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Characterization of changes in mechanical responses to histamine in omental resistance arteries in pre-eclampsia

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1 Changes in the effect of histamine on the smooth muscle of resistance arteries in pre-eclampsia were investigated by measuring isometric contractions in endothelium-denuded strips of omental resistance arteries from pre-eclamptic and normotensive pregnant women (pregnancy-term matched).

2 Histamine (0.03–1 μM) caused concentration-dependent relaxation of the contraction induced by 9,11-epithio-11,12-methano-thromboxane A_2 (STA_2) in strips from both groups. Sensitivity (for pre-eclampsia: $pD_2 = 6.66 \pm 0.04$, $n = 5$ and for normotensive pregnant women: $pD_2 = 7.07 \pm 0.03$, $n = 10$, $P < 0.001$) was lower and the maximum response ($90.6 \pm 0.6\%$ vs $95.5 \pm 1.1\%$, $P < 0.05$) was smaller in strips from pre-eclamptic women.

3 Although 8-bromoadenosine-3′, 5′-cyclic monophosphorothioate (Sp-isomer: Sp-8-Br-cAMPS, 0.1–0.3 mM), a phosphodiesterase (PDE)-resistant activator of adenosine-3′,5-cyclic monophosphate (cyclic AMP)-dependent protein kinase, concentration-dependently attenuated the contraction induced by STA_2 in strips from both groups, the sensitivity (for pre-eclampsia: $pD_2 = 3.68 \pm 0.04$, $n = 5$ and for normotensive pregnant women: 3.94 ± 0.09, $n = 7$, $P = 0.02$) was lower and the maximum response ($64.2 \pm 2.4\%$ vs $74.9 \pm 4.4\%$, $P < 0.05$) was smaller in pre-eclampsia.

4 In β-escin-skinned strips, the pD_2 value for the contraction-inducing effect of Ca^{2+} did not differ significantly between the two groups (for pre-eclampsia, $n = 6$; for normotensive pregnant women, $n = 6$).

5 Thus, omental resistance arteries from human subjects with pre-eclampsia showed (i) a weaker H_2-receptor-mediated relaxation to histamine and (ii) a weaker cyclic AMP-analogue-induced relaxation, suggesting that the reduced action of histamine may be partly due to a decreased effect of cyclic AMP.

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Abbreviations: cyclic AMP, adenosine-3′,5′-cyclic monophosphate; PDE, phosphodiesterase; PKA, adenosine-3′,5′-cyclic-monophosphate-dependent protein kinase; Sp-8-Br-cAMPS, 8-bromoadenosine-3′,5′-cyclic monophosphorothioate, Sp-isomer; STA_2, 9,11-epithio-11,12-methano-thromboxane A_2

Introduction

In human peripheral vascular beds, histamine is present in high concentrations in the vessel wall, either in a free form or stored in mast cells (El-Ackad & Brody, 1975; Kohler *et al*., 1988) and basophils (Wasmoen *et al*., 1987). This agonist is thought to play a significant role in the regulation of the microcirculation by controlling both vascular resistance and vascular permeability (Hill *et al*., 1997). Significant changes in histamine concentration have been found to occur during physiological processes involved in reproduction and, moreover, mast cells are abundant in female reproductive tissues (Rudolph *et al*., 1993).

Pre-eclampsia is characterized by increases in peripheral vascular resistance and vascular permeability together with a disturbance of blood coagulation (Lenfant *et al*., 1990; Cunningham, 1998; Cines *et al*., 1998). In general, histamine produces a relaxation *via* H_1-receptors located on endothelial cells (leading to the release of endothelium-derived relaxing factors) and H_2-receptors on smooth muscle cells [increasing the cellular concentration of adenosine-3′,5′-cyclic monophosphate (cyclic AMP)] in human arterial preparations (Hill *et al*., 1997). It has been suggested that in human subcutaneous resistance arteries, histamine produces a potent relaxation mainly due to its activation of H_2-receptors on smooth muscle cells (Van de Voorde *et al*., 1998). This action of histamine is much more potent than those of acetylcholine and bradykinin, which produce relaxation *via* a release of endothelium-dependent relaxing factors (Van de Voorde *et al*., 1998). These results suggest that H_2-receptors on smooth muscle cells play a significant role in histamine-induced vascular relaxation in human resistance arteries. However, it is unknown whether the H_2-receptor-mediated response in smooth muscle cells is modulated in pre-eclampsia. Furthermore, it is also unknown whether the relaxing action of cyclic AMP on smooth muscle is altered in resistance arteries in pre-eclampsia.

The present study was undertaken to identify and characterize any changes in H_2-receptor-mediated regulation of smooth muscle tone in resistance arteries in pre-eclampsia. To this end, 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-denuded strips obtained from normotensive pregnant and pre-eclamptic women. Furthermore, the effect of 8-bromoadenosine-3′,5′-cyclic monophosphorothioate (Sp-isomer: Sp-8-Br-cAMPS, a membrane-permeable cyclic AMP analogue, Schaap *et al*., 1993), on the STA_2-induced contraction was investigated in

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strips from both groups of patients. Finally, changes in myofilament Ca^{2+}-sensitivity were examined using β-escin-skinned smooth muscle strips.

Methods

Preparations

Muscle strips were cut from omental resistance arteries (outer diameter 0.1–0.2 mm) obtained from 20 normal pregnant women and 13 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 Programme (Lenfant *et al*., 1990). Patients details are shown in Table 1. After their removal from the patients, the tissue specimens were immediately placed in Krebs solution and transported to the laboratory. Omental artery segments (1 cm in length) were excised and the connective tissue was carefully removed in Krebs solution. The artery was then cut along its long axis using small scissors and the endothelium was removed using a small razor blade, as described previously (Itoh *et al*., 1992a,b; Izumi *et al*., 1994; Yamakawa *et al*., 1997).

Recording of mechanical responses

Each endothelium-denuded strip (0.10–0.20 mm in width, 0.05–0.08 mm in thickness, 0.30 mm in length) was mounted horizontally in an experimental recording chamber with a capacity of 0.3 ml and the tissue was superfused with modified Krebs solution. Each end of the preparation was fixed using pieces of 'Scotch' double-sided adhesive tape (3M, St. Paul, MN, U.S.A.) and isometric tension was recorded using a strain-gauge transducer (U-Gauge; Shinko, Tokyo, Japan), as described previously (Itoh *et al*., 1992a,b). 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 1–2 h before the start of the experiment. Diclofenac sodium (3 μM, to inhibit synthesis of prostanoids) and 5 μM guanethidine (to prevent effects due to release of sympathetic transmitters) were present throughout the experiments. Diclofenac sodium itself had no effect on the contractions induced by 128 mM K^+ or STA_2.

To obtain a concentration-response relationship for histamine, this agonist (0.01–10 μM) was applied cumulatively from low to high concentration during an STA_2-induced maintained contraction. When the effect of famotidine (an inhibitor of the H_2-receptor) on the histamine-induced relaxation was to be examined, the strips were first contracted with STA_2. Histamine (1 μM) was then applied during the ongoing STA_2-contraction. Finally, famotidine (3 μM) was applied in the presence of histamine plus STA_2.

To examine the concentration-dependent effects of Sp-8-Br-cAMPS (30–300 μM) on the STA_2-induced contraction, STA_2 was applied for 6 min at 45 min intervals, so that a reproducible contraction was obtained (normally, STA_2 was given three or four times). Once a reproducible contraction had been obtained, Sp-8-Br-cAMPS was pre-treated for 20 min and STA_2 [at a concentration of 1 nM (pre-eclampsia) or 3 nM (normotensive pregnancy)] was applied for 6 min in the presence of Sp-8-Br-cAMPS. This protocol was repeated with a step-wise increase in the concentration of Sp-8-Br-cAMPS from low to high.

Table 1 Patient details

	Normotensive (n=20)	*Pre-eclampsia (n=13)*
Age (year)	30±1	30±2
Gestational age (week) at caesarean section	39±1	37±1
Blood pressure		
systolic (mmHg)	116±3	162±9*
diastolic (mmHg)	73±9	106±8*
Proteinuria (g l^{-1})	–	4.1±2.1
Generalized oedema	–	6/13

Data are expressed as mean±s.e.mean. The number of patients is given in parenthesis. *$P<0.05$ by unpaired *t*-test.

β-escin skinned muscle strips

Endothelium-denuded muscle strips obtained from pre-eclamptic and normotensive pregnant women strips (0.50–0.75 mm in width, 0.03–0.04 mm in thickness, 0.3 mm in length) were skinned by an application of β-escin (40 μM) for 30 min in a relaxing solution (for composition, see 'Solutions'). A-23187 (3 μM) was included in the relaxing solution to avoid effects due to Ca^{2+} release from intracellular storage sites in the skinned muscle (Itoh *et al*., 1985). Various concentrations of Ca^{2+} (0.1–10 μM) were cumulatively applied, from low to high concentration, and the amplitude of the contraction induced by a given concentration of Ca^{2+} was normalized with respect to that induced by 10 μM Ca^{2+} in one and the same strip.

Solutions

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) and guanethidine (5 μM). The solutions were bubbled with 95% oxygen and 5% carbon dioxide and the pH was adjusted to 7.3–7.4.

The relaxing solution used for skinned-muscle experiments contained (mM) EGTA 4, potassium methanesulphonate (KMS) 87, Mg(MS), 5.1, ATP 5.2, creatine phosphate 5, PIPES 20. The pH of the solution was adjusted to 7.1 at 25°C using KOH and the ionic strength was standardized at 0.18 M by changing the amount of KMS added. A-23187 (3 μM) was present in the relaxing solution throughout the experiments. Calmodulin (0.1 μM) was also added to the relaxing solution (to prevent deterioration of the Ca^{2+}-induced contraction, Itoh *et al*., 1992b). The free Ca^{2+} concentration was calculated as described previously (Itoh *et al*., 1992b).

Chemicals

The drugs used in the current experiments were as follows: β-escin, calmodulin and diclofenac sodium (Sigma Chemical Co., St. Louis, MO, U.S.A.), Sp-8-Br-cAMPS (Biolog Life Science Inst., Bremen, Germany). A-23187 (free acid; Calbiochem, La Jolla, CA, U.S.A.) and guanethidine (Tokyo Kasei, Tokyo, Japan). STA_2 was kindly provided by Ono Pharmaceutical Co. Ltd. (Osaka, Japan). Famotidine was kindly provided by Yamanouchi Pharmaceutical Co. Ltd. (Tokyo, Japan).

Data analysis

The pD_2 values ($-\log EC_{50}$; EC_{50} being the concentration producing 50% of the maximal effect) for the relaxant actions of histamine and Sp-8-Br-cAMPS on the STA_2-induced contraction were obtained by fitting the data points for each strip by a non-linear least-squares method using software (Kaleida graph; Synergy Software, PA, U.S.A.) written for Macintosh Computer (Apple Co. Ltd.), as described previously (Shiraishi *et al*., 1998). The E_{max} value represents the maximum response induced by a given agent. All results are expressed as the mean ± s.e. 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 (Table 1) an unpaired *t*-test was used. Probabilities less than 5% ($P<0.05$) were considered significant.

Results

STA_2-induced contraction

STA_2 (0.03 – 10 nM) produced a concentration-dependent contraction in endothelium-denuded strips obtained from both groups of women (Figure 1). The pD_2 values for STA_2 were 8.81 ± 0.10 ($n=4$) in strips from normotensive pregnant women and 9.21 ± 0.03 ($n=4$) in strips from pre-eclamptic women, the two values being significantly different from each other ($P<0.001$). To obtain contractions of approximately equal amplitude from the two groups of patients, in the following experiments STA_2 was used at 1 nM in strips from pre-eclamptic women and at 3 nM in strips from normotensive pregnant women. The mean force induced by 1 nM STA_2 in strips from pre-eclamptic women was 48.5 ± 7.8 mg ($n=4$) and that induced by 3 nM in strips from normotensive pregnant women was 51.8 ± 5.4 mg ($n=4$), the two values being not significantly different from each other ($P>0.1$). The maximum force induced by 10 nM STA_2 was 57.1 ± 9.2 mg for pre-eclamptic women ($n=4$) and 64.8 ± 6.6 mg for normotensive pregnant women ($n=4$, $P>0.1$).

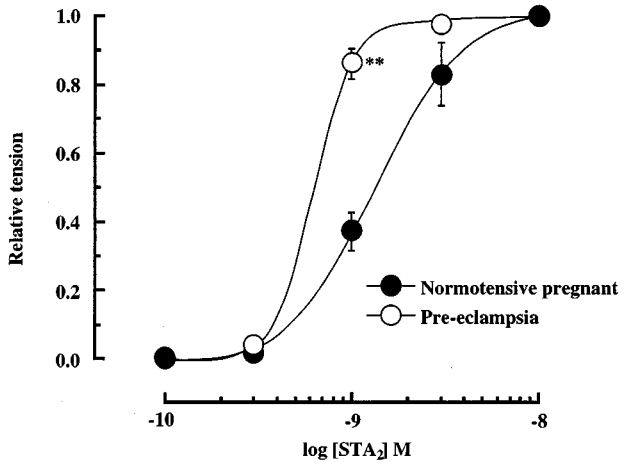

Figure 1 Concentration-dependent effects of 9,11-epithio-11,12-methano-thromboxane A_2 (STA_2) in endothelium-denuded strips from normotensive pregnant and pre-eclamptic women. STA_2 (0.003 – 10 nM) was applied cumulatively from low to high concentration in strips from normotensive pregnant ($n=4$) and pre-eclamptic ($n=4$) women. The maximum amplitude of contraction induced by 10 nM STA_2 was normalized as a relative tension of 1.0 for each strip. Mean of data with s.e. shown by vertical line. $^{**}P<0.001$ vs corresponding value for normotensive pregnant women.

Effects of histamine on STA_2-induced contraction

In strips from normotensive pregnant women, histamine (0.03 – 10 μM) produced a concentration-dependent relaxation during the contraction induced by 3 nM STA_2. The maximum relaxation was 95.5 ± 1.1% and the pD_2 value was 7.07 ± 0.03 ($n=10$) (Figure 2). In strips from pre-eclamptic women, histamine produced a relaxation during the contraction induced by 1 nM STA_2 (Figure 2). The pD_2 value (6.66 ± 0.04, $n=5$, $P<0.001$) was significantly larger than the corresponding value in normotensive pregnant women, while the maximum relaxation (by 90.6 ± 0.6%, $n=5$, $P<0.05$) was slightly but significantly smaller. Famotidine (3 μM), an H_2-receptor blocker, completely blocked the relaxation induced by 1 μM histamine in strips obtained from both groups of women (for pre-eclampsia, $n=6$ and for normotensive pregnant women, $n=5$) (Figure 3).

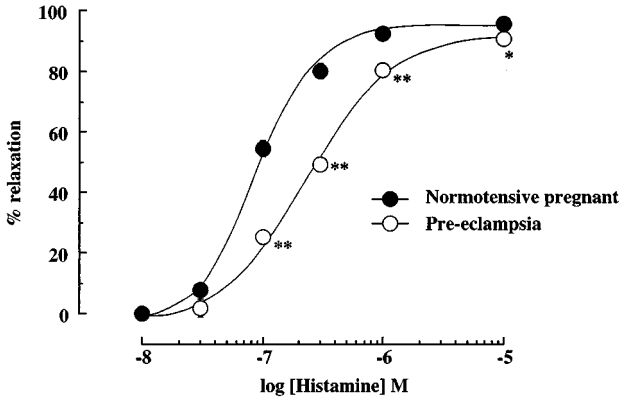

Figure 2 Concentration-dependent relaxing effect of histamine on contraction induced by STA_2 in endothelium-denuded strips of human omental resistance artery. The concentration of STA_2 was 3 nM for strips obtained from normotensive pregnant women ($n=10$) and 1 nM for those from pre-eclamptic women ($n=5$). Histamine was applied in a step-wise fashion from low to high concentration during the maintained contraction observed in the presence of STA_2. Mean of data with s.e. shown by vertical line. $^{*}P<0.05$, $^{**}P<0.01$, significantly different from corresponding value in normotensive pregnant group (two-way repeated measures ANOVA with Scheffé's *F*-test).

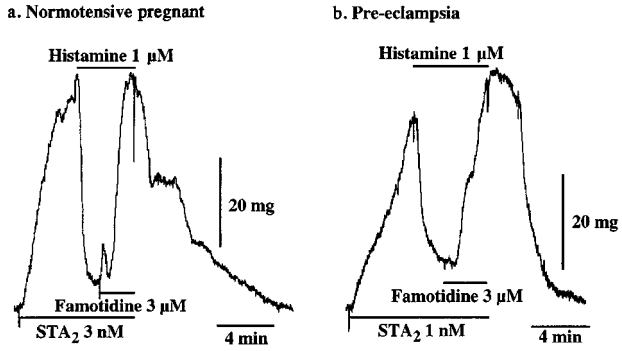

Figure 3 Actual tracings of the effect of famotidine (3 μM) on the relaxation induced by histamine (1 μM) in the presence of STA_2 in endothelium-denuded strips from normotensive pregnant (a) and pre-eclamptic women (b). Each agent was applied as indicated by the bar. Famotidine (3 μM) was applied in the presence of histamine at the peak of the histamine-induced relaxation observed in the presence of STA_2. The concentration of STA_2 was 3 nM for the strip obtained from a normotensive pregnant woman and 1 nM for the strip from a pre-eclamptic woman.

Effects of Sp-8-Br-cAMPS on STA_2-induced contraction

Sp-8-Br-cAMPS (0.1 and 0.3 mM), a phosphodiesterase (PDE)-resistant activator of cyclic AMP-dependent protein kinase (PKA), concentration-dependently inhibited the contraction induced by 3 nM STA_2 in strips from normotensive pregnant women ($pD_2 = 3.94 \pm 0.09$, $E_{max} = 74.9 \pm 4.4\%$, $n = 5$). Over the same concentration range, this kinase activator also attenuated the contraction induced by 1 nM STA_2 in strips from pre-eclamptic women. The sensitivity to Sp-8-Br-cAMPS ($pD_2 = 3.68 \pm 0.04$, $n = 7$, $P = 0.02$) was significantly lower than the corresponding value in normotensive pregnant women, while the maximum response ($E_{max} = 64.2 \pm 2.4\%$, $n = 7$, $P = 0.04$) was significantly smaller (Figure 4).

Ca^{2+}-force relationship in β-escin-skinned smooth muscle

In β-escin-treated smooth muscle strips from normotensive pregnant women, Ca^{2+} (0.3–3 μM) concentration-dependently produced a contraction ($pD_2 = 6.16 \pm 0.02$, $n = 6$). Over the same concentration range, Ca^{2+} also produced a contraction in skinned strips from pre-eclamptic women ($pD_2 = 6.19 \pm 0.01$, $n = 6$). These pD_2 values were not significantly different ($P > 0.1$) (Figure 5).

Discussion

In the present experiments, histamine produced a relaxation during the contraction induced by STA_2 in endothelium-denuded strips of omental resistance arteries from both normotensive pregnant and pre-eclamptic women. The histamine-induced relaxation was blocked by famotidine (an antagonist of the H_2-receptor), indicating that H_2-receptors located on smooth muscle are responsible for this relaxation. It is generally believed that in various types of vascular tissues in many species, when histamine binds to H_2-receptors the cellular concentration of cyclic AMP is increased, thus leading to a vascular relaxation *via* an action of this second messenger (Hill *et al*., 1997). In the present experiments, Sp-8-Br-cAMPS, an activator of PKA (cyclic AMP agonist; Schaap *et al*., 1993), potently inhibited the STA_2-induced contraction in endothelium-denuded strips of human omental resistance arteries. These results suggest that as in other tissues, histamine binds to the H_2-receptor to inhibit the STA_2-induced contraction, possibly with mediation by cyclic AMP, in smooth muscle cells of human omental arteries.

Importantly, in the present experiments, we found that the sensitivity to histamine for relaxation was significantly less in strips obtained from pre-eclamptic women than in those from normotensive pregnant women and that the maximum

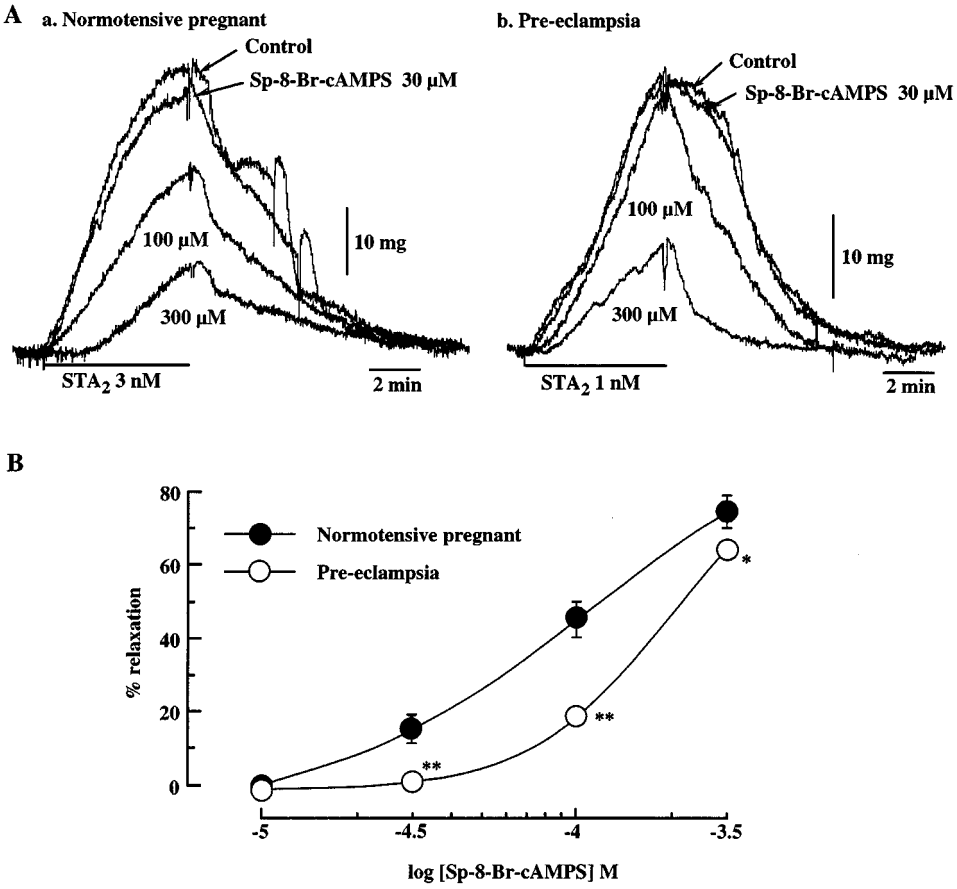

Figure 4 Concentration-dependent relaxing effect of Sp-8-Br-cAMPS on contraction induced by STA_2 in endothelium-denuded strips from human omental resistance artery. (A) Actual tracing of the effects of Sp-8-Br-cAMPS in strips obtained from a normotensive pregnant woman (a) and from a pre-eclamptic woman (b). STA_2 was applied for 6 min at 45 min intervals. Sp-8-Br-cAMPS was pre-treated for 30 min and was present during the subsequent application of STA_2. (B) Summary of the effects of Sp-8-Br-cAMPS. The concentration of STA_2 was 3 nM in strips obtained from normotensive pregnant women and 1 nM in those from pre-eclamptic women. Mean of data with s.e. shown by vertical line. $*P < 0.05$, $**P < 0.01$, significantly different from corresponding value in normotensive pregnant group (two-way repeated measures ANOVA with Scheffé's *F*-test).

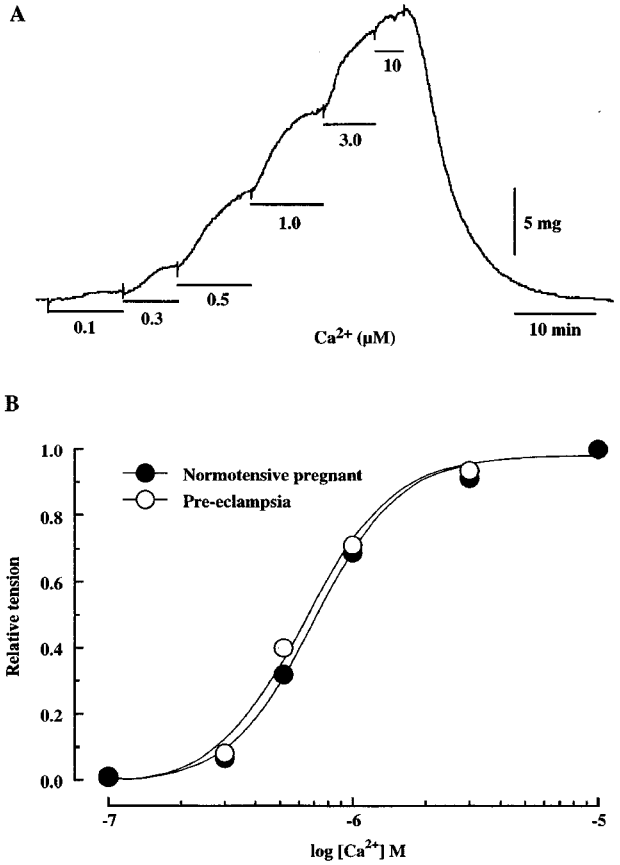

Figure 5 Ca^{2+}-tension relationship in β-escin-skinned strips of omental resistance arteries obtained from normotensive pregnant and pre-eclamptic women. (A) Actual tracing of the effect of Ca^{2+} on contraction in β-escin-skinned strip from a pre-eclamptic woman. (B) Summary of the Ca^{2+}-tension relationship in β-escin-skinned strips from normotensive pregnant women ($n=6$) or pre-eclamptic women ($n=5$). Mean of data is shown; s.e. did not exceed the diameter of the symbols.

response was significantly smaller. Similarly, the sensitivity to Sp-8-Br-cAMPS for relaxation was significantly less and the maximum response was significantly smaller in the pre-eclamptic group than in the normotensive pregnant group. These results suggest that in pre-eclampsia, the decrease in the response to histamine seen in the smooth muscle of omental resistance arteries is in part related to a reduced action of cyclic AMP in the smooth muscle itself. Since Sp-8-Br-cAMPS is a PDE-resistant analogue of cyclic AMP (Schaap *et al*., 1993), the role of PDE in this weakening of the action of Sp-8-Br-cAMPS in pre-eclampsia is likely to be negligible. Three possible mechanisms have been proposed for the smooth muscle relaxation induced by cyclic AMP-increasing agents: (i) cyclic AMP inhibits Ca^{2+} influxes through its membrane repolarizing action (Rembold & Chen, 1998; Ohashi *et al*., 2000); (ii) cyclic AMP inhibits Ca^{2+} mobilization through an activation of Ca^{2+}-uptake into the intracellular stores (Ito *et al*., 1993; Chen & Rembold, 1996); and (iii) cyclic AMP decreases myofilament Ca^{2+}-sensitivities in the smooth muscle cells (Kuriyama *et al*., 1998; Van Riper *et al*., 1995). It is possible that these actions of cyclic AMP are attenuated in resistance arteries in pre-eclampsia. However, we could find no published evidence on functional changes in cyclic AMP in human omental resistance arteries in pre-eclampsia. Thus, the mechanism underlying the weaker action of cyclic AMP we noted in the smooth muscle of resistance arteries in pre-eclampsia could not be interpreted using data already in the literature. However, what we found in the present experiments was that the pD_2 values for the Ca^{2+}-induced contraction in β-escin-skinned smooth muscle were identical in strips obtained from normotensive pregnant and pre-eclamptic women, indicating that the myofilament Ca^{2+}-sensitivity is not significantly modified in the smooth muscle of omental resistance arteries in pre-eclampsia. Furthermore, in the present experiments, the concentration of STA_2 was adjusted so as to produce the same amplitude of contraction in strips from both groups of women. Thus, under our experimental conditions, it is unlikely that an increase in the myofilament Ca^{2+} sensitivity and/or an enhancement of STA_2-induced Ca^{2+} mobilization contributed to the weaker action of cyclic AMP seen in pre-eclampsia.

Finally, it is possible that H_2-receptors are desensitized or reduced in number in smooth muscle in omental resistance arteries in pre-eclampsia. Unfortunately, in the present experiments we could not examine whether the increase in the cellular concentration of cyclic AMP induced by histamine in the vascular smooth muscle of omental arteries was altered in pre-eclampsia, since the available sample was too small to allow us to measure the cellular concentration of cyclic AMP. Thus, we cannot exclude the possibility that the observed decrease in the relaxation response to histamine may be partly due to a decrease in the histamine-induced synthesis of cyclic AMP in this tissue in pre-eclampsia.

In conclusion, in the smooth muscle of human omental resistance arteries, histamine produces a relaxation *via* the H_2-receptor. This relaxation is reduced in pre-eclampsia. It is suggested that this reduction in the action of histamine in pre-eclampsia is at least partly due to an attenuation of the relaxing action of cyclic AMP.

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