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Vasopressin receptor subtypes on mesenteric and cremasteric arterioles in rat

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Abstract

We studied the effects of a selective vasopressin V_{1A} receptor antagonist [1-(1-(4-(3-acetylaminopropoxy)benzoyl)-4-piperidyl)-3,4-dihydro-2(1*H*)-quinolinone (OPC-21268)] and a selective vasopressin V_2 receptor antagonist [5-dimethylamino-1(4-(2-methylbenzoylamino)benzoyl)-2,3,4,5-tetrahydro-1*H*-benzazepine (OPC-31260)] on vasopressin-induced contraction of mesenteric and cremasteric arterioles in urethane-anaesthetized rats. Vasopressin was infused intravenously for 60 min or applied topically to arterioles directly. Vasopressin infusion (50, 100 or 500 ng/kg/min) decreased the diameter of both mesenteric and cremasteric arterioles. Vasopressin (500 ng/kg/min)-induced vasoconstriction was antagonized by OPC-21268 (0.2, 1.0 and 5.0 mg/kg, i.v.), dose-dependently, but not by OPC-31260. Topically applied vasopressin (4.6×10^{-10}–4.6×10^{-8} M) dose-dependently constricted both microvessels. Pre-administration of OPC-21268 (5.0 mg/kg, i.v.) completely inhibited topically applied vasopressin-induced vasoconstriction in both microvessels, and OPC-31260 partially inhibited it in cremasteric arterioles. These results suggest that vasopressin induces vasoconstriction in rat mesenteric and cremasteric arterioles mainly by stimulating vasopressin V_{1A} receptors, while vasoconstriction in cremasteric arterioles is partly associated with stimulation of vasopressin V_2 receptors.

Keywords: Vasopressin; Microvascular constriction; Mesenteric arteriole; Cremasteric arteriole; OPC-21268; OPC-31260

1. Introduction

Vasopressin plays an important role in cardiovascular homeostasis through both its vasoconstrictor and antidiuretic actions. These activities of vasopressin are believed to be exerted through stimulation of specific vasopressin receptors. Vasopressin receptor subtypes (V_{1A}, V_{1B} and V_2) have been identified, cloned and found to belong to a family of seven membrane-spanning receptors that transduce signals via G proteins (Birnbaumer et al., 1992; Sugimoto et al., 1994; Thibonnier et al., 1994).

Vasopressin causes potent vasoconstriction by stimulating vasopressin V_{1A} receptors located on vascular smooth muscle cells (Stam et al., 1998). The antidiuretic action of vasopressin is due to stimulation of vasopressin V_2 receptors on kidney cells (Ausiello et al., 1987). In arteries from different sources, vasoconstriction is mediated by vasopressin V_{1A} receptor activity (Angus et al., 1994; Burrell et al., 1994; Stam et al., 1998). However, an early study demonstrated that the potency order of [Arg[8]]vasopressin analogs on rat mesenteric arterioles differed from that produced on the rat aorta, suggesting involvement of distinct receptors (Altura, 1975). This notion was substantiated by the use of a selective vasopressin V_{1A} receptor antagonist, 1-(1-(4-(3-acetylaminopropoxy)benzoyl)-4-piperidyl)-3,4-dihydro-2(1*H*)-quinolinone (OPC-21268) (Yamamura et al., 1991) and by a selective vasopressin V_2 receptor antagonist, 5-dimethylamino-1(4-(2-methylbenzoylamino)benzoyl)-2,3,4,5-tetrahydro-1*H*-benzazepine (OPC-31260) (Yamamura et al., 1992). To our knowledge there have been no reports on the effects of vasopressin receptor antagonists on mesenteric and cremasteric microvessels. This is important because of the heterogeneity of response in different vessels. In the present study, we investigated the effects of nonpeptide vasopressin V_{1A} and V_2 receptor antagonists on [Arg[8]]vasopressin-induced vasoconstriction of mesenteric and cremasteric arterioles in anaesthetized rats.

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2. Materials and methods

2.1. Experimental protocol

All studies were carried out by direct microscopic observation of arterioles in the mesenteries and cremasters of urethan-anaesthetized (1.3 g/kg, i.m.) male Wistar rats (250–350 g). Animal care, surgical preparation, and experimental procedures were approved by the Committee for Animal Experiments in Kagoshima University. After induction of anaesthesia, tracheostomy was performed and polyethylene catheters were placed in the left femoral artery (SP37, Natsume, Tokyo, Japan) and right femoral vein (SP10, Natsume, Tokyo, Japan) to monitor arterial pressure directly and to administer drug, respectively.

The rat mesenteric or cremasteric microvessels were exposed and kept under physiological conditions according to procedures described previously (Nishio et al., 1988). Each microvessel was superfused with a Ringer–gelatin bicarbonate solution (pH 7.4) (Altura, 1975). In vivo microscopic observations for discrete quantitative changes in microvascular lumen size (internal diameter) were made at magnifications up to 1550 times using a video–television microscope recording system (Angus et al., 1994; Baez, 1973; Nishio et al., 1988).

Systemic intravenous [Arg^8]vasopressin was administered by an infusion pump (Model 11, Harvard Apparatus, South Natick, MA, USA). After collection of baseline data for about 10 min, vasopressin (50, 100 or 500 ng/kg/min) was infused for 60 min at 20 μl/min. Parallel control experiments were conducted with saline vehicle infused for 60 min. At 30 min of vasopressin infusion, either a selective vasopressin V_{1A} receptor antagonist, OPC-21268, or a selective vasopressin V_2 receptor antagonist, OPC-31260, was intravenously administered to examine the contribution of vasopressin V_{1A} or V_2 receptors to the mesenteric and cremasteric microvascular response to vasopressin. During topical application of [Arg^8]vasopressin, superfusion of Ringer–gelatin bicarbonate solution was temporarily interrupted and the changes in arteriolar lumen size recorded for 2 min or until the response disappeared. In the experiments on topical application of vasopressin, OPC-21268, OPC-31260 or vehicle was administered intravenously 10 min before each application of vasopressin.

Changes in lumen size for each arteriole examined were observed on a television monitor and recorded on videotape, then measured using the NIH Image 1.56 software package. This method allows measurement of variations in arteriole diameter with a precision close to 0.1 μm.

2.2. Statistical analysis

Statistical analyses were performed using a Statistical Analysis System (R6.12, SAS Institute Japan, Tokyo, Japan). Differences between control (saline vehicle) group and vasopressin-treated groups were analyzed by repeated measures analysis of variance (ANOVA) followed by two-tailed Dunnett's multiple-comparison test at each time point using the values expressed as changes from the baseline. Differences between the control group and vasopressin receptor antagonist (OPC-21268 or OPC-31260)-treated groups were analyzed by repeated measures ANOVA followed by the two-tailed Dunnett's multiple-comparison test at each time point using values expressed as changes from the value just before administration of the antagonist. Regression analysis was performed on concentration–response curves of vasopressin concentration versus IC_{50} values (the concentration producing a 50% decrease in microvessel diameter from the baseline diameter) and 95% confidence intervals were calculated with the logarithmically transformed concentrations. Differences between the antagonist-treated and vehicle-treated groups in Table 1 were analyzed by one way-ANOVA followed by two-tailed Dunnett's multiple comparison and two-tailed *t*-test. Difference were considered significant at $P < 0.05$. Values are presented as mean ± S.E.M.

2.3. Materials

OPC-21268 and OPC-31260 were synthesized by Otsuka Pharmaceutical (Tokyo, Japan). OPC-21268 was dissolved in dimethylformamide at a concentration of 2.5 mg/ml and diluted with distilled water to the desired concentrations and injected at a volume of 2.0 ml/kg. OPC-31260 was dissolved in distilled water at a concentration of 2.5 mg/ml and diluted with distilled water to the desired concentrations and injected at a volume of 2.0 ml/kg. [Arg^8]vasopressin, urethane (carbamic acid ethyl ester) and heparin sodium salt were purchased from Sigma (St. Louis, MO, USA), Tokyo Kasei (Tokyo, Japan) and Nacalai Tesque (Kyoto, Japan), respectively.

3. Results

3.1. Effects of systemic [Arg^8]vasopressin infusion on microvascular diameter

Continuous infusion of vasopressin (50, 100 and 500 ng/kg/min) produced a significant decrease in the arteriolar diameters of mesenteric and cremasteric microvessels in a dose-dependent manner (Fig. 1). In both vessel types, the decreases in arteriolar diameter during vasopressin infusion were significantly different from those in the saline-infused controls. The responses of cremasteric arterioles to vasopressin infusion were faster than those of mesenteric arterioles.

Systemic mean arterial blood pressure increased to near the maximal level within 10 min at any dose of vaso-

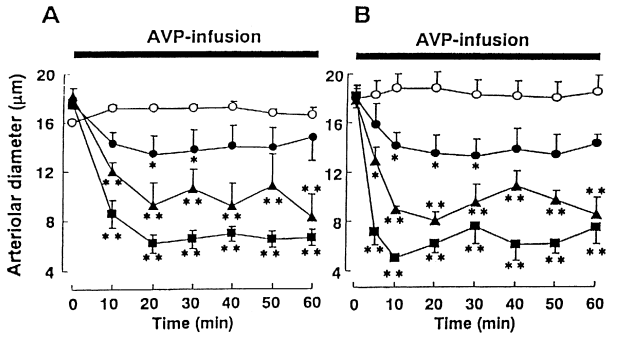

Fig. 1. Microvascular response to continuous intravenous infusion of [Arg^8]vasopressin in mesenteric and cremasteric arteriole of rats. (A) Mesenteric arteriolar diameter after administration of [Arg^8]vasopressin at doses of 50 (●, $n=5$), 100 (▲, $n=5$) and 500 ng/kg/min (■, $n=11$) and control (saline 20 μl/kg/min, ○, $n=5$). (B) Cremasteric arteriolar diameter after administration of [Arg^8]vasopressin at doses of 50 (●, $n=6$), 100 (▲, $n=6$) and 500 ng/kg/min (■, $n=6$) and vehicle (saline 20 μl/kg/min, ○, $n=7$). Each point represents mean ± S.E.M. * and ** represent $P<0.05$ and $P<0.01$, respectively, vs. control group at each time point by two-tailed Dunnett's multiple comparison test. AVP: [Arg^8]vasopressin.

pressin infusion in this experiment. After 30 min of vasopressin infusion at 50, 100 and 500 ng/kg/min, mean arterial blood pressure increased from 111.7 ± 8.3 to 158.3 ± 1.7, from 116.1 ± 4.5 to 156.1 ± 2.5, and from 117.8 ± 3.0 to 155.9 ± 2.7 mm Hg, respectively. There were no significant differences in the final values among these three groups.

3.2. Effect of bolus intravenous administration of OPC-21268 or OPC-31260 on microvascular diameter during [Arg^8]vasopressin infusion

Intravenous administration of OPC-21268 produced a significant increase in both mesenteric (Fig. 2A) and cremasteric (Fig. 2B) microvessel diameters ($P<0.01$). The dilation effect of OPC-21268 was of greater magnitude in cremasteric arterioles than in mesenteric arterioles.

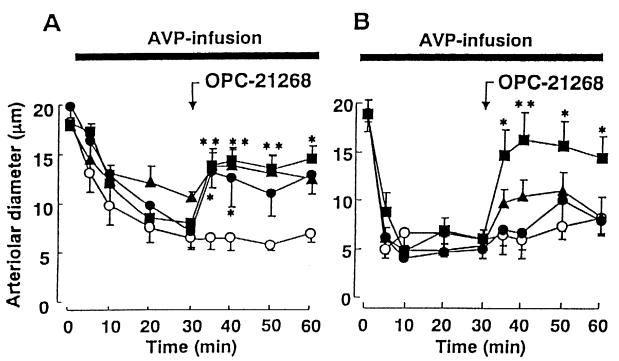

Fig. 2. Effects of intravenously administered OPC-21268 on microvascular diameters during [Arg^8]vasopressin infusion (500 ng/kg/min) in mesenteric and cremasteric arteriole of rats. (A) Mesenteric arteriolar diameter after administration of OPC-21268 at doses of 0.2 (●, $n=5$), 1.0 (▲, $n=6$) and 5.0 mg/kg (■, $n=8$) and vehicle (dimethylformamide; 2.0 ml/kg, ○, $n=8$). (B) Cremasteric arteriolar diameter after OPC-21268 at doses of 0.2 (●, $n=5$), 1.0 (▲, $n=4$) and 5.0 mg/kg (■, $n=7$) and vehicle (dimethylformamide 2.0 ml/kg, ○, $n=6$). Each point represents mean ± S.E.M. * and ** represent $P<0.05$ and $P<0.01$, respectively, vs. control group at each time point by two-tailed Dunnett's multiple comparison test. AVP: [Arg^8]vasopressin.

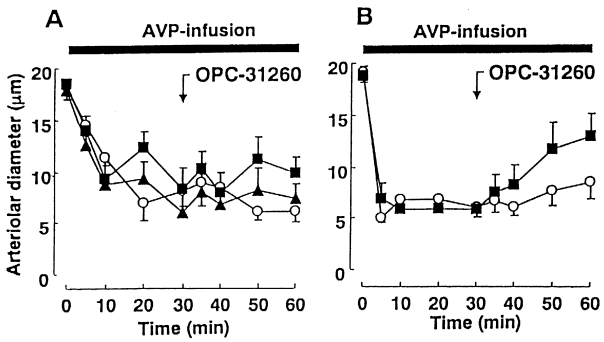

Fig. 3. Effects of intravenously administered OPC-31260 on microvascular diameters during [Arg^8]vasopressin infusion (500 ng/kg/min) in mesenteric and cremasteric arteriole of rats. (A) Mesenteric arteriolar diameter after administration of OPC-31260 at doses of 1.0 (▲, $n=6$) and 5.0 mg/kg (■, $n=6$) and vehicle (distilled water 2.0 ml/kg, ○, $n=6$). (B) Cremasteric arteriolar diameter after OPC-31260 at doses of 5.0 mg/kg (■, $n=6$) and vehicle (distilled water 2.0 ml/kg, ○, $n=6$). Each point represents mean ± S.E.M. AVP: [Arg^8]vasopressin.

OPC-21268 (0.2, 1.0, and 5.0 mg/kg, i.v.) decreased the vasopressin(500 ng/kg/min)-induced increase in systemic mean arterial blood pressure from 154.0 ± 4.3 to 139.0 ± 4.3, from 155.8 ± 3.0 to 133.3 ± 2.1, and from 152.9 ± 1.5 to 113.6 ± 3.0 mm Hg, respectively, within 10 min.

OPC-31260 (1.0 or 5.0 mg/kg, i.v.) showed no significant effect in mesenteric (Fig. 3A). or cremasteric (Fig. 3B) arteriolar diameter. In cremasteric arterioles, however, OPC-31260 (5.0 mg/kg, i.v.) showed a tendency to antagonize the vasopressin(500 ng/kg/min)-induced vasoconstriction, and decreased the vasopressin-induced increase in systemic mean arterial blood pressure from 146.7 ± 2.8 to 130.0 ± 3.7 mm Hg within 10 min, but 1.0 mg/kg OPC-31260 showed no significant effect on the vasopressin-induced increase in systemic mean blood pressure.

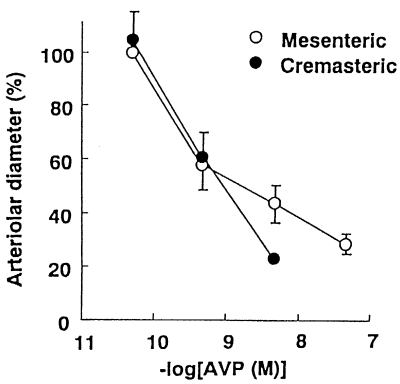

Fig. 4. Concentration–response curve for topically applied [Arg^8]vasopressin in mesenteric and cremasteric arteriole of rats. Diameter of mesenteric (○, $n=8$ each concentration), and cremasteric (●, $n=5$ each concentration) arterioles were normalized by their diameters before vasopressin treatment. Each point represents mean ± S.E.M. AVP: [Arg^8]vasopressin.

OPC-21268 (5.0 mg/kg, i.v.) and OPC-31260 (5.0 mg/kg, i.v.) showed no significant effects on both microvessel diameters in rats in the absence of vasopressin infusion.

3.3. Effect of perivascular application of [Arg^8]vasopressin on microvessel diameter

Mesenteric and cremasteric arterioles both responded to topically applied vasopressin with constriction in a dose-dependent manner (Fig. 4). IC_{50} values and their 95% confidence intervals for mesenteric and cremasteric arterioles were 2.84 nM (1.48–5.43 nM) and 0.90 nM (0.49–1.93 nM), respectively. Vasoconstriction of cremasteric arterioles induced by topically applied vasopressin was relatively stronger than that of mesenteric arterioles.

Table 1 shows the effects of pre-administration of OPC-21268 or OPC-31260 on the degree of microvascular constriction induced by topically applied vasopressin (4.6×10^{-8} M). Pre-administration of OPC-21268 (5.0 mg/kg, i.v.) nearly completely blocked the vasoconstriction induced by topically applied vasopressin in both mesenteric and cremasteric arterioles.

OPC-31260 (5.0 mg/kg, i.v.) showed no significant effect on vasopressin-induced microvascular constriction in mesenteric arterioles, however, in cremasteric arterioles OPC-31260 partly blocked the vasoconstriction induced by topically applied vasopressin.

Table 1
Effects of intravenous administration of OPC-21268 or OPC-31260 on arteriolar reactivity to topically applied [Arg^8]vasopressin (AVP)

	Diameter (μm)			
	Control	Treatment[a]	AVP	*n*
Mesenteric arteriole			AVP (4.6×10^{-8} M)	
	18.55 ± 1.07	Vehicle	4.92 ± 0.47	8
		OPC-21268		
	18.83 ± 0.85	1 mg/kg	4.40 ± 0.92	11
	19.19 ± 0.87	5 mg/kg	16.77 ± 1.60[b]	12
		OPC-31260		
	18.39 ± 0.32	5 mg/kg	4.60 ± 1.98	6
Cremasteric arteriole			AVP (4.6×10^{-9} M)	
	17.42 ± 1.26	Vehicle	4.00 ± 0.32	5
		OPC-21268		
	17.81 ± 1.09	5 mg/kg	17.03 ± 1.23[b]	5
		OPC-31260		
	17.16 ± 0.93	5 mg/kg	8.77 ± 2.54[c]	5

[a] OPC-21268, OPC-31260 or vehicle (dimethylformamide; 2.0 ml/kg) was injected intravenously 10 min before topical application of AVP. *n* represents numbers of rat used. Values are expressed as mean ± S.E.M.

[b] Represents $P < 0.01$ vs. corresponding vehicle group treated with AVP.

[c] Represents $P < 0.05$ vs. corresponding vehicle group treated with AVP.

4. Discussion

Little is known about the receptor subtypes involved in vasopressin-induced contraction of mesenteric and cremasteric arterioles. In the present study, the effects of two selective vasopressin receptor antagonists on vasopressin-induced contraction of these two microvessels were investigated in anaesthetized rats.

Systemic infusion of vasopressin produced contractions of both mesenteric and cremasteric arterioles and increased systemic arterial blood pressure. Both of these effects were dose-dependently antagonized by intravenous administration of the vasopressin V_{1A} receptor antagonist, OPC-21268. The vasopressin V_2 receptor antagonist, OPC-31260, at dose of 5.0 mg/kg, i.v. had no effect on the vasopressin-induced contraction of mesenteric arterioles, however, this dose of OPC-31260 did show a tendency to antagonize vasopressin-induced contraction in cremasteric arterioles and significantly decreased the vasopressin-induced increase in systemic arterial blood pressure.

IC_{50} values of OPC-21268 for vasopressin V_{1A} and V_2 receptor binding in rats were reported to be 4.1×10^{-7} and $> 10^{-4}$ M, respectively (Yamamura et al., 1991), while those of OPC-31260 were 1.2×10^{-6} and 1.4×10^{-8} M, respectively (Yamamura et al., 1992). These results strongly suggest that the contractile responses to vasopressin in rat mesenteric and cremasteric arterioles are mediated mainly via stimulation of vasopressin V_{1A} receptors in both arterioles. However, in cremasteric arterioles vasopressin V_2 receptor stimulation might be involved.

To confirm the above possibility, we applied vasopressin to both arterioles directly. The physiological concentration of vasopressin in plasma is about 10^{-11} M (Cameron et al., 1985). The increase in vasopressin concentrations in the present study was about 10^{-11}–5×10^{-11} M. It is well known that high vasopressin levels occur in certain pathological conditions, such as haemorrhagic shock and severe hypoxia (Cameron et al., 1985; Wang et al., 1981). Topical application of vasopressin (4.6×10^{-10}–4.6×10^{-8} M) to mesenteric and/or cremasteric arterioles induced a constriction in both arterioles. The degree of constriction was stronger in cremasteric than in mesenteric arterioles. This phenomenon was also observed in vasopressin infusion experiments in the present study. These results suggest that vasopressin receptor density or sensitivity to vasopressin of skeletal muscle terminal arterioles is higher than that of splanchnic terminal arterioles. This possibility is supported by a study demonstrating that the resistance vessels in skeletal muscle were more sensitive to the constrictive effect of vasopressin than those in the splanchnic region, such as the small intestine (Liard et al., 1982).

Pre-administration of OPC-21268 completely blocked the vasoconstriction induced by topically applied vasopressin in both mesenteric and cremasteric arterioles. In contrast, OPC-31260 did not significantly affect the vaso-

constriction induced by topically applied vasopressin in mesenteric arterioles, but partially blocked the vasoconstriction in cremasteric arterioles. These results strongly support the above suggestion.

An in vivo study using anaesthetized rats has shown that cremasteric arterioles of about 100 μm diameter respond to topically applied vasopressin (10^{-6} M) with constriction, and that this constriction is completely blocked by a specific vasopressin V_1 receptor antagonist d(CH_2)$_5$Tyr(Me)arginine vasopressin (Baker et al., 1990). In an in vitro study of isolated intracerebral arterioles of rats, vasopressin induced vasoconstriction which was abolished by d(CH_2)$_5$Tyr(Me)arginine vasopressin (10^{-6} M) (Takayasu et al., 1993). These results and the present data suggest that in rat arterioles, including intracerebral, mesenteric and cremasteric microvessels, vasopressin induces vasoconstriction mainly by stimulating vasopressin V_{1A} receptors.

It has been reported that rat intracerebral arterioles were maintained in a dilated state by endothelium-derived relaxing factor activated by vasopressin (Takayasu et al., 1993). However, Vanner et al. (1990) suggested that in isolated submucosal arterioles from humans, rabbits and guinea pigs, endothelium-derived relaxing factor did not play a role in vasoconstrictor responses produced by vasopressin. It seems important to investigate whether or not vasopressin-induced vasoconstrictions of mesenteric and cremasteric arterioles are dependent on endothelium-derived relaxing factor.

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