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Enhanced reactivity to vasopressin in rat basilar arteries during vasospasm after subarachnoid hemorrhage

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Abstract

Subarachnoid hemorrhage increases the plasma level of vasopressin, a well-known vasoconstrictor. We examined the sensitivity to vasopressin in rat basilar artery after subarachnoid hemorrhage using a rat subarachnoid hemorrhage model. Vasospasm was observed 1–2 days after subarachnoid hemorrhage induction, and the contractile response to vasopressin in rat basilar arteries was assessed. The concentration–response curve for vasopressin in subarachnoid hemorrhage (1 day) rats shifted leftward compared with that of control rats. The concentration–response curve for vasopressin V_1 receptor agonist also shifted leftward and upward compared with that of control rats. The concentration–response curve for vasopressin was inhibited not by vasopressin V_2 receptor antagonist but by vasopressin V_1 receptor antagonist. Thus, it was demonstrated that the vasoconstricting effect of vasopressin was significantly enhanced in the vasospasm phase after subarachnoid hemorrhage.

Keywords: Subarachnoid hemorrhage; Rat basilar artery; Vasopressin; Vasopressin V_1 receptor; Endothelium-dependent contraction

1. Introduction

Vasospasm following subarachnoid hemorrhage is a serious complication, occurring 7–10 days after hemorrhage in 70% of all patients who present with aneurysmal subarachnoid hemorrhage, leading to symptomatic brain ischemia or infarcts in 36% of all patients (Biller et al., 1988). Many substances such as oxyhemoglobin, endothelin-1, serotonin, reactive oxygen species, protein kinase C, and cyclooxygenase have been reported as possible spasmogens (Hansen-Schwartz, 2004; McGirt et al., 2002; Laher and Zhang, 2001; Osuka et al., 1998; Macdonald and Weir, 1991; Voldby et al., 1982). Furthermore, from a histological point of view, vascular wall changes are observed in smooth muscle cells (Ogihara et al., 2001) and endothelial dysfunction is caused (Maeda et al., 2004). In spite of various studies in the past few years, the mechanism of cerebral vasospasm following subarachnoid hemorrhage remains a matter of debate.

Reportedly, vasopressin may contribute to the development of vasospasm following subarachnoid hemorrhage (Trandafir et al., 2004; Delgado et al., 1988) and the plasma vasopressin level increases after subarachnoid hemorrhage (László et al., 1995; Mather et al., 1981). As is now well known, vasopressin activates two types of cell surface receptors: vasopressin V_1 receptor, linked to a Ca^{2+}-dependent vascular contraction system (Doyle and Ruegg, 1985), and vasopressin V_2 receptor, coupled to adenylate cyclase and the production of cAMP, which is associated with antidiuresis (Thibonnier, 1988). Vasopressin V_1 receptors, present mainly in vessel smooth muscle cells, are responsible for vasoconstriction through inositol-triphosphate (IP_3) formation and thus Ca^{2+} mobilization from Ca^{2+} stores (Doyle and Ruegg, 1985). However, it is questionable whether vasopressin-induced contraction is mediated only by receptors on smooth muscle cells. Further investigations are warranted to elucidate the mechanism of vasopressin-induced contraction in vessels completely, and the relation-

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ship between vasopressin and vasospasm following subarachnoid hemorrhage.

In this study, we first investigated the diameter of the basilar artery after subarachnoid hemorrhage induction using a rat subarachnoid hemorrhage model, in order to reveal when the vasospasm developed following subarachnoid hemorrhage. It has been reported with angiography that vasospasm in the rat subarachnoid hemorrhage model is biphasic (Suzuki et al., 1999; Delgado et al., 1985). So far, the delayed vasospasm in the rat subarachnoid hemorrhage model was considered to resemble the human vasospasm, and many studies of the rat subarachnoid hemorrhage model were performed to elucidate the mechanism of developing vasospasm after subarachnoid hemorrhage (Hansen-Schwartz et al., 2003; Josko, 2003; Clark et al., 2002; Lambert et al., 2002; Svendgaard et al., 1985). Second, the contractile response of the rat basilar artery to vasopressin was assessed. Third, we investigated more in detail using its related agonists and antagonists and examined the endothelium dependency in the vasopressin-induced contraction.

2. Materials and methods

Male Sprague–Dawley rats, weighing 250–350 g, were supplied by Shimizu Laboratory Supplies (Kyoto, Japan). The animals were housed in steel cages at 22–24 °C with a 12-h light/dark cycle and humidity of approximately 60%, and allowed free access to food and water. Animal care and general protocol for animal use conformed to the Kyoto University rules for the care and use of laboratory animals.

2.1. Induction of subarachnoid hemorrhage

After the administration of atropine sulfate (50 μg/kg, i.p.), the rats were anesthesized with pentobarbital sodium (40 mg/kg, i.p.). As soon as autologous blood (0.3 ml) was withdrawn from a femoral artery, the rat was held in a vertical position. After a 26-gauge needle was carefully inserted into the cisterna magna, the blood was injected in a 3-min time frame. We also prepared the sham-operated group. They received an infusion of 0.3 ml of saline in the cisterna magna.

2.2. Diameter of rat basilar artery

To reveal when early and delayed vasospasms are developed in subarachnoid hemorrhage rats, diameters of rat basilar arteries were measured at several time courses after subarachnoid hemorrhage. Rats were anesthesized with pentobarbital sodium (40 mg/kg, i.p.) and sacrificed by bleeding the abdominal aorta. The brain was rapidly removed and put into Krebs–Henseleit solution. The solution consisted of 120 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4 \cdot 7H_2O$, 1.2 mM KH_2PO_4, 2.5 mM $CaCl_2 \cdot 2H_2O$, 25 mM $NaHCO_3$, and 10 mM glucose. The pH of the solution was 7.4. As soon as the brain was isolated, a photograph around the area of the basilar artery was taken with a camera (Polaroid Digital Microscope Camera 2; Olympus, Osaka, Japan). The basilar artery diameter was determined at three locations: 0.5 mm above the junction of the vertebral arteries, at the midpoint of the basilar artery, and just below the bifurcation of the posterior cerebral arteries. The diameter data were expressed as the average of these three locations. In the present study, the angiographical method was not used in order to avoid the side effects of the contrast medium.

2.3. In vitro pharmacology

The diameter of the basilar artery was measured and then it was dissected free and excised after acupuncture needle (120 μm diameter) insertion. The basilar artery was then helically cut into strips 5 mm long and 0.5 mm wide. The basilar segments were vertically fixed between hooks for continuous recording of isometric tension. Rat basilar artery reactivity was recorded in a temperature-controlled (37 °C) polygraph (Japan GE Marquette Medical System, Kyoto, Japan) containing 10 ml of Krebs–Henseleit buffer. The solution was continuously equilibrated with 5% CO_2 in O_2 resulting in a stable pH of 7.4. One-hour equilibration was performed by washing every 20 min and adjusting the basal tension to 300 mg. Each segment was contracted with 80 mM KCl to test the contractile function. Once this contraction reached plateau, the spiral arterial strip was washed repeatedly, then allowed to equilibrate for 30 min and return to the original basal tone before experiments were performed. The experiments were performed with these spiral arterial strips from both control and subarachnoid hemorrhage rats. To examine changes in reactivity to vasopressin, we assessed vasopressin (3×10^{-10} M)-induced contraction according to time courses after subarachnoid hemorrhage. Concentration–response curves for vasopressin (3×10^{-12} to 10^{-8} M) were obtained by its cumulative addition to the organ bath, using basilar arteries from the control, subarachnoid hemorrhage (1 h), and subarachnoid hemorrhage (1 day) rats. To assess which receptor contributes to the enhancement of vasopressin-induced contraction, we constructed the concentration–response curves for vasopressin V_1 and V_2 receptor agonists in basilar arteries isolated from control and subarachnoid hemorrhage (1 day) rats, and examined the inhibitory effect of vasopressin V_1 and V_2 receptor antagonists on dose–response curve for vasopressin. We used (Phe2, Orn8)-oxytocin as vasopressin V_1 receptor agonist, desmopressin as vasopressin V_2 receptor agonist, SR49059 as vasopressin V_1 receptor antagonist, and SR121463B as vasopressin V_2 receptor antagonist. Furthermore, to assess the dependence of the endothelium on the contractile effect of vasopressin and the vasopressin V_1 receptor agonist, concentration–response curves were constructed from the arteries in which the

endothelium had been removed. The endothelium was removed by saponin perfusion at a concentration of 100 mg/l for 10 min, as previously described (Büyükafsar et al., 2004). After saponin perfusion, the contraction induced by 80 mM KCl was not affected significantly and the relaxation evoked by acetylcholine (3×10^{-6} M) was almost abolished. The contraction induced by 80 mM KCl was used as a measure of tissue contractile response. There were no significant differences (unpaired Student's t test) in the response to KCl between arteries from control and subarachnoid hemorrhage (1 day) rats (control, 50.9±2.4 mg, n=55; subarachnoid hemorrhage, 50.8±3.1 mg, n=41), in agreement with previous studies of in vitro pharmacology regarding subarachnoid hemorrhage (Hansen-Schwartz et al., 2003; Alabadí et al., 1997).

2.4. Drugs and chemicals

Vasopressin and (Phe2, Orn8)-oxytocin were purchased from Auspep (Parkville, Victoria, Australia), saponin was from MP Biomedicals (Ohio, USA), and desmopressin was from Peninsula Laboratories (Australia). SR49059 and SR121463B were generously supplied by Sanofi Recherche (Toulouse, France). All chemicals were dissolved in distilled water except for saponin, which was added and dissolved in Krebs–Henseleit solution so that the vascular network could be perfused for effective endothelium removal, as previously described (Büuÿkafsar et al., 2004).

2.5. Statistical analysis

All data are shown as mean±S.E.M. The diameter of the basilar artery was expressed in microns. For in vitro pharmacology, contraction values were expressed as percentages of the previous depolarization induced by 80 mM KCl. For each concentration–response curve, the maximum effect (E_{max}), the concentration of the drug which made half of E_{max} (EC_{50}), and the negative logarithm of EC_{50} (pD_2) were calculated. As for comparisons, one-way analysis of variance (ANOVA), followed by unpaired Student's t-test or Dunnett's test, if appropriate, was used. P values less than 0.01 were considered as significant.

3. Results

3.1. Diameter of the basilar artery

The diameter of the basilar artery in control rats was 249.8±4.9 μm. It was significantly reduced to 120.9±9.1 μm in subarachnoid hemorrhage (1 h) rats. In subarachnoid hemorrhage (16 h) rats, the diameter was not significantly different from control rats and was significantly reduced in subarachnoid hemorrhage (1 day) and subarachnoid hemorrhage (2 days) rats. Diameters of basilar arteries from subarachnoid hemorrhage (3–7 days) rats were not significantly different from control rats. These results suggested that early and delayed vasospasms developed 1 h and 1–2 days after subarachnoid hemorrhage induction, respectively (Fig. 1). In the sham-operated group, the diameter was not significantly different from control rats, even 1 day after the sham operation (241.7±12.2 μm, n=6).

3.2. In vitro pharmacology

By assessing vasopressin-induced contraction at the concentration of 3×10^{-10} M over several time courses after subarachnoid hemorrhage induction, it was revealed that the contractile response of the basilar artery to vasopressin significantly increased 1 day after subarachnoid hemorrhage induction (Fig. 2). For further research, cumulative concentration–response curves for vasopressin were constructed from control, subarachnoid hemorrhage (1 h), and subarachnoid hemorrhage (1 day) rats (Fig. 3). There were no significant differences between control and subarachnoid hemorrhage (1 h) rats in the contractile response to vasopressin with the pD_2 (control, 9.51±0.06; subarachnoid hemorrhage, 9.35±0.08) and the E_{max} (control, 200±16%; subarachnoid hemorrhage, 222±12%). In arteries from subarachnoid hemorrhage (1 day) rats, the concentration–response curve shifted leftward compared with that of control rats, and the pD_2 (10.03±0.06) was significantly higher than that of arteries from control rats (9.51±0.06), while there were no significant differences between the E_{max} (Fig. 3; Table 1). In the sham-operated group, the pD_2 (9.82±0.07, n=8) was not significantly different from that of control rats.

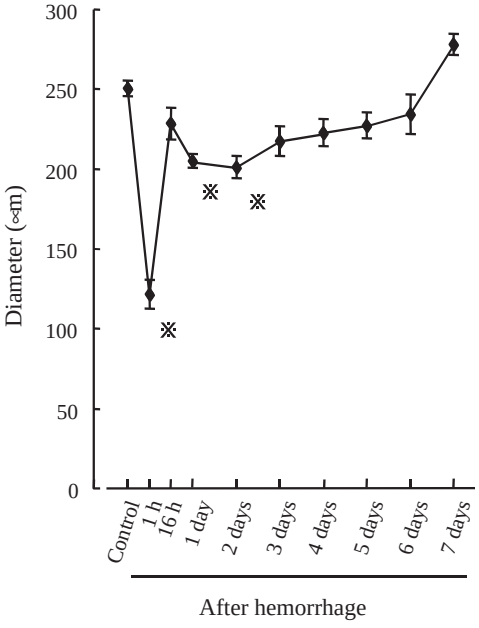

Fig. 1. The diameter of rat basilar arteries after subarachnoid hemorrhage. Data are expressed as mean±S.E.M. of at least six rats. Statistical comparisons were performed by ANOVA followed by Dunnett's test. ※ indicates P<0.01 vs. control rats.

The cumulative concentration–response curve for vasopressin V_1 receptor agonist, (Phe2, Orn8)-oxytocin, also was constructed (Fig. 4A). In arteries from subarachnoid hemorrhage (1 day) rats, the concentration–response curve shifted leftward and upward compared with that of control rats, and both the pD_2 (9.24±0.04) and the E_{max} (300±29%) were significantly higher than the values of arteries from control rats (pD_2, 8.81±0.08; E_{max}, 193±15%) (Fig. 4A; Table 1). As for the cumulative concentration–response curve for vasopressin V_2 receptor agonist, desmopressin, there was a slight contractile response in rat basilar arteries (Fig. 4B). By vasopressin V_1 receptor antagonist, the pD_2 was significantly reduced in arteries from both control and subarachnoid hemorrhage (1 day) rats (Fig. 5A; Table 1). The pD_2 was not affected by vasopressin V_2 receptor antagonist, SR121463B, in arteries from both control and subarachnoid hemorrhage (1 day) rats (Fig. 5B; Table 1).

After endothelium removal with saponin, the pD_2 calculated from concentration–response curves for vasopressin in basilar arteries with endothelium denuded (control rats, 9.13±0.03; subarachnoid hemorrhage rats, 9.48±0.08) were reduced in both control and subarachnoid hemorrhage (1 day) rats compared with those with endothelium intact (control rats, 9.51±0.06; subarachnoid hemorrhage rats, 10.03±0.06). Moreover, in basilar arteries with the endothelium denuded, the E_{max} was significantly reduced in control rats (139±14%), while it was not significantly reduced in subarachnoid hemorrhage (1 day) rats (220±25%), compared with those with endothelium intact (control rats, 200±16%; subarachnoid hemorrhage rats, 239±32%) (Fig. 6A and B). Under physiological conditions, the plasma vasopressin level was approximately 10^{-11}–1.5×10^{-11} M and increased to approximately 3×10^{-11} M in the phase of delayed vasospasm after subarachnoid hemorrhage (De Smet et al., 2003; Lászlo et al., 1995). After endothelium removal, vasopressin-induced contraction at 10^{-11} M was abolished in control rats, while vasopressin-induced contraction at 3×10^{-11} M was also abolished in subarachnoid hemorrhage (1 day) rats (Fig. 6A and B). As for the endothelium dependency in (Phe2, Orn8)-oxytocin-induced contraction, there were no significant differences between both the pD_2 (endothelium-intact, 8.82±0.08; endothelium-denuded, 8.68±0.06) and the E_{max} (endothelium-intact, 198±14%; endothelium-denuded, 150±24%) in basilar arteries from control rats (Fig. 6C).

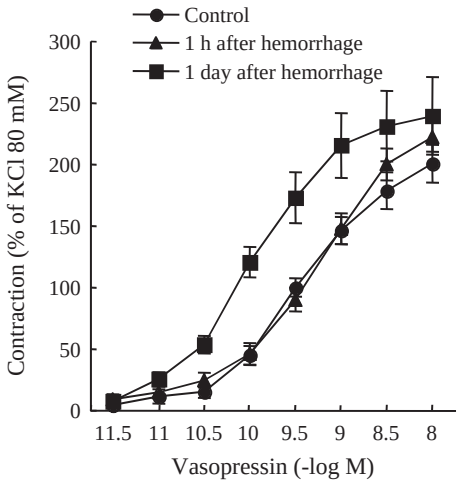

Fig. 3. Cumulative concentration–response curves for vasopressin in basilar arteries isolated from control and subarachnoid hemorrhage rats. Contraction values are expressed as percentages of the previous depolarization induced by 80 mM KCl; mean±S.E.M. of at least six rats.

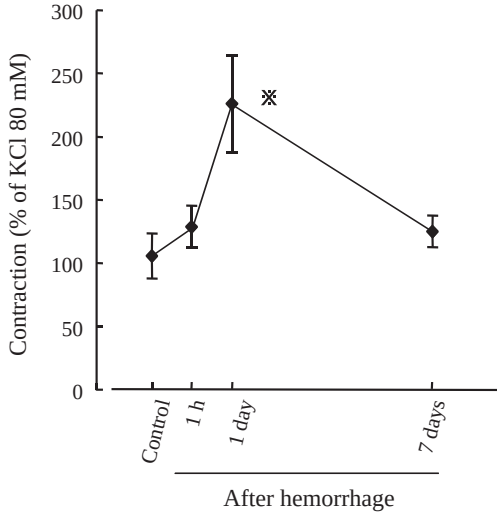

Fig. 2. Changes in vasopressin-induced contraction at 3×10^{-10} M in basilar arteries according to time courses after subarachnoid hemorrhage. Contraction values are expressed as percentages of the previous depolarization induced by 80 mM KCl; mean±S.E.M. of at least six rats. ※ indicates $P<0.01$ vs. control rats.

4. Discussion

In this study, we demonstrated increased sensitivity of the basilar artery to vasopressin in the vasospasm phase after subarachnoid hemorrhage. To date, increased vascular sensitivity to vasoconstrictors has been reported in many pathological conditions such as diabetes (Alabadí et al., 2004), chronic airway inflammation (Zhang et al., 2004), and hypertension (Cardillo et al., 1999). Regarding vasospasm after subarachnoid hemorrhage, upregulations of 5-hydroxytryptamine and endothelin-1 receptors have been reported (Hansen-Schwartz, 2004; Alabadí et al., 1997). Vasopressin is a well-known and potent vasoconstrictor and has also been reported to contribute the development of vasospasm following subarachnoid hemorrhage (Trandafir et al., 2004; Delgado et al., 1988).

It has been demonstrated that vasospasm is biphasic in a model of subarachnoid hemorrhage using the Sprague–Dawley rat, and maximum early vasospasm developed 10 min after subarachnoid hemorrhage induction and maximum delayed vasospasm 2 days later angiographically

Table 1
The pD_2 and E_{max} values for each concentration–response curve

	Time after hemorrhage	Endothelium	n	pD_2	EC_{50} (M)	E_{max} (% KCl)
Vasopressin	Control	(+)	7	9.51±0.06	3.09×10^{-10}	200±15
Vasopressin	1 h	(+)	8	9.35±0.08	4.46×10^{-10}	221±12
Vasopressin	1 day	(+)	8	10.03±0.06[a]	9.33×10^{-11} [a]	239±31
(Phe2, Orn8)-oxytocin	Control	(+)	7	8.82±0.08	1.51×10^{-9}	197±14
(Phe2, Orn8)-oxytocin	1 day	(+)	8	9.24±0.04[a]	5.75×10^{-10} [a]	300±29[a]
Vasopressin	Control	(−)	9	9.13±0.03[b]	7.14×10^{-10} [b]	139±14[b]
Vasopressin	1 day	(−)	6	9.48±0.08[a,b]	3.31×10^{-10} [a,b]	220±25[a]
(Phe2, Orn8)-oxytocin	Control	(−)	6	8.68±0.06	2.08×10^{-9}	150±24
SR49059+vasopressin	Control	(+)	6	8.60±0.11	2.51×10^{-9} [c]	183±10
SR49059+vasopressin	1 day	(+)	6	9.05±0.09	8.91×10^{-10} [c]	278±24
SR121463B+vasopressin	Control	(+)	6	9.45±0.07	3.54×10^{-10}	208±22
SR121463B+vasopressin	1 day	(+)	6	9.86±0.06	1.38×10^{-10}	280±41

E_{max} values are expressed as percentages of the previous depolarizations induced by 80 mM KCl. The pD_2 and the E_{max} values are mean±S.E.M. n indicates the number or rats in each experiment.

[a] Significantly different from the corresponding value of control rats, $P<0.01$.

[b] Significantly different from the corresponding value of endothelium-intact rats, $P<0.01$.

[c] Significantly different from the corresponding value without antagonists, $P<0.01$.

(Suzuki et al., 1999; Delgado et al., 1985). So far, delayed vasospasm in rats has been considered to resemble the human vasospasm and very large studies of rat subarachnoid hemorrhage models have been performed to elucidate the mechanism of developing vasospasm after subarachnoid hemorrhage (Hansen-Schwartz et al., 2003; Josko, 2003; Clark et al., 2002; Lambert et al., 2002; Svendgaard et al., 1985). In the present study, the angiographical method was not used in order to avoid the side effects of the contrast medium. Here, as for diameter, a significant difference from control rats was observed 1 h and 1–2 days after subarachnoid hemorrhage induction. It was demonstrated that early and delayed vasospasms developed 1 h and 1–2 days after subarachnoid hemorrhage induction in rats, respectively, in agreement with previous studies by angiography (Suzuki et al., 1999; Delgado et al., 1985).

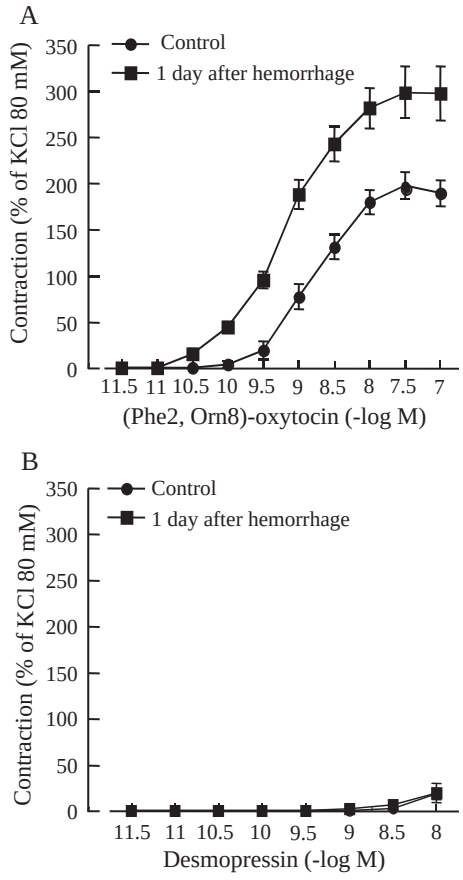

Fig. 4. Cumulative concentration–response curves for vasopressin V_1 receptor agonist, (Phe2, Orn8)-oxytocin (A), and vasopressin V_2 receptor agonist, desmopressin (B), in basilar arteries isolated from control and subarachnoid hemorrhage (1 day) rats. Contraction values are expressed as percentages of the previous depolarization induced by 80 mM KCl; mean±S.E.M. of at least six rats.

From the results of in vitro pharmacology, it was demonstrated that the contractile response to vasopressin was enhanced 1 day after subarachnoid hemorrhage induction, which corresponds to the phase of delayed vasospasm. Vasopressin activates two types of cell surface receptors (vasopressin V_1 receptor and vasopressin V_2 receptor), and has been reported to cause vasoconstriction via the activation of vasopressin V_1 receptor in the basilar artery of the rat (Katori et al., 2001; Faraci, 1989; Rusch and Hermsmeyer, 1985), rabbit (García-Villalón et al., 1996), and human (Martín de Aguilera et al., 1990). In concentration–response curves for (Phe2, Orn8)-oxytocin of basilar arteries from subarachnoid hemorrhage (1 day) rats, both the pD_2 and the E_{max} were significantly enhanced compared with the values from control rats, and SR49059 inhibited vasopressin-induced contraction directly. As for the concentration–response curves for desmopressin, the contraction was negligible and SR121463B had no influence on the concentration–response curves for vasopressin. These results indicate enhanced reactivity of vasoconstriction via vasopressin V_1 receptors in the vasospasm phase. In the vasospasm phase, the plasma vasopressin level is significantly increased (De Smet et al., 2003; Lászlo et al., 1995). Therefore, it seems possible that enhanced reactivity of

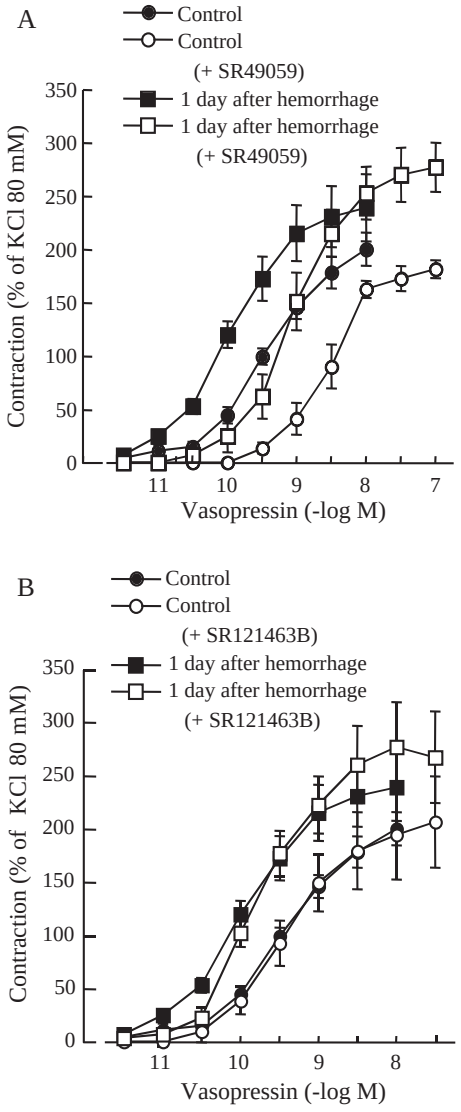

Fig. 5. Inhibitory effect of vasopressin V_1 receptor antagonist, SR49059 (A), and vasopressin V_2 receptor antagonist, SR121463B (B), on cumulative concentration–response curves for vasopressin in basilar arteries isolated from control and subarachnoid hemorrhage (1 day) rats. Contraction values are expressed as percentages of the previous depolarization induced by 80 mM KCl; mean±S.E.M. of at least six rats.

vasoconstriction via vasopressin V_1 receptors might contribute to the development of vasospasm following subarachnoid hemorrhage.

In both control and subarachnoid hemorrhage (1 day) rats, vasopressin-induced contraction was reduced after endothelial removal with saponin. Especially in the concentration range 3×10^{-12} to 3×10^{-11} M, which corresponds to the physiological vasopressin level, vasopressin-induced contraction was abolished. This result suggests that vasopressin-induced contraction at these concentrations is endothelium-dependent. Moreover, vasopressin-induced contraction in the vasospasm phase increased at these concentrations compared with control rats. Thus, endothelium-dependent contraction by vasopressin at physiological concentration significantly increases in the vasospasm phase. To date, it has been reported that vasopressin-induced contraction is mediated

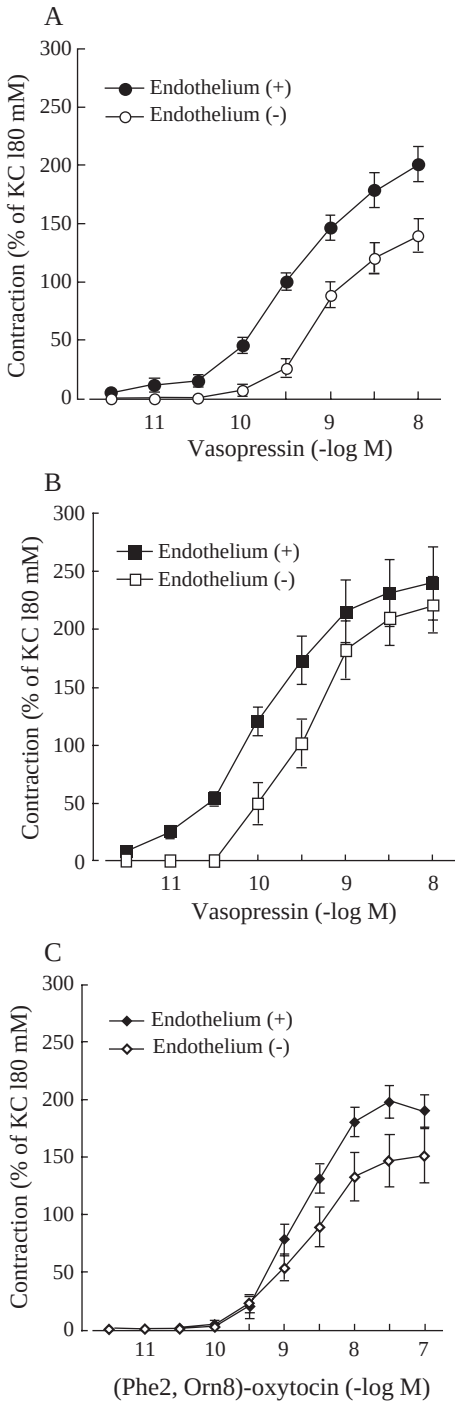

Fig. 6. Influence of endothelium removal on cumulative concentration–response curves for vasopressin in basilar arteries isolated from control rats (A) and subarachnoid hemorrhage (1 day) rats (B). Influence of endothelium removal on cumulative concentration–response curves for vasopressin V_1 receptor agonist, (Phe2, Orn8)-oxytocin, in basilar arteries isolated from control rats (C). Contraction values are expressed as percentages of the previous depolarization induced by 80 mM KCl; mean±S.E.M. of at least six rats.

by vasopressin V_1 receptors located in the vascular smooth muscle cells (Doyle and Ruegg, 1985), while the endothelium has been reported to play a role in vasopressin-induced contraction (Streefkerk et al., 2003). From the results of the contractile effect of vasopressin V_1 receptor agonist after endothelium removal, it was demonstrated that there were no significant differences in the contractile effect of (Phe2, Orn8)-oxytocin between endothelium-intact and endothelium-denuded control rats, although there was a significant difference in the contractile effect of vasopressin between endothelium-intact and endothelium-denuded rats. This result indicates that there might be vasopressin V_1-like receptors, which cause vasoconstriction, on the surface of the endothelium. Further investigations are warranted to elucidate the mechanism of endothelium-dependent contraction by vasopressin.

In conclusion, the enhancement of vasopressin-induced contraction via vasopressin V_1 receptor was observed in the vasospasm phase. We have previously reported that the administration of vasopressin V_1 receptor antagonist prevented the change of basilar artery diameter in the vasospasm phase (Trandafir et al., 2004). It seems possible that enhanced reactivity to vasopressin via vasopressin V_1 receptor might contribute to the development of the vasospasm after subarachnoid hemorrhage.

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