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Enhanced pressor response in spontaneously hypertensive rats induced by stimulation of vasopressin-V1 receptors.

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Abstract

To elucidate the effect of the arginine vasopressin (AVP) system in vivo, especially V1 and V2 activity, on blood pressure, we measured the acute changes in blood pressure and heart rate after AVP, OPC-21,268 (a V1 receptor antagonist), and OPC-31,260 (a V2 receptor antagonist) were injected intravenously in anesthetized spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats at the age of 15 weeks. Compared with the control period, single injection of AVP 5 ng/kg significantly increased systolic blood pressure in WKY rats without a concomitant increase in heart rate, but there was no significant increase in blood pressure in SHR. In contrast, single injection of either OPC-21,268 3 mg/kg or OPC-31,260 3 mg/kg did not affect blood pressure or heart rate in either SHR or WKY rats. Injection of AVP after the administration of OPC-31,260 induced a greater increase in blood pressure in SHR than in WKY rats, whereas injection of AVP after the administration of OPC-21,268 did not induce any clear increase in blood pressure in SHR or WKY rats. These results suggest that SHR have enhanced pressor activity mediated by V1 receptors and that this increase may be due to an increase in their number. In conclusion, enhancement of V1 activity may contribute to the development of high blood pressure in SHR.

KEYWORDS: vasopressin, V1 and V2 receptor antagonist, hypertension, pressor response, OPC-31260

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Enhanced Pressor Response in Spontaneously Hypertensive Rats Induced by Stimulation of Vasopressin-V_1 Receptors

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To elucidate the effect of the arginine vasopressin (AVP) system *in vivo*, especially V_1 and V_2 activity, on blood pressure, we measured the acute changes in blood pressure and heart rate after AVP, OPC-21268 (a V_1 receptor antagonist), and OPC-31260 (a V_2 receptor antagonist) were injected intravenously in anesthetized spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats at the age of 15 weeks. Compared with the control period, single injection of AVP 5ng/kg significantly increased systolic blood pressure in WKY rats without a concomitant increase in heart rate, but there was no significant increase in blood pressure in SHR. In contrast, single injection of either OPC-21268 3mg/kg or OPC-31260 3mg/kg did not affect blood pressure or heart rate in either SHR or WKY rats. Injection of AVP after the administration of OPC-31260 induced a greater increase in blood pressure in SHR than in WKY rats, whereas injection of AVP after the administration of OPC-21268 did not induce any clear increase in blood pressure in SHR or WKY rats. These results suggest that SHR have enhanced pressor activity mediated by V_1 receptors and that this increase may be due to an increase in their number. In conclusion, enhancement of V_1 activity may contribute to the development of high blood pressure in SHR.

Key words: vasopressin, V_1 and V_2 receptor antagonist, hypertension, pressor response, OPC-31260

The role of the arginine vasopressin (AVP) system in regulating arterial pressure in hypertension remains controversial. Although plasma and urinary levels of AVP have been reported to be elevated in an animal models of hypertension (1-3), in human essential hypertension (4, 5), and in patients with congestive heart failure (6), it is unclear whether or not the elevated plasma AVP level contributed to the development of hypertension. Möhring *et al.* reported that injection of AVP antiserum lowered blood pressure in stroke-prone spontaneously hypertensive rats (SHR-SP) during the early phase (7). Long-term administration of AVP does not sustain elevated blood pressure, contrary to the increase in blood pressure caused by its short-term administration in the dog (8). Although the role of AVP in the short-term regulation of blood pressure is now firmly established, whether the vasoconstrictive and antidiuretic actions of AVP are related to the development of hypertension or whether the increase in blood pressure induced by administration of AVP is mediated through V_1 or V_2 activity has been confirmed. We previously reported that the number of V_2 receptors in the kidney of spontaneously hypertensive rats (SHR) is larger than that in Wistar-Kyoto (WKY) rats after the development of hypertension in SHR (9). The number of V_1 receptors in smooth muscle cells was also reported to be much greater in SHR than in WKY rats (10). Recently, we observed a change in the affinity of renal V_2 receptors when SHR were treated with indapamide, an antihypertensive diuretic (11), and cilazapril, an angiotensin-converting enzyme (ACE) inhibitor (12). These findings suggested that not only V_1 receptors but also V_2 receptors may participate in the control of blood pressure in SHR.

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OPC-21268 and OPC-31260 were recently developed as nonpeptide specific V_1 and V_2 antagonists, respectively (13, 14). In the present study, we investigated differences between SHR and WKY rats in pressor response when rats were treated with AVP, OPC-21268, or OPC-31260 and with AVP after pretreatment with OPC-21268 or OPC-31260. The aim of this study was to determine whether SHR and WKY rats differ in V_1 and V_2 activity.

Materials and Methods

Materials. Male SHR and WKY rats (12 weeks old) were obtained from Charles River Japan (Kanagawa, Japan). All rats were housed in climate-controlled metabolic cages with a 12h light/dark cycle. Food (MF, Oriental Yeast Co., Tokyo, Japan) and water were supplied *ad libitum*. SHR (379 ± 5.7 g, $n = 5$) and WKY rats (342 ± 2.5 g, $n = 5$) were used in this study.

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. At 15 weeks of age, all 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 0.965mm, and inner diameter of 0.58mm) was inserted into the right jugular vein, and physiological saline was infused continuously at 0.2ml/min. Systolic blood pressure was 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 5ng/kg was injected intravenously and the systolic blood pressure and heart rate were monitored. Secondly, OPC-31260 3mg/kg was administered intravenously to a new group of rats. Five minutes later, AVP 5ng/kg was injected intravenously and systolic blood pressure and heart rate were monitored. Thirdly, OPC-21268 3mg/kg was administered intravenously to another group of rats. Five minutes later, AVP 5ng/kg was injected. All drug injections were in a volume of 0.1ml and were followed by intravenous injection of 0.2ml of physiological saline. These rats were kept at 38°C in the cage during these experiments.

Statistical analysis. Results are expressed as mean ± SE, 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 systolic blood pressure or heart rate of that in the control period (mean systolic blood pressure or heart rate 2.5min before drug injection).

Results

Table 1 shows systolic blood pressure and heart rate of anesthetized SHR and WKY rats in each control period. The systolic blood pressure and heart rate of the

Table 1 Systolic blood pressure and heart rate of anesthetized spontaneously hypertensive rats (SHR) and Wistar-Kyoto (WKY) rats in the control period

Control period	Systolic blood pressure (mmHg)		Heart rate (beats/min)	
	WKY	SHR	WKY	SHR
Phase 1	111 ± 3	200 ± 4*	298 ± 7	381 ± 34*
Phase 2	113 ± 2	206 ± 2*	298 ± 8	381 ± 17*
Phase 3	133 ± 5	218 ± 7*	297 ± 9	397 ± 17*
Phase 4	121 ± 5	184 ± 16*	304 ± 11	378 ± 13*

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 ± SE. *, $P < 0.01$ compared with WKY rats.

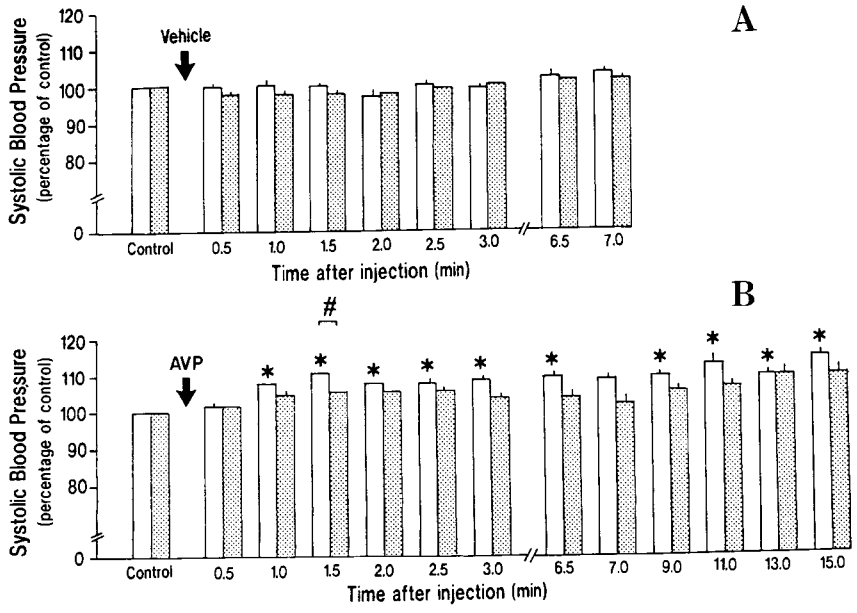

Fig. 1 Change in systolic blood pressure in SHR (shaded bars) and WKY rats (open bars) injected intravenously with vehicle (physiological saline: **A**, n = 5) or with AVP 5 ng/kg (**B**, n = 5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test. *, $P 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

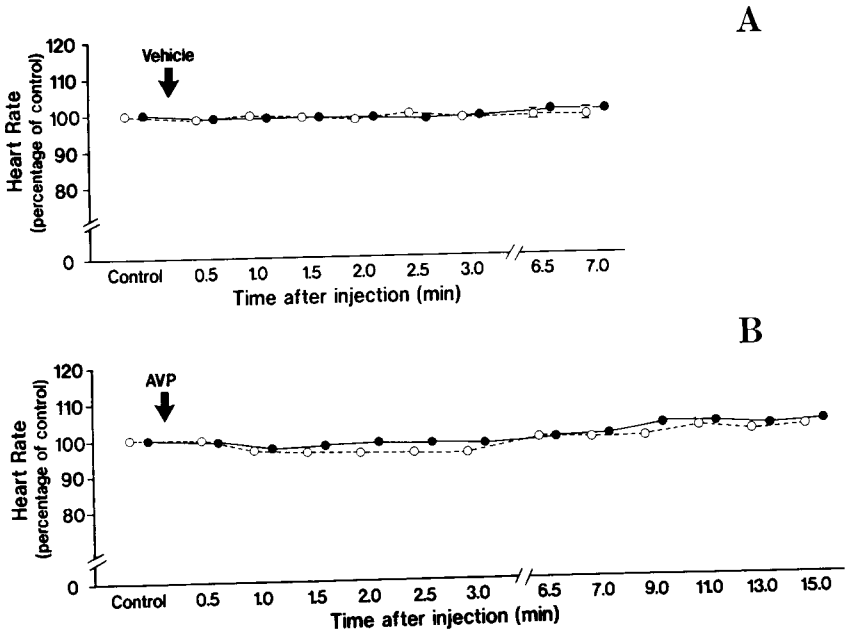

Fig. 2 Change in heart rate in SHR (closed circles) and WKY rats (open circles) injected intravenously with vehicle (**A**, n = 5) or with AVP 5 ng/kg (**B**, n = 5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test.

SHR were significantly higher than those of the WKY rats in each control period. In each strain of rats, the blood pressure and heart rate were almost the same in each control period. Injection of vehicle caused no significant change in blood pressure or heart rate in either SHR or WKY rats (Fig. 1A). The injection of AVP 5 ng/kg caused a significant increase in systolic blood pressure in WKY rats (Fig. 1B), but not in SHR. Under these conditions, there was no significant change in heart rate in either SHR or WKY rats (Fig. 2). Next, we evaluated the effect of V_1 and V_2 antagonists on blood pressure and heart rate in SHR and WKY rats. Adminis-

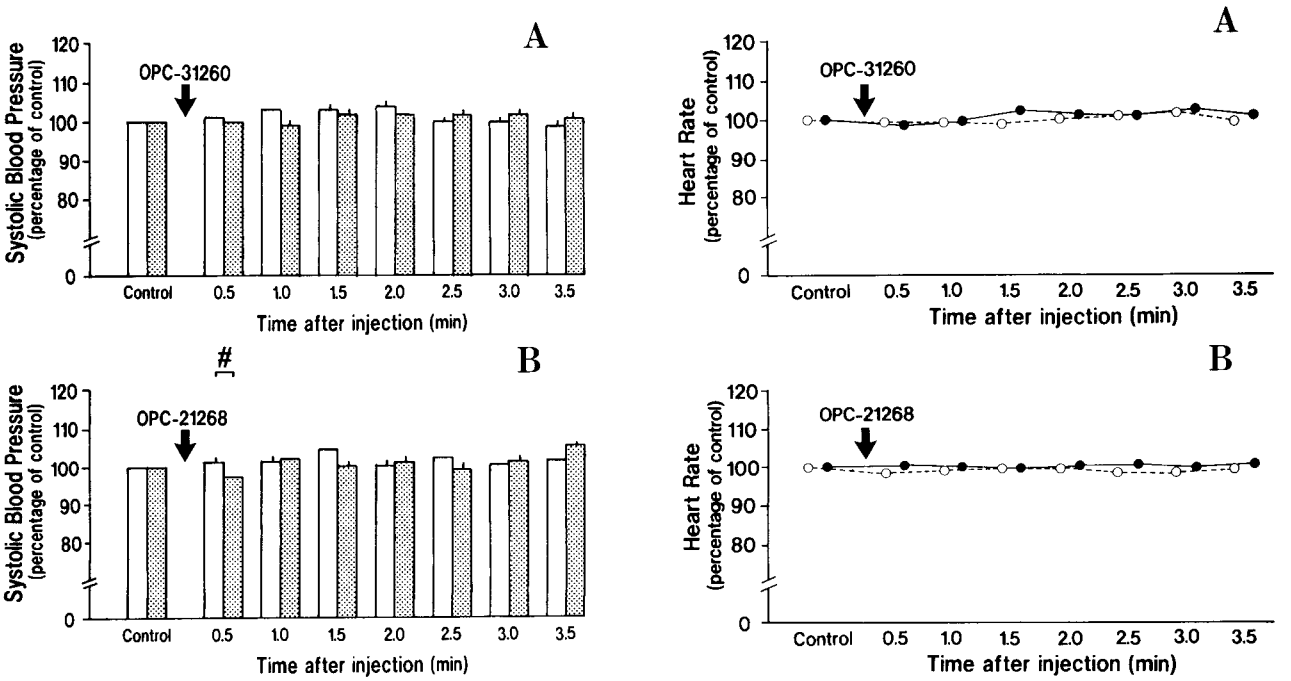

Fig. 3 (Left) Change in systolic blood pressure in SHR (shaded bars) and WKY rats (open bars) injected intravenously with OPC-31260 3 mg/kg (**A**, n = 5) or OPC-21268 3mg/kg (**B**, n = 5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test. #, $P < 0.05$ compared with WKY rats.

Fig. 4 (Right) Change in heart rate in SHR (closed circles) and WKY rats (open circles) 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.

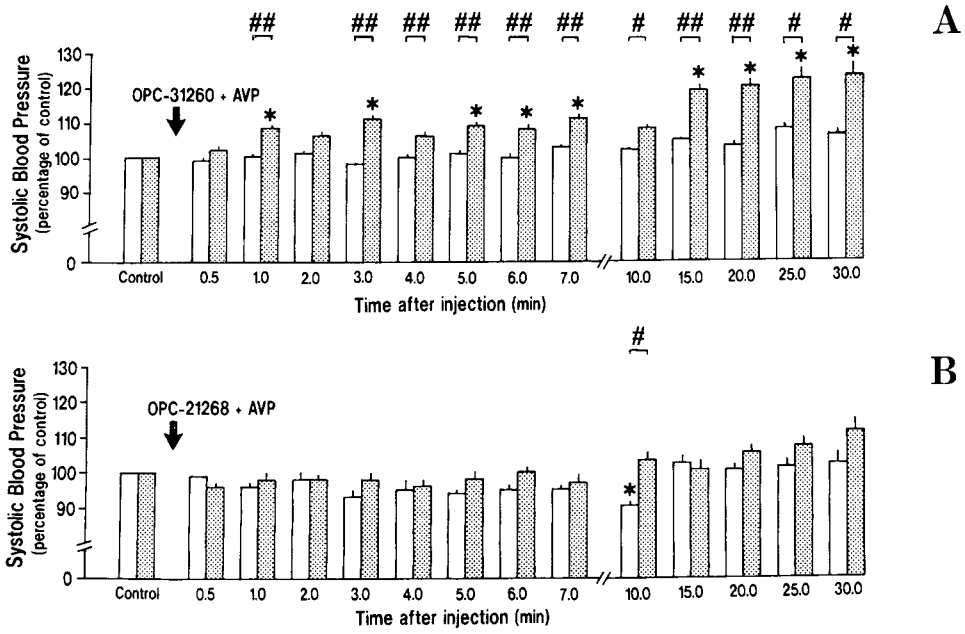

Fig. 5 Change in systolic blood pressure in SHR (shaded bars) and WKY rats (open bars) injected intravenously with AVP 5ng/kg, following the injection of OPC-31260 3mg/kg (**A**, n = 5) or OPC-21268 3mg/kg (**B**, n = 5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's *t*-test. *, $P < 0.05$ compared with control period. #, $P < 0.05$; ##, $P < 0.01$ compared with WKY rats.

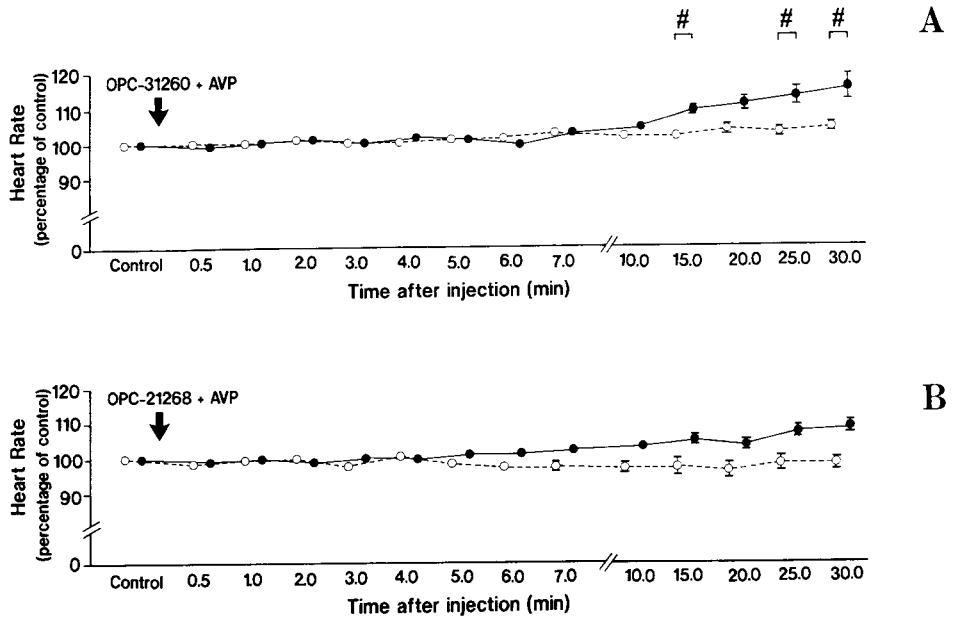

Fig. 6 Change in heart rate in SHR (closed circles) and WKY rats (open circles) injected intravenously with AVP 5 ng/kg, following the injection of OPC-31260 3 mg/kg (**A**, n = 5) or OPC-21268 3 mg/kg (**B**, n = 5). Results are expressed as the mean ± SE and analyzed statistically by unpaired Student's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

tration of either OPC-31260 or OPC-21268 alone did not significantly change in systolic blood pressure (Fig. 3) or heart rate (Fig. 4). Finally, to assess any differences between SHR and WKY rats in V_1 and V_2 activity *in vivo*, we investigated changes in blood pressure in SHR and WKY rats that occurred when AVP was administered following the injection of OPC-31260 or OPC-21268. When AVP 5 ng/kg was injected after pretreatment with OPC-31260 3 mg/kg, the systolic blood pressure in SHR was significantly increased (Fig. 5). Although systolic blood pressure in WKY rats also increased, the extent of the AVP-induced increase in blood pressure in WKY rats was significantly smaller than that in SHR (Fig. 5A). When AVP 5 ng/kg was injected after pretreatment with OPC-21268 3 mg/kg, no significant change in blood pressure was observed in either SHR or WKY rats. However, 25 min after the administration of AVP, blood pressure in SHR (Fig. 5B) tended to increase. With both OPC-31260 and OPC-21268, the heart rate in WKY rats continued to be stable, but the heart rate of SHR increased gradually over 10 min after administration of AVP (Fig. 6).

Discussion

AVP has a marked vasoconstrictive effect on systemic and coronary arteries which is mediated through V_1 receptors in vascular smooth muscle cells and hepatocytes (15). Stimulation of V_1 receptors induces coupling to phosphoinositide turnover without the accumulation of cyclic AMP (16–18). The antidiuretic effect of AVP is mediated by V_2 receptors located mainly in the renal collecting ducts. Stimulation of V_2 receptors induces coupling to a cyclic AMP-dependent mechanism (19). AVP was reported to produce vasodilation of several arteries such as femoral (20) and pulmonary arteries (21) via V_2 receptors in experimental animals, suggesting that stimulation of V_2 receptors decreased blood pressure. How these two types of receptors relate to the regulation of blood pressure is controversial. OPC-21268 and OPC-31260 are recently developed nonpeptide selective V_1 and V_2 receptor antagonists, respectively (13, 14). Since these antagonists do not have the partial agonistic action seen with some peptide antagonists of AVP receptors (22), they are useful for investigating the role of AVP in hypertension. We observed the individual effects

of V_1 and V_2 stimulation on blood pressure in hypertensive and normotensive rats when these two antagonists were injected. In this study, we chose the tail-cuff method for monitoring blood pressure to keep rats in the stable experimental condition.

In anesthetized rats, AVP increased systolic blood pressure without a change in heart rate. The increment of blood pressure in SHR in the present study was not remarkable, even though enhanced pressor responsiveness to AVP in SHR and SHR-SP had been reported (7, 23). One possible reason for our finding is that, since systolic blood pressure in 15-week-old SHR was 1.8 times higher than that in age-matched WKY rats, some homeostatic mechanism, such as an increase in plasma atrial natriuretic polypeptide, may have attenuated the increase in blood pressure. Another possible reason for the absence of a significant increase in blood pressure in SHR is an impaired baroreceptor reflex or the anesthetized condition of the animals studied.

OPC-21268 is known to have a strong effect in blocking vasopressin-induced vasoconstriction in experimental animals (24, 25) or in humans (26). Nevertheless, administration of OPC-21268, which blocked the V_1 receptors that are closely related to vasoconstriction, did not appreciably decrease blood pressure (26). We suggest that, since the vessels were not preconstricted by AVP in the present experiment, the administration of AVP receptor antagonists alone did not induce alterations in blood pressure or heart rate in either SHR or WKY rats. Yamada *et al.* reported that OPC-21268 exerted a hypotensive effect in 38- and 70-week-old SHR and in 25-week-old SHR-SP, but not in 25-week-old SHR (27). OPC-21268 may be effective as an antihypertensive agent for conditions characterized by an elevated plasma AVP level, such as exists in DOCA-salt hypertensive rats (28) or in aged animals.

Since pretreatment with OPC-21268 or OPC-31260 3 mg/kg is considered to be enough to block effects on V_1 and V_2 receptors *in vivo* (13, 14, 29), we deduced that the administration of AVP after pretreatment with OPC-31260 or OPC-21268 caused AVP-induced stimulation of V_1 and V_2 receptors, respectively. Stimulation of V_1 receptors induced by AVP after pretreatment with OPC-31260 resulted in a marked increase in blood pressure 1.0 min after injection in SHR, whereas no such increment in blood pressure was observed in WKY rats. The heart rate in SHR was not altered until 10 min after injection of AVP. Stimulation of V_2 receptors induced by AVP after pretreatment with OPC-21268 resulted in no significant elevation in blood pressure. These results suggest that SHR possess an enhanced V_1 activation, possibly due to hypersensitivity of V_1 receptors. Okada *et al.* reported that the number of V_1 receptors in SHR was five to seven times greater than that in WKY rats and that the AVP-induced increase in intracellular sodium concentration is augmented in the vascular smooth muscle cells of SHR. They suggested that these changes may cause hypertension in SHR (10). On the contrary, when V_2 receptors were stimulated by exogenous injection of AVP after pretreatment with OPC-21268, no significant change in blood pressure were observed in SHR and the blood pressure in WKY rats tend to decrease. Although long-term administration of a peptide V_1 selective antagonist, d (CH_2) 5-Tyr (Me) AVP, did not alter the course of systolic hypertension in SHR (30), a nonpeptide antagonist that blocks the action of AVP at both vascular AVP receptors (V_1) and renal AVP receptors (V_2) attenuated the development of systolic hypertension in SHR from 4 to 12 week without altering the blood pressure in normotensive WKY rats (31). These reports suggested that an interaction between V_1 and V_2 receptors contributed to the development of hypertension. Since AVP is a strong mitogenic agent for smooth muscle cells or mesangial cells *in vitro* (32), administration of these AVP antagonists may cause not only a reduction in blood pressure but also protection against AVP-related proliferation.

In summary, the present results suggest that the pressor effect of V_1 receptor stimulation was enhanced in SHR after acute administration of AVP. We are now actively investigating the effect of long-term stimulation of V_1 and V_2 receptors on blood pressure and vascular or renal proliferation, using these selective antagonists.

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