

## OPC-21268 Antagonizes Arginine Vasopressin-Induced Vasoconstrictor Response in the Spinally-Anesthetized Dog

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**ABSTRACT**—We studied the antagonistic actions of OPC-21268 (1-{1-[4-(3-acetylamino-propoxy)-benzoyl]-4-piperidyl}-3,4-dihydro-2(1*H*)-quinolinone) on the arginine vasopressin (AVP)-induced vasoconstrictor response in the spinally-anesthetized dog. OPC-21268 at doses of 0.3, 1.0 and 3.0 mg/kg, i.v. produced a rightward parallel shift of the dose-response curves for AVP in a dose-dependent manner. The doses of OPC-21268 were similar to those that inhibited the AVP-induced vasoconstrictor response in the rat. This observation suggests that OPC-21268 acts as a  $V_1$ -AVP-receptor antagonist in peripheral resistance vessels in dogs as well as in rats.

**Keywords:** Nonpeptide vasopressin antagonist, Vascular action, OPC-21268

Arginine vasopressin (AVP), a hormone released from the posterior pituitary gland, exerts vasoconstrictor response through  $V_1$ -receptors (1). Recently, we developed the first nonpeptide selective  $V_1$ -receptor antagonist, OPC-21268 (1-{1-[4-(3-acetylamino-propoxy)-benzoyl]-4-piperidyl}-3,4-dihydro-2(1*H*)-quinolinone) (2). OPC-21268 competitively displaced [ $^3$ H]-AVP binding to the plasma membrane of the liver, cultured vascular smooth muscle cells (3) and cultured mesangial cells (4) of the rat. OPC-21268 also antagonized the AVP-induced vasoconstrictor response in the pithed rat by intravenous administration and in the intact rat by oral administration (2). It was also demonstrated that OPC-21268 inhibited the AVP-induced vasoconstrictor response in humans (5). On the other hand, OPC-21268 failed to inhibit or only weakly inhibited AVP-induced vascular constriction or contraction in isolated larger vessels of dogs (6), monkeys (7) and humans (8). These discrepancies may be explained by species differences in antagonist action or differences between large conductance vessels and small vessels that determine peripheral resistance. In this study, we examined the action of OPC-21268 on AVP-induced blood pressure increase in the dog. To eliminate the effects of the vasopressor reflex mechanism, we chose the spinally-anesthetized dog as a preparation and compared the results with those obtained

in the pithed rat (2).

Eight mongrel dogs, weighing 8–12 kg, were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). The trachea of each dog was intubated, and the animal was artificially respired with room air in a tidal volume of 20 ml/kg at 18 breath/min with a dog respirator (SN-480-4; Shinano, Tokyo). In these dogs, polyvinyl catheters for measurement of blood pressure and drug injection were introduced into the left femoral artery and vein, respectively. Spinal anesthesia at the level of the first segment of the cervical cord was induced by an injection of dibucaine at a dose of 0.6 mg/kg into the *Cisterna magna* (9). Both vagus nerves were cut at the midcervical level, and atropine and propranolol were injected at doses of 1.0 mg/kg and 0.2 mg/kg, respectively. Blood pressure was monitored with a pressure transducer (MPU-0.5; NEC-San-ei, Tokyo) and recorded on a thermal pen recorder (Recti-Horiz 8S, NEC-San-ei). AVP (Sigma, St. Louis, MO, USA) was dissolved in saline at a concentration of 5 U/ml and diluted to the desired concentrations with saline. OPC-21268 was dissolved in 20% dimethylformamide (DMF; Wako Pure Chemicals, Osaka) at concentrations of 1.5, 5 and 15 mg/ml and injected at a volume of 0.2 ml/kg. The vasoconstrictor response of AVP was examined by cumulative injection of 0.3 to 30 or 100 mU/kg. Each dose of OPC-21268 or its vehicle, 20% DMF, were injected 2 min before the examination of AVP-treatment (doses of AVP were increased up to 3000 mU/kg). This

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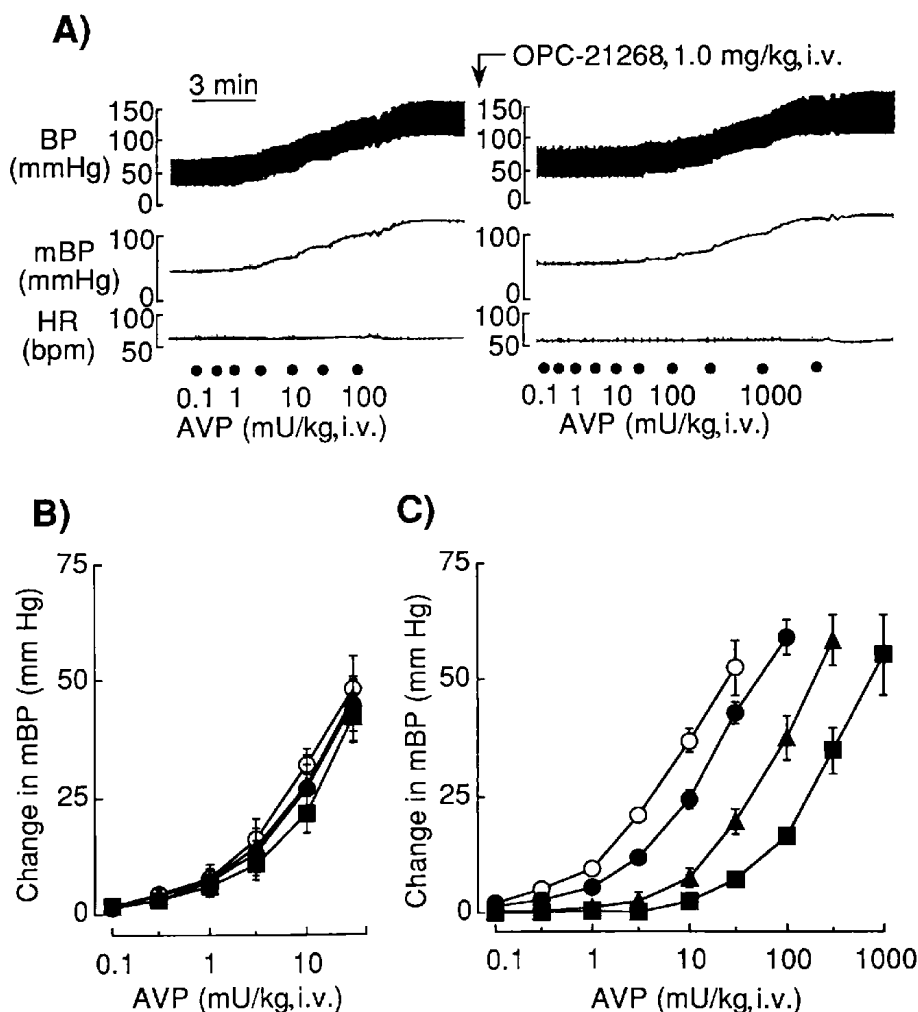
procedure was repeated three times with an increase in OPC-21268 dose. The data are presented as means  $\pm$  S.E.M.

Basal values of systolic, mean and diastolic blood pressure and heart rate of eight dogs were  $129 \pm 9$  mmHg,  $99 \pm 8$  mmHg,  $85 \pm 7$  mmHg and  $151 \pm 10$  beats/min, respectively. After spinal anesthesia, these values were decreased by  $81 \pm 6$  mmHg,  $55 \pm 4$  mmHg,  $43 \pm 3$  mmHg and  $98 \pm 5$  beats/min, respectively. These dogs were divided into two groups. Basal parameters of the two groups were not significantly different.

When AVP was cumulatively injected at doses of 0.3 to 100 mU/kg, blood pressure increased dose-dependently, but heart rate did not change (Fig. 1A). In some prepara-

tions, the highest dose of AVP (100 mU/kg) produced a transient blood pressure decrease. As shown in Fig. 1B, the vasoconstrictor response induced by AVP was not affected by the previous treatment of DMF and observed repetitively. The treatment with OPC-21268 at doses of 0.3, 1.0 and 3.0 mg/kg, i.v. produced a rightward parallel shift of the dose-response curves for AVP in a dose-dependent manner (Fig. 1C). This result suggests that OPC-21268 competitively antagonizes the AVP-induced vasoconstrictor response in the dog.

Previously, we demonstrated that OPC-21268 at doses of 0.1, 0.3 and 1.0 mg/kg, i.v. exerted a parallel shift of the AVP-induced vasoconstrictor response curves for AVP in the pithed rat (2). The doses in the spinally-



**Fig. 1.** Effects of OPC-21268 on arginine vasopressin (AVP)-induced vasoconstrictor response in the spinally-anesthetized dog. Panel A shows an example of the actual traces of AVP-induced blood pressure (BP), mean BP (mBP) and heart rate (HR) changes and the action of OPC-21268 on those parameters. The dose-response curves for AVP were obtained by cumulative injection. OPC-21268 (panel C) and its vehicle, 20% dimethylformamide (DMF) (panel B), were administered 2 min before AVP injection. Open circles, filled circles, filled triangles and filled squares represent the control, the 1st, 2nd and 3rd treatment of 20% DMF, respectively in panel B. They stand for the control, 0.3, 1.0 and 3.0 mg/kg, i.v. administration of OPC-21268, respectively in panel C. Changes in mBP are presented as means  $\pm$  S.E.M. of four experiments.

anesthetized dog were similar to those in the pithed rat. We observed an increase in systemic blood pressure in these studies and it seems that the blood pressure increase reflects the contraction of peripheral resistance vessels. On the other hand, Chiba and Tsukada (6) demonstrated that only high concentrations of OPC-21268 shifted the AVP-induced vasoconstriction in the large femoral arteries. Therefore, the difference in the vascular action of AVP between large conductance vessels and small resistance vessels is the most plausible explanation for the results. Although we cannot discuss species differences from the results of this study, species differences of AVP antagonists are described in a recent report (10). We must keep in mind species differences and organ part differences to solve the physiological roles of AVP.

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