the presence (■) and absence of L-NNA (□) in strips from pre-eclamptic women ($n = 9$) and normotensive pregnant women ($n = 11$). Means, with S.E.M. shown by vertical line. * indicates values that are significantly different from each other ($P < 0.01$, paired or unpaired t-test with F-test).

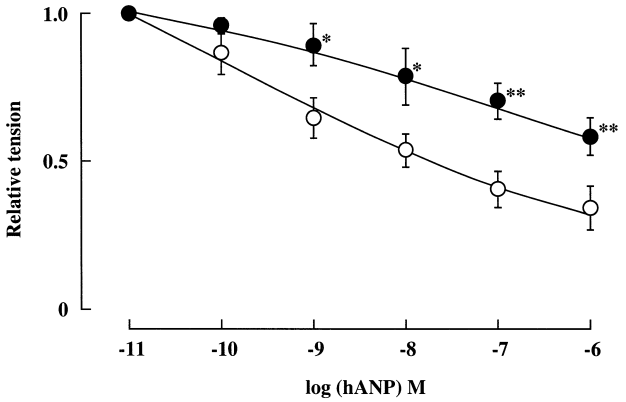

Fig. 4. Concentration-dependent effect of human atrial natriuretic peptide (hANP) on contraction induced by 1 nM STA_2 in endothelium-intact strips treated with L-NNA (0.3 mM). (●), pre-eclamptic women ($n = 4$); (○), normotensive pregnant women ($n = 8$). Means, with S.E.M. shown by vertical line. $^{*}P < 0.05$, $^{**}P < 0.01$, significantly different from corresponding value in normotensive pregnant group (two-way repeated-measures ANOVA and Scheffé's F test).

duced by 1 μM hANP was significantly smaller for pre-eclamptic women ($E_{max} = 41.7 \pm 6.4\%$, $n = 4$) than for normotensive pregnant women ($E_{max} = 62.7 \pm 8.7\%$, $n = 8$; $P < 0.05$) (Fig. 4).

4. Discussion

Histamine produces a relaxation on the contraction induced by STA_2 in endothelium-intact strips of omental resistance arteries from both normotensive pregnant and pre-eclamptic women. Famotidine is found to be a competitive H_2-blocker and more potent H_2-antagonist than cimetidine or ranitidine (Gajtkowski et al., 1983; Black et al., 1985). We previously found that in endothelium-denuded strips of these arteries from both types of women, the relaxation induced by histamine in the presence of STA_2 was completely blocked by famotidine (Suzuki et al., 2000b). In contrast, mepyramine (3 μM), an inhibitor of H_1-receptors, had no effect on the histamine-induced relaxation in endothelium-denuded strips from both types of women (unpublished observations). These results suggest that histamine binds to H_2-receptors located on the smooth muscle cells to cause a relaxation. In the present experiments (using endothelium-intact strips from the same arteries), famotidine partly attenuated the histamine-induced relaxation, and a combined application of famotidine and mepyramine was needed completely to block the histamine-induced relaxation in each group of women. It has previously been reported that in human resistance arteries, histamine produces relaxation via both H_1-receptors located on endothelial cells (leading to the release of endothelium-derived relaxing factors) and H_2-receptors on smooth muscle cells (Hill et al., 1997; Van de Voorde et al., 1998). Taken together, these results suggest that in endothelium-intact human omental resistance arteries, histamine activates both H_1-receptors (possibly on endothelial cells) and H_2-receptors (on smooth muscle cells) and that these two receptors account for the histamine-induced relaxation.

We previously found that the histamine-induced, H_2-receptor-mediated relaxation was significantly smaller in endothelium-denuded strips from pre-eclamptic women than in those from normotensive pregnant women (Suzuki et al., 2000b). In the present experiments, we found that the histamine-induced relaxation in endothelium-intact strips, too, was significantly smaller for pre-eclamptic women than for normotensive pregnant women (whether in the presence or absence of famotidine). These results indicate that like the H_2-receptor-mediated relaxation (Suzuki et al., 2000b), the H_1-receptor-mediated, endothelium-dependent relaxation is also down-regulated in omental resistance arteries in pre-eclampsia.

Endothelium-stimulating agents, such as acetylcholine, bradykinin and histamine, act on endothelial cells and induce the release not only of NO and prostanoids but also of an endothelium-derived, membrane hyperpolarizing factor (EDHF) (Kuriyama et al., 1998). In the present experiments we found that in the presence of famotidine, while L-NNA attenuated the histamine-induced relaxation by more than one-half in strips from normotensive pregnant women, it had no effect in those from pre-eclamptic women. Since the present experiments were conducted in the presence of the cyclo-oxygenase inhibitor diclofenac, the role of prostanoids in this histamine-induced relaxation would have been negligible. Possibly, the residual histamine-induced relaxation seen in the presence of L-NNA plus famotidine may be produced by the action of endothelium-derived-NO- and prostanoid-independent factor (possibly EDHF). Certainly, the magnitude of this residual relaxation was similar for the two groups of women. The functional role of EDHF in agonist-induced endothelium-dependent relaxation in human resistance arteries has recently received considerable attention (Knock and Poston, 1996; Pascoal et al., 1998; Suzuki et al., 2000a). Interestingly, it was very recently suggested that in resistance arteries from pre-eclamptic women, the EDHF-mediated relaxations induced by bradykinin and substance P are preserved (i.e. they are comparable to those seen in normotensive pregnant women; Suzuki et al., 2000a). These results seem to suggest that in human omental resistance arteries treated with diclofenac, histamine produces an endothelium-dependent relaxation via both NO and EDHF in normotensive pregnant women but via EDHF alone in pre-eclamptic women.

In contrast to NO (which increases the cellular concentration of cyclic GMP via an activation of soluble guanylyl cyclase), hANP increases cyclic GMP via an activation of ANP-receptor-coupled particulate guanylyl cyclase in smooth muscle cells (Kuriyama et al., 1998). In the present

experiments using endothelium-intact strips treated with L-NNA, the magnitude of the relaxation induced by hANP at any given concentration (0.3 nM–1 μM) was significantly smaller for pre-eclamptic women than for normotensive pregnant women. Recently, we found that the relaxing activity of the NO donor sodium nitroprusside on the STA_2-induced contraction in endothelium-intact, L-NNA-treated omental artery strips was significantly less for pre-eclamptic than for normotensive pregnant women [(Suzuki et al., 2000a)]. Furthermore, the relaxing potency of a phosphodiesterase-resistant membrane-permeable cyclic GMP analogue, 8-para-chlorophenyl thioguanosine-3′,5′-cyclic monophosphate, was also weaker in endothelium-denuded strips from pre-eclamptic women than in those from normotensive pregnant women (Suzuki et al., 2000a). Taken together, these results suggest that the reduction in the histamine-mediated relaxation seen in pre-eclampsia is due, at least in part, to a reduction in cyclic GMP-mediated relaxation in the smooth muscle cells of omental resistance arteries. However, we cannot exclude the possibility that a reduced synthesis of endothelial NO may also play a part (Knock and Poston, 1996; Pascoal et al., 1998).

In conclusion, in human omental resistance arteries histamine produces a relaxation that is mediated by H_1-receptors (on endothelial cells) and H_2-receptors (on smooth muscle cells). It is suggested that the decrease in H_1-receptor-mediated relaxation seen in pre-eclampsia may be due, at least in part, to an attenuation of the action of cyclic GMP in smooth muscle cells.

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