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Effect of vasopressin V1- and V2-receptor stimulation on blood pressure in DOCA-salt hypertensive rats.

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Abstract

We recently reported that stimulation of the arginine vasopressin (AVP) V1-receptor enhanced the pressor response in spontaneously hypertensive rats (SHR). In the present study, we investigated acute changes in systolic blood pressure (SBP) and heart rate (HR) after intravenous injections of AVP, OPC-21268 (a V1-receptor antagonist), and OPC-31260 (a V2-receptor antagonist), in anesthetized DOCA-salt hypertensive rats (DOCA) and age-matched sham-operated Wistar rats (control) to determine whether the pressor effect is specific to SHR or is present in other hypertensive animal models. SBP increased significantly in DOCA rats 9 min after injection of AVP 5 ng/kg without a concomitant increase in HR. Neither OPC-21268 3mg/kg nor OPC-31260 3mg/kg caused significant changes in SBP or HR. SBP tended to increase when AVP was administered after injection of OPC-31260. HR increased significantly 15 min after the combined treatment with OPC-31260 and AVP in DOCA rats compared with control rats. SBP did not change significantly when AVP was administered after injection of OPC-21268 in DOCA or control rats, but HR decreased significantly from 1 to 4 min after injection of AVP in DOCA rats. Our results suggest that V1-receptor stimulation does not enhance the pressor response in the DOCA rat, which is a model of volume-dependent hypertension, suggesting that the AVP system, especially V1-receptor, is not as important in the development or maintenance of hypertension in DOCA rats as in SHR.

KEYWORDS: vasopressin, DOCA-salt hypertensive rat, V1-and V2-receptor antagonist, spontaneously hypertesive rat(SHR), OPC-21268

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Effect of Vasopressin V_1- and V_2-Receptor Stimulation on Blood Pressure in DOCA-Salt Hypertensive Rats

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We recently reported that stimulation of the arginine vasopressin (AVP) V_1-receptor enhanced the pressor response in spontaneously hypertensive rats (SHR). In the present study, we investigated acute changes in systolic blood pressure (SBP) and heart rate (HR) after intravenous injections of AVP, OPC-21268 (a V_1-receptor antagonist), and OPC-31260 (a V_2-receptor antagonist), in anesthetized DOCA-salt hypertensive rats (DOCA) and age-matched sham-operated Wistar rats (control) to determine whether the pressor effect is specific to SHR or is present in other hypertensive animal models. SBP increased significantly in DOCA rats 9 min after injection of AVP 5 ng/kg without a concomitant increase in HR. Neither OPC-21268 3 mg/kg nor OPC-31260 3 mg/kg caused significant changes in SBP or HR. SBP tended to increase when AVP was administered after injection of OPC-31260. HR increased significantly 15 min after the combined treatment with OPC-31260 and AVP in DOCA rats compared with control rats. SBP did not change significantly when AVP was administered after injection of OPC-21268 in DOCA or control rats, but HR decreased significantly from 1 to 4 min after injection of AVP in DOCA rats. Our results suggest that V_1-receptor stimulation does not enhance the pressor response in the DOCA rat, which is a model of volume-dependent hypertension, suggesting that the AVP system, especially V_1-receptor, is not as important in the development or maintenance of hypertension in DOCA rats as in SHR.

Key words: vasopressin, DOCA-salt hypertensive rat, V_1- and V_2-receptor antagonist, spontaneously hypertesive rat (SHR), OPC-21268

In the field of hypertension research, various hypertension animal models have been used, such as spontaneously hypertensive rats (SHR), stroke-prone SHR (SHR-SP), DOCA-salt hypertensive rats (DOCA), Goldblatt hypertensive rats, Dahl salt-sensitive (Dahl-S) or Dahl salt-resistant (Dahl-R) rats. SHR are often used as a model of human essential hypertension, whereas the DOCA model is considered to be a model of volume-dependent hypertension. We previously found that the number of renal atrial natriuretic peptide (ANP) receptors was genetically reduced in SHR (1), whereas the reduction in the number of ANP receptors in DOCA rats was down-regulated by an increase in the blood level of ANP (2). We also found that renal AVP receptors were increased in the presence of established hypertension in SHR (3, 4) and that treatment with indapamide, an antihypertensive diuretic (5), and cilazapril, an angiotensin-converting enzyme (ACE) inhibitor (6), altered the affinity of renal AVP receptors. In contrast, AVP receptors on the mesenteric vasculature have been found to be reduced in DOCA rats (7). Although the exact causes of hypertension in SHR and DOCA rats have not been clarified, these findings suggest that high blood pressure is caused by different mechanisms in these animal models. OPC-21268 and OPC-31260 are specific V_1 and V_2 nonpeptide antagonists, respectively (8, 9). We previously found that stimulation of AVP-V_1-receptors, but not AVP-V_2-receptors, induced a marked increase in systolic blood pressure in SHR (10), suggesting that V_1 activation may be enhanced in SHR, possibly due to an increased number of V_1-receptors. This effect has not been demonstrated in different models of hypertension. In the present study, we investigated the effects of AVP, OPC-21268 and OPC-31260 alone and the effects of treatment with AVP after pretreatment with OPC-

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21268 or OPC-31260 on blood pressure and heart rate (HR) in DOCA rats to clarify whether the effects of V_1 and V_2 stimulation are similar in SHR and DOCA rats.

Materials and Methods

Materials. A total of 12 male Wistar rats (4 weeks old) were obtained from Charles River Japan (Kanagawa, Japan) and 6 were subjected to unilateral nephrectomy at 5 weeks of age. The remaining rats underwent sham-operations (control). The DOCA model was produced according to a previously described method (2). Briefly, after rats were anesthetized with sodium pentbarbital, a midline abdominal incision was made and the left kidney was removed. After surgery, 6 rats received weekly subcutaneous injections of 10 mg of deoxycorticosterone acetate (Sigma, St. Louis, MO, USA) in a suspension of 0.2 ml sesame oil for 6 weeks. Salt was administered by substituting a saline solution (0.9 %) for drinking water. The 6 control rats received 0.2 ml of sesame oil alone and no added salt in their drinking water. Animals were housed in a temperature- and humidity-controlled room with a 12-h light-dark cycle and were allowed to eat and drink *ad libitum*. After 6 weeks, DOCA and control rats (11-week-old Wistar rats) were used in the following experiments.

Arginine[8] vasopressin was purchased from the Peptide Institute (Osaka, Japan). OPC-21268 (1- (1- [4- (3-acetylaminopropoxy) benzoyl] -4-piperidyl) -3, 4-dihydro-2 (1*H*) -quinolinone), a selective V_1 receptor antagonist, and OPC-31260 (5-dimethylamino-1 (4- (2-methylbenzoyl-amino) benzoyl) -2, 3, 4, 5-tetrahydro-1*H*-benzazepine), a selective V_2 receptor antagonist, were donated by Otsuka Pharmaceutical Co., Ltd. (Tokushima, Japan). AVP and OPC-31260 were dissolved in physiological saline and OPC-21268 was dissolved in 20 % dimethylformamide (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

Experimental protocol. DOCA and control rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). A right cervical incision was made and a polyethylene catheter (PE-50, Becton-Dickinson, Franklin Lakes, NJ, USA, outer diameter of 0.965 mm, and inner diameter of 0.58 mm) was inserted into the right jugular vein. Physiological saline was infused continuously at 0.2 ml/min. Systolic blood pressure (SBP) and HR were measured in the anesthetized rats by tail-cuff plethysmography (UR-5000, Ueda Seisakusyo, Tokyo, Japan) every 30 sec. Ten minutes after vehicle (physiological saline, 0.3 ml/body) had been injected, AVP 5 ng/kg was injected intravenously and SBP and HR were monitored until 20 min after AVP injection. Secondly, OPC-31260 3 mg/kg was administered intravenously to a new group of rats. Five minutes later, AVP 5 ng/kg was injected intravenously and SBP and HR were monitored. Thirdly, OPC-21268 3 mg/kg was administered intravenously to another group of rats. Five minutes later, AVP 5 ng/kg was injected. All drug injections were in a volume of 0.1 ml and were followed by intravenous injection of 0.2 ml of physiological saline. These rats were kept at 38°C in the cage during these experiments.

Statistical analysis. The results are expressed as mean ± SEM, and analyzed statistically by unpaired Student's *t*-test. A value of $P < 0.05$ was considered statistically significant. Data in the figures show the percentage of SBP or HR of that in the control period (mean SBP or HR 2.5 min before drug injection).

Results

Table 1 shows body weight, SBP and HR of DOCA and control rats in a conscious state. The body weight of DOCA rats was lower than that of the control rats, and the SBP and HR of DOCA rats were significantly higher than those of the control rats. Table 2 shows SBP and HR of anesthetized DOCA and control rats in each control period. The SBP of the DOCA rats was also higher than those of the control rats. In each group, the SBP and HR were almost the same in each control period except for the SBP of DOCA rats in phase 3 ($P < 0.05$ *vs* phase 1). The injection of vehicle caused no significant changes in SBP and HR in either DOCA and control rats compared with the control period (Figs. 1A and 2A). The injection of AVP 5 ng/kg caused a significant increase in SBP in DOCA rats from 9 min after injection to the

Teble I Body weight, systolic blood pressure and heart rate in DOCA-salt hypertensive rats (DOCA) and sham-operated rats (control)

	No. of rats	Body weight (g)	Systolic blood pressure (mmHg)	Heart rate (beats/min)
Control	5	371 ± 8	136 ± 21	348 ± 17
DOCA	5	351 ± 21*	211 ± 16*	465 ± 19*

Values are expressed as mean ± SEM. *, $P < 0.01$ compared with the control rats.

Table 2 Systolic blood pressure and heart rate of anesthetized DOCA-salt hypertensive rats (DOCA) and sham-operated rats (control) in the control period

Control period	Systolic blood pressure (mmHg)		Heart rate (beats/min)	
	Control	DOCA	Control	DOCA
Phase 1	128 ± 6	172 ± 7**	387 ± 18	424 ± 11
Phase 2	131 ± 4	170 ± 6**	378 ± 14	415 ± 10*
Phase 3	134 ± 6	199 ± 12**	363 ± 13	410 ± 13*
Phase 4	137 ± 4	172 ± 8**	374 ± 16	407 ± 19

Phase 1: Before vehicle injection; Phase 2: Before arginine vasopressin 5ng/kg; Phase 3: Before OPC-31260 3mg/kg; Phase 4: Before OPC-21268 3mg/kg. Values are expressed as mean ± SEM. *, $P < 0.05$ **, $P < 0.01$ compared with the control rats.

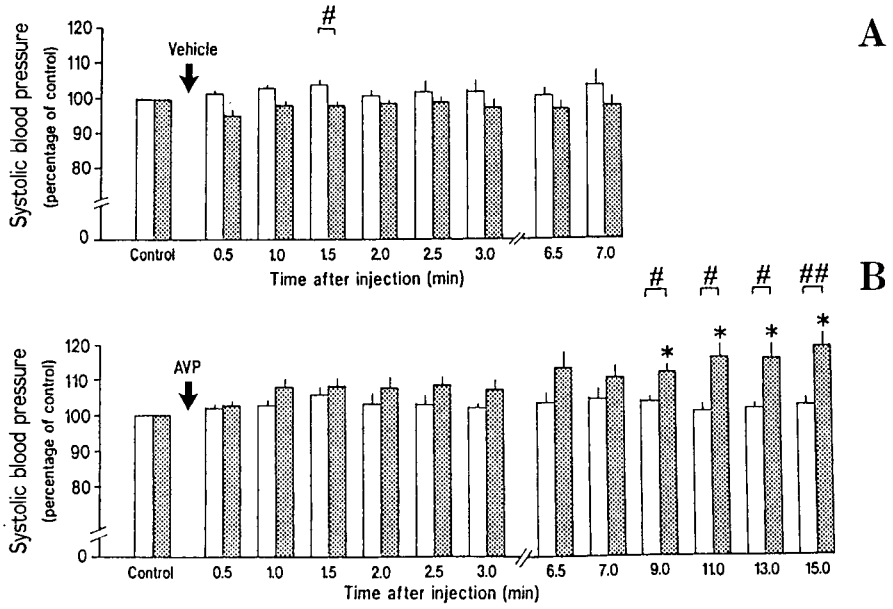

Fig. 1 Changes in systolic blood pressure in DOCA-salt hypertensive rats (DOCA: shaded bars) and control rats (open bars) injected intravenously with vehicle (physiological saline: **A**, n=5) or with AVP 5ng/kg (**B**, n=5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test. *, $P < 0.05$ compared with control period. #, $P < 0.05$ and ##, $P < 0.01$ compared with control rats.

observation period and there was a significant change between DOCA and control rats. Under these conditions, there was no significant change in HR in either DOCA or control rats compared with the control period (Figs. 1B and 2B). Next, we evaluated the effect of V_1- and V_2-antagonists on SBP and HR in DOCA and control rats. Neither OPC-31260 nor OPC-21268 alone significantly changed SBP (Fig. 3) or HR (Fig. 4) in DOCA and control rats. Finally, to assess any differences between DOCA and control rats in V_1 and V_2 activity *in vivo*, we investigated changes in SBP in DOCA and control rats that occurred when AVP was administered following the injection of OPC-31260 or OPC-21268. In each group of rats, there was no significant change in SBP (Fig. 5). However, when AVP 5ng/kg was injected after pretreatment with OPC-31260 3mg/kg, AVP tended to increase SBP. In contrast, when AVP was injected after pretreatment with OPC-21268, AVP tend-

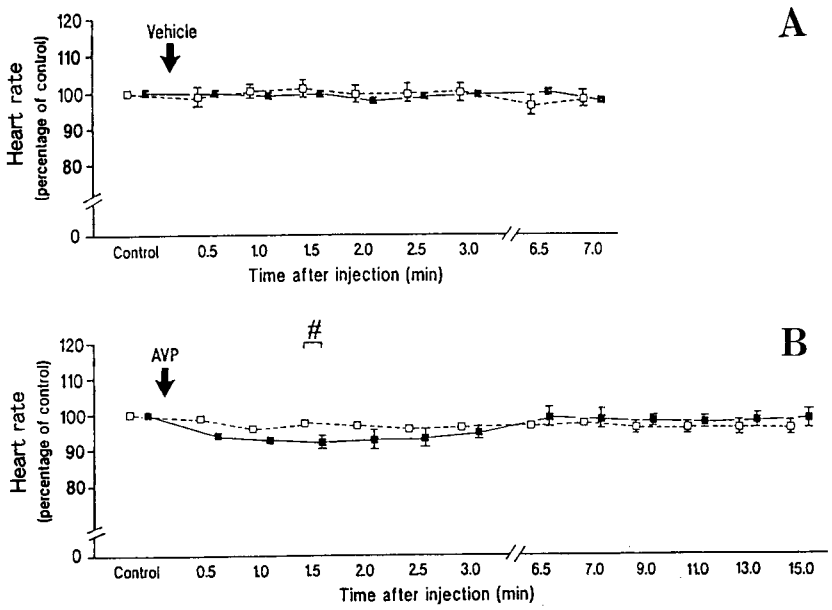

Fig. 2 Changes in heart rate in DOCA (closed squares) and control rats (open squares) injected intravenously with vehicle (physiological saline: **A**, n=5) or with AVP 5 ng/kg (**B**, n=5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test. *, $P < 0.05$ compared with control period. #, $P < 0.05$ compared with control rats. DOCA: See Fig. 1.

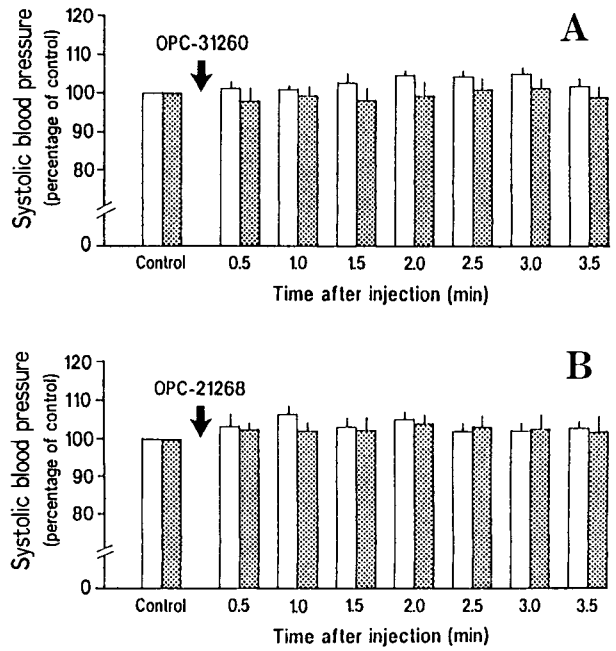

Fig. 3 Changes in systolic blood pressure in DOCA (shaded bars) and control rats (open bars) injected intravenously with OPC-31260 3 mg/kg (**A**, n=5) or OPC-21268 3mg/kg (**B**, n=5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test. DOCA: See Fig. 1.

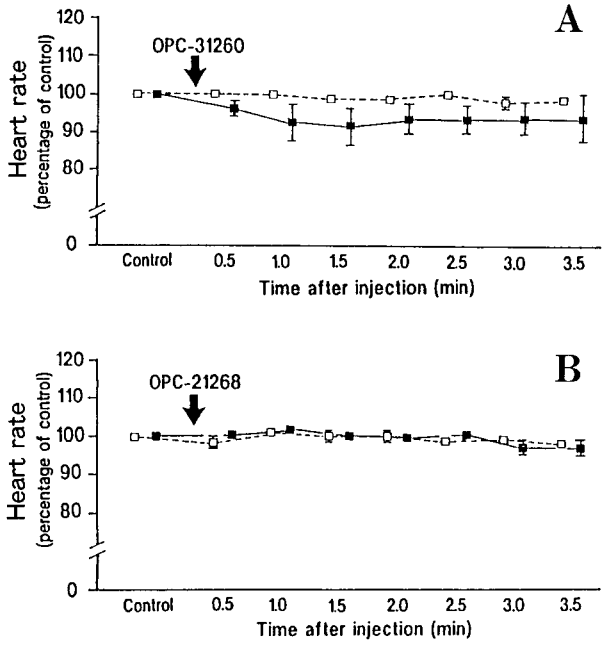

Fig. 4 Changes in heart rate in DOCA (closed squares) and control rats (open squares) injected intravenously with OPC-31260 3mg/kg (**A**, n=5) or with OPC-21268 3mg/kg (**B**, n=5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test. DOCA: See Fig. 1.

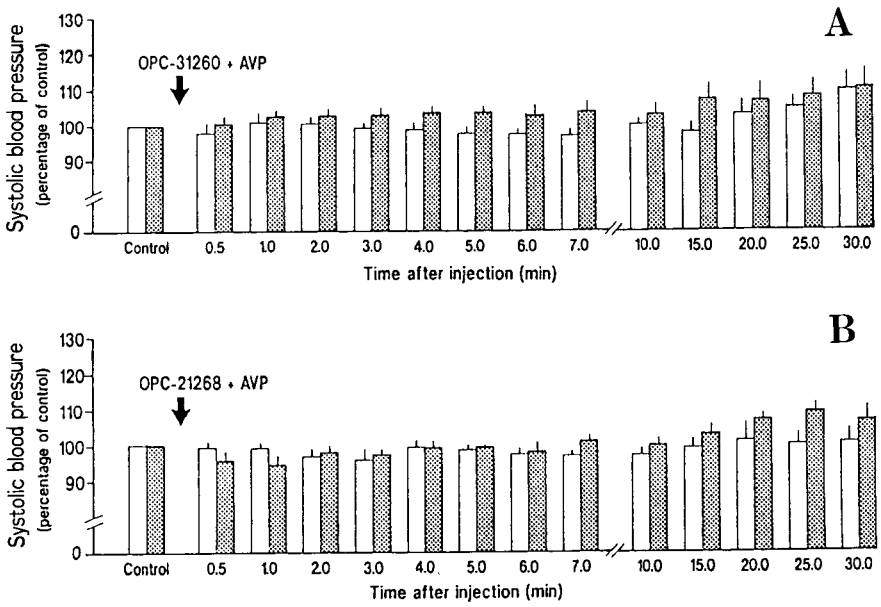

Fig. 5 Changes in systolic blood pressure in DOCA (shaded bars) and control rats (open bars) injected intravenously with AVP 5 ng/kg, following the injection of OPC-31260 3 mg/kg (**A**, n=5) or OPC-21268 3 mg/kg (**B**, n=5). Results are expressed as the mean ± SE and analyzed statitstically by unpaired Student's *t*-test. DOCA: See Fig. 1.

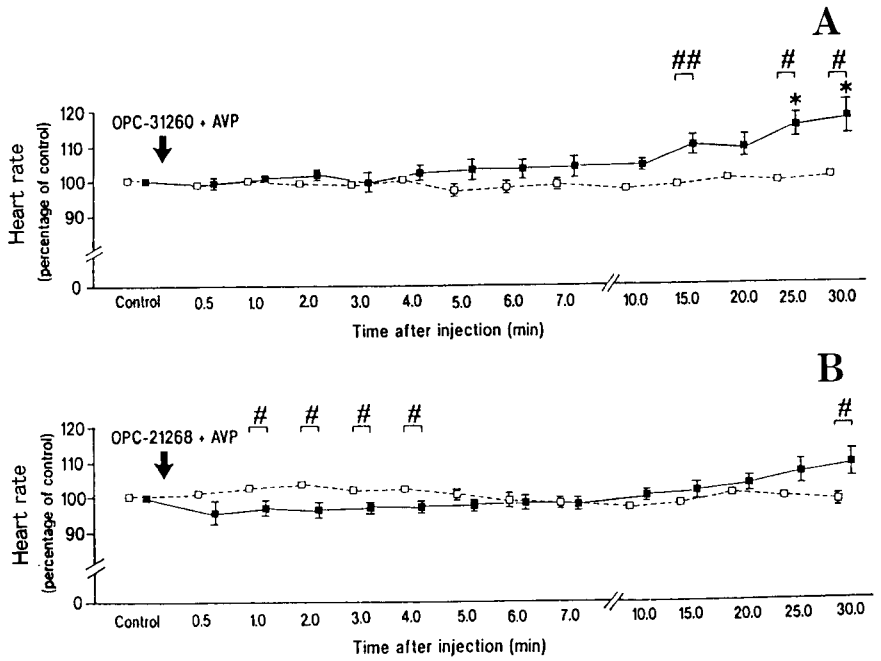

Fig. 6 Changes in heart rate in DOCA (closed squares) and control rats (open squares) injected intravenously with AVP 5 ng/kg, following the injection of OPC-31260 3 mg/kg (**A**, n=5) or OPC-21268 3 mg/kg (**B**, n=5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test. *, $P < 0.05$ compared with control period. #, $P < 0.05$ and ##, $P < 0.01$ compared with control rats. DOCA: See Fig. 1.

ed to decrease SBP in the early phase. With both OPC-31260 and OPC-21268, the heart rate in control rats continued to be stable (Fig. 4). However, HR in DOCA rats increased gradually over 15 min after the administration of AVP following OPC-31260 (Fig. 6), and injection of AVP after pretreatment with OPC-21268 caused HR to decrease from 1 to 4 min (Fig. 6B).

Discussion

AVP exerts a potent vasoconstrictive action via V_1-receptors in smooth muscle cells, resulting in in-

creased blood pressure (11-13). AVP may also increase blood pressure via V_2-receptors, primarily by inducing volume retention. The plasma level of AVP in hypertensive patients was reported to be much higher than that in normotensive subjects (14, 15). However, the role of the AVP system in the maintenance of hypertension in humans and in animal models is unclear. The plasma level of AVP detected by Os *et al.* in humans (14) in physiological and pathological conditions was much lower than the dose of exogenous AVP required to induce a significant increase in blood pressure in rats (16). In contrast to the increase in blood pressure induced by short-term administration of AVP (16), long-term administration of AVP is not associated with a sustained increase in blood pressure. We recently found that when AVP was administered after the administration of OPC-31260, SHR showed a greater increase in blood pressure than Wistar-Kyoto (WKY) rats, suggesting that enhancement of V_1 activity may contribute to the development of high blood pressure in SHR (10). The plasma level of AVP is elevated in the DOCA rat model, which is generally regarded as a model of volume-dependent hypertension (17, 18). When Ganten *et al.* (19) crossbred stroke-prone SHR (SHR-SP) with Brattleboro strain rats homozygous for hypothalamic diabetes insipidus (DI), which are unable to synthesize AVP (20), blood pressure was markedly elevated in the new strain, whose DI gene was introduced into the SHR-SP. The investigators concluded that AVP is not essential for the development and maintenance of hypertension in SHR. However, other studies have shown that, although DOCA-salt treatment alone does not induce hypertension in Brattleboro rats, additional treatment with DDAVP, a selective V_2 agonist, results in high blood pressure (21, 22). Treatment with AVP, which has both V_1 and V_2 actions, resulted in a greater increase in blood pressure in Brattleboro rats than treatment with DDAVP (22). Treatment with selective V_1-antagonists which included both peptide and nonpeptide antagonists has been found to reduce blood pressure in DOCA rats (23, 24) and the contractile sensitivity of mesenteric artery has been found to be increased in DOCA rats, despite a decreased number of AVP receptors (25). These findings suggest that both V_1-and V_2-receptors are involved in the pathogenesis of high blood pressure in DOCA rats.

In the present study, blood pressure increased significantly from 9 min after administration of AVP to observation period in DOCA rats. We previously found that AVP did not increase blood pressure in SHR (10). The plasma level of AVP is increased (17, 18, 25) and the V_1-receptor is down-regulated in DOCA rat (7), suggesting that the effect of exogenous V_1 stimulation on blood pressure is attenuated. Thus, the increase in blood pressure in the late phase in DOCA rats observed in the present study appeared to be mainly related to volume retention induced by V_2 stimulation. Nevertheless, since this increase in blood pressure was abolished by administration with both OPC-21268 and OPC-31260 pretreatments, it is suggested that not only V_2 stimulation but also V_1 stimulation contribute to the increase in blood pressure induced by AVP administration. Previous studies showed that intravenous administration of AVP-antiserum or a V_1-receptor antagonist reduced blood pressure in DOCA rats (17, 23, 24). However, in the present study, neither OPC-31260 nor OPC-21268 alone caused significant changes in blood pressure or heart rate in DOCA rats. The dose of OPC-21268 used in the present study, which was effective for blocking V_1-receptors in SHR, seems to be insufficient in DOCA. Since the DOCA rats used in the present study had markedly elevated blood pressure (systolic blood pressure above 200 mmHg in the conscious state) and exhibited the so-called malignant phase of DOCA, which is associated with markedly elevated blood pressure and AVP levels, weight loss, and a high mortality rate (24), it is possible that smooth muscle cells in arterioles, where V_1-receptors are present, were altered histologically (26) and that the responsiveness of blood pressure to AVP (V_1 stimulation) and V_1-antagonists may have been diminished. It is also possible that the effects of the V_1-antagonist on blood pressure may have been obscured because the escape phenomenon blunts volume expansion in DOCA in the malignant phase (27). The reduced baroreceptor reflex in anesthetized rats may also have influenced the blood pressure response.

In the present study, V_1 stimulation induced by the administration of AVP after pretreatment with OPC-31260 caused only a small increase in blood pressure in DOCA rats. In contrast, V_1 stimulation produced a marked increase in blood pressure in SHR in our previous study (10). The factors responsible for hypertension in DOCA rats have not been clarified. The plasma level of AVP is higher in SHR with established hypertension than in age-matched normotensive WKY rats (4, 18), and 12-week-old SHR possess an increased density of V_1-(28) and V_2-(4) receptors. The plasma level of AVP in

DOCA rats is higher than in control rats (17, 18, 25) and AVP receptors are down-regulated in DOCA rats (7). The differences in the response of blood pressure to V_1 stimulation between DOCA rats and SHR, may be related to the differences in the density of AVP receptors. Administration of AVP after pretreatment with OPC-21268 tended to reduce blood pressure in the early phase in DOCA rats, which is consistent with our previous findings in SHR. V_2 stimulation has been found to induce vasodilatation in several types of vessels (29, 30). Thus, it is possible that the small decrease in blood pressure observed in DOCA rats was caused by V_2 stimulation. In the present study, we observed an increase in heart rate in DOCA rats over 15 min after administration of AVP following OPC-31260. Although the precise cause of these observations is unknown, it is suggested that these changes in heart rate are possibly due to the dehydration caused by V_2 block.

In summary, the acute administration of AVP increased the blood pressure in the late phase in our experiment using DOCA rats. V_1 stimulation was not associated with a significant increase in blood pressure, in contrast to our previous findings in SHR. These findings suggest that V_1-receptors may not be as important in the regulation of blood pressure in DOCA rats as in SHR. The combined effects of V_1 and V_2 stimulation may be necessary for the development of hypertension in DOCA rats, as Saito and Yajima found in Brattleboro rats (22).

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