Original Article

Are Sodium-Dependent V₁ Receptors and Sympathetic Nerve Activations Involved in Regulation of Blood Pressure in Borderline-Hypertensive Hiroshima Rats?

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Sympathetic nerve activity (SNA) was estimated by the magnitude of depressor response after ganglionic blockade with hexamethonium bromide (C6; 25 mg/kg weight). The depressor effects of C6 were significantly less in borderline-hypertensive Hiroshima rats (BHR) than in deoxycorticosterone acetate (DOCA)-salt hypertensive rats (DOCA rats) or in spontaneously hypertensive rats (SHR), but they were not different in BHR and normotensive control Wistar rats (NCR). After sympatho-inhibition, the depressor effects of a selective vasopressin V₁ receptor antagonist (V₁A; 10⁻⁶g/kg: [d(CH₂)₅]₁, O-Me-Tyr₂, Arg⁸]-vasopressin) were significantly greater in BHR than in DOCA rats, SHR or NCR. In a previous study, we reported that the depressor effects of C6 were significantly less in BHR than in SHR, but after sympatho-inhibition, the depressor effects of V₁A were significantly greater in BHR than in SHR (Hypertens Res 2002; 25: 241–248). After high-salt diet loading in the present study (8% salt-containing diet for 10 weeks), the magnitudes of increase in mean arterial pressure in BHR and NCR were almost the same. There was almost no difference in the depressor effects of V₁A after sympatho-inhibition between BHR with high-salt intake and BHR without high-salt intake. The depressor effects of an angiotensin-converting enzyme inhibitor, captopril (1 mg/kg), were almost the same between BHR and NCR both before and after sympatho-inhibition. However, these effects were completely inhibited after the high-salt diet. The results show that SNA was within the normal range in BHR and that no further accelerated responsiveness of endogenous vasopressin was observed in BHR after high-salt intake. (Hypertens Res 2002; 25: 763–771)

Key Words: V₁ receptor antagonist, sympathetic nervous system, ganglionic blockade, salt loading, borderline-hypertensive rats

Introduction

Borderline-hypertensive Hiroshima rats (BHR) were acquired by repeated sib-mating of Wistar rats that were occasionally hypertensive. The normotensive control rats (NCR) used in this study were derived from the same strain by repeated mating of sibling male and female rats exhibiting normal systolic blood pressure. In our previous study using conscious BHR, the mean arterial pressures were 131 ± 1.3 mmHg (mean ± SEM) in male BHR (n = 53) and 117 ± 1.2 mmHg in male NCR (n = 46) (1). The mean arterial pressure (MAP) of the BHR was significantly higher than that of the NCR (p < 0.01). Our recent study showed that sodium pentobarbital-anesthetized BHR have increased plasma contents of endogenous vasopressin and that an accelerated respon-

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sensitivity to exogenous vasopressin, [Arg8]-vasopressin, results in a significant increase in MAP (2). We also found more recently that administration of a selective V1 receptor antagonist (V1A) after infusion of hexamethonium bromide (C6) significantly potentiated the decreases in renal, mesenteric and hindquarter vascular resistances of BHR (1), suggesting that BHR may be a good model for studying the involvement of vasopressinergic regulation in blood pressure, since the enhanced vasopressin release and activation of the V1 receptors are involved in hypertension in BHR. Furthermore, we have previously reported that the plasma concentration of arginine vasopressin (AVP) was significantly greater in BHR than in NCR at baseline, and it was significantly increased by ganglionic blockade (AVP_BHR baseline = 1.60 ± 0.20 ng/ml vs. AVP_BHR after C6 = 2.29 ± 0.18 ng/ml; p < 0.01). However, the level of AVP in NCR was not changed by ganglionic blockade (AVP_NCR baseline = 1.10 ± 0.18 ng/ml vs. AVP_NCR after C6 = 1.24 ± 0.20 ng/ml) (1).

With regard to the mechanisms of hypertension, it is well known that intracorporal vasopressin plays a major role as a pressor agent in both the pathogenesis and maintenance of hypertension in deoxycorticosterone acetate (DOCA)-salt hypertensive rats (DOCA rats) (3–8) but not in spontaneously hypertensive rats (SHR) (9–10). It was recently reported that the vasopressin system, and especially the V1 receptors, is not important in the development or maintenance of hypertension in anesthetized DOCA rats (11) or conscious SHR (12). In the first series of our experiments, therefore, we compared the data obtained from conscious BHR with those obtained from NCR, SHR and DOCA rats.

On the other hand, it is well known that a high-NaCl intake stimulates sympathetic activity and increases the plasma concentration of vasopressin in Dahl salt-sensitive rats (13). However, V1A fails to lower the arterial pressure in Dahl salt-sensitive rats unless a compensatory increase in the renin secretion is prevented (14). These authors have suggested that the renin-angiotensin system is a key point for V1 receptor activation. It has also recently been demonstrated that centrally released arginine vasopressin is involved in mediation of the pressor effect exerted by centrally applied angiotensin II in renin transgenic hypertensive rats (15). Taken together, the findings suggest that there is a partial but close interaction between V1 receptor activation and the renin-angiotensin system in BHR. Therefore, the present study was designed to determine whether the hypotensive effects of V1A induced by a ganglionic blockade in BHR are altered under the condition of high NaCl intake and to determine the most likely interaction between the activation of V1 receptors and the renin-angiotensin system in blood pressure in the conscious state.

Materials and Methods

The present study was approved by the Animal Welfare Committee of the Hiroshima University Faculty of Medicine. The BHR and NCR were inbred in the experimental animal center of the Hiroshima University Faculty of Medicine. SHR were purchased from Charles River Japan, Inc. (Yokohama, Japan).

Animal Preparations

To obtain DOCA rats, male Wistar rats at 10–12 weeks of age, weighing 250–350 g, were anesthetized with 50 mg/kg (i.p.) of sodium thiamylal (Isozol; Yoshitomi Pharmaceuticals, Osaka, Japan). The right kidney was removed from each rat after tying the renal artery and vein. Immediately after the operation and once a week thereafter, 30 mg/kg of DOCA (Tokyo-Kasei Kogyo, Tokyo, Japan) was injected subcutaneously into each rat. The rats’ drinking water was changed from tap water to water containing 1% NaCl after the operation.

The BHR and NCR at 12 to 18 weeks of age were divided into two groups: One group in which arterial pressure (AP) and heart rate were measured immediately after the operation as described below and another group in which these parameters were measured after the rats had been fed a high-sodium diet (8% salt-containing food pellets; Oriental Food Co., Tokyo, Japan) for 10 weeks.

Measurements of Arterial Pressure and Heart Rate

Each rat was anesthetized with sodium thiamylal (50 mg/kg i.p.). A polyethylene tube (PE-10 fused to PE-20) for measuring AP was inserted into the terminal aorta from the right femoral artery. Drugs were administered through another tube inserted into the left external jugular vein. The opposite end of each tube was exteriorized at the neck.

After this operation, each rat was housed separately in a plastic cage (35 cm in length × 30 cm in width × 17 cm in height) containing wood chips. Water and normal food pellets (for one group each of NCR and BHR) or 8% salt-containing food pellets (for the other groups of NCR and BHR) were given ad libitum. Three days after the operation, AP and heart rate were measured while the rat was moving freely in its home cage. The AP value was smoothed using a resistance and capacitance filter with a time constant of one second and recorded using a pen writer. We considered the smoothed AP value to be the mean arterial pressure (MAP). After baseline values of MAP and heart rate had been obtained, 10 µg/kg of an effective peptide V1A, [d(CH2)x7, O-Me-Tyr2, Arg8]-vasopressin (Bachem Inc., Torrance, USA), was administered intravenously as a bolus. In a separate series of experiments, C6 (Nacalai Tesque, Kyoto, Japan) was infused at a rate of 0.08 ml/min to obtain a total dose of 25 mg/kg for ganglionic blockade. Immediately after C6 administration, an angiotensin-converting enzyme inhibitor, captopril (CAP; 1 mg/kg; Sankyo, Tokyo, Japan), or V1A was intravenously injected as a bolus, and then finally CAP was administered. In the present experiments, we postulated that the sympathetic nervous activity could be evaluated by the hypotensive effect of the ganglionic blockade. All of the rats were killed with an overdose of thiamylal sodium at the
end of the experiments.

Statistical Analysis

All values are expressed as the means ± SEM. One-way analysis of variance (ANOVA) followed by Dunnett’s or Tukey’s test was used for each group where appropriate. We used the paired Student’s t-test to determine the significance of changes in MAP or heart rate caused by the administration of each drug in each rat group. We also used the unpaired Student’s t-test to determine the significance of the differences in changes in MAP or heart rate caused by V1A, C6 or CAP in each rat group. Values of \( p < 0.05 \) were considered to indicate statistical significance.

Results

Comparison of MAP and Heart Rate in the Resting State

The mean values of MAP and heart rate in the BHR in the resting state were compared with those in the NCR, SHR and DOCA rats (Table 1). The MAP in the BHR was significantly higher than that in the NCR (\( p < 0.01 \)) but was significantly lower than those in the SHR (\( p < 0.01 \)) and DOCA rats (\( p < 0.01 \)). In contrast, there was no significant difference

| Table 1. Comparison of Mean Arterial Pressure (MAP) and Heart Rate in the Resting State |
|---------------------------------|-----|-----|-----|-----|
|                                | NCR | BHR | SHR | DOCA |
| n                               | 42  | 40  | 17  | 20   |
| MAP (mmHg)                      | 120 ± 1.1 | 138 ± 1.5* | 163 ± 2.4* | 177 ± 3.1* |
| Heart rate (beats/min)          | 367 ± 6.0  | 385 ± 7.4  | 327 ± 8.8* | 379 ± 12.0 |
| Body weight (g)                 | 344 ± 9.1  | 313 ± 4.5* | 294 ± 5.4  | 356 ± 6.4* |
| Age (weeks)                     | 16.3 ± 0.6 | 17.6 ± 0.4 | 17.5 ± 0.8 | 16.1 ± 0.2 |

Values are the mean ± SEM of the number (n) of rats shown in the table. Borderline-hypertensive Hiroshima rats (BHR), normotensive control rats (NCR), spontaneously hypertensive rats (SHR) and DOCA-salt hypertensive rats (DOCA rats). * indicates a significant difference between BHR and NCR by one-way analysis of variance (ANOVA) at \( p < 0.05 \). † indicates a significant difference between BHR and either SHR or DOCA rats by ANOVA at \( p < 0.05 \).
between the heart rates in the groups of rats except for the SHR, in which it was significantly lower than that in the BHR (*p < 0.01).

As shown in Table 2, the MAP in the BHR was again significantly higher than that in the NCR (*p < 0.01) and there was no significant difference between the heart rates in the BHR and NCR. After the 10-week period of feeding with an 8% salt diet, MAP had increased in both the BHR and NCR, but it was significantly higher in the former (*p < 0.01). The heart rate was also significantly greater in the BHR than in the NCR (**p < 0.02).

Depressor Effects of C6

Figure 1 shows typical recordings of AP from a) NCR, b) BHR, c) DOCA rats and d) SHR. During the recording period shown, C6 was first infused and then V1 A was injected at the times indicated by the arrows. Sympathetic nerve activity (SNA) was estimated by the magnitude of depressor response after the ganglionic blockade (C6) treatment. The intravenous infusion of C6 resulted in a significant decrease in MAP in all of the rat groups. The magnitude of decrease in MAP was significantly less in the BHR (ΔMAP\textsubscript{BHR} = -27.7 ± 2.8 mmHg) than in the DOCA rats (ΔMAP\textsubscript{DOCA} = -72.4 ± 6.0 mmHg) and SHR (ΔMAP\textsubscript{SHR} = -41.7 ± 3.6 mmHg), but there was no significant difference in the magnitudes of decrease in MAP between the BHR and NCR (ΔMAP\textsubscript{NCR} = -27.1 ± 1.7 mmHg) (Fig. 2, left). These findings indicate that SNA was not elevated in the borderline-hypertensive Hiroshima rats, unlike in DOCA rats and SHR.

Depressor Effects of V1 A

Injection of V1 A alone produced a slight but significant hy-
potensive effect only in the BHR (ΔMAPBHR = -6.22 ± 1.5 mmHg), while no appreciable hypotensive effect was observed in the NCR, SHR and DOCA rats (Fig. 2, right). In contrast, after the ganglionic blocking caused by pretreatment with C6, the depressor effect of V1A increased markedly in all rat groups except for the NCR group. The magnitude of depressor response to injection of V1A after sympatho-inhibition was significantly greater in the BHR (ΔMAPBHR = -27.0 ± 2.5 mmHg) than in the NCR (ΔMAPNCR = -2.42 ± 1.1 mmHg), SHR (ΔMAPSHR = -16.3 ± 2.0 mmHg), or DOCA rats (ΔMAPDOCArats = -19.3 ± 1.9 mmHg). These results indicate that endogenous vasopressin after sympatho-inhibition was activated to compensate for the increase in blood pressure to a greater degree in the BHR than in the SHR or DOCA rats (Fig. 2, right). These results shown in Fig. 2 agree well with the results in our previous studies (1).

**Depressor Effects of V1A, CAP and C6 after Salt Loading**

Representative measurements of AP in NCR and BHR without salt loading (top, pairs) and with salt loading (bottom, pairs) are shown in Fig. 3.

**Fig. 4.** Changes in mean arterial pressure (top) and heart rate (bottom) about 5 min after injection of a vasopressin V1 receptor antagonist (V1A, 10 µg/kg, i.v.), immediately after infusion of hexamethonium bromide (C6, 25 mg/kg, i.v.), and about 10 min after injection of an angiotensin converting enzyme inhibitor, captopril (CAP, 1 mg/kg, i.v.), in conscious normotensive control rats (NCR; open bars) and borderline-hypertensive Hiroshima rats (BHR; closed bars) without salt loading or with salt-loading (NCR; dotted bars, BHR; oblique bars). Data are the means ± SEM of the number of rats shown in parentheses. *p < 0.05 vs. the value in NCR.

MAP
In the first series of experiments, each hypotensive effect of V1A C6 or CAP alone in BHR and NCR was compared between the group without salt loading (control group) (Fig. 4, left) and the group with salt-diet loading (salt-loading group) (Fig. 4, right). A comparison of the means ± SEM of MAP and heart rate in NCR (n = 10–23) and BHR (n = 7–22) is shown in Fig. 4. In the control group, the hypotensive effect of V1A alone was significantly greater in BHR than in NCR (ΔMAPBHR = -6.2 ± 1.5 mmHg vs. ΔMAPNCR = -2.1 ± 0.7 mmHg, *p < 0.02). In contrast, there was no significant difference in the hypotensive effects of CAP alone between BHR and NCR (ΔMAPBHR = -5.9 ± 1.2 mmHg vs. ΔMAPNCR = -5.8 ± 1.7 mmHg). There was also no significant difference between BHR and NCR in the magnitudes of decrease in MAP caused by C6 injection (ΔMAPBHR = -27.7 ± 2.4 mmHg vs. ΔMAPNCR = -27.1 ± 1.7 mmHg), although the magnitude of the hypotensive effect of C6 alone was greater than those of V1A and CAP in both BHR and NCR (Fig. 4, top left). On the other hand, there was almost no change in the hypotensive effects of V1A in the salt-loading group (ΔMAPBHR = -5.0 ± 1.8 mmHg vs. ΔMAPNCR = -3.0 ± 1.6 mmHg), and there was also almost no
change in the hypotensive effects of CAP in BHR ($\Delta$MAP$_{\text{BHR}} = 5.6 \pm 1.1$ mmHg, not measured for NCR). In contrast, although the depressor effect of C6 was augmented in both of these rat groups after salt loading, there was no significant difference in the magnitudes of decrease in MAP between BHR and NCR ($\Delta$MAP$_{\text{BHR}} = -34.8 \pm 4.0$ mmHg vs. $\Delta$MAP$_{\text{NCR}} = -43.9 \pm 3.7$ mmHg) (Fig. 4, top right). It should be noted that SNA was enhanced almost equally in both rat groups after salt-diet loading.

**Heart Rate**

In the control group, V1A did not cause any significant change in heart rate in BHR or NCR, whereas CAP slightly increased the heart rate in both the control and salt groups. In contrast, C6 caused a decrease in heart rate only in BHR ($\Delta$Heart Rate$_{\text{BHR}} = -55.7 \pm 13.4$ beats/min). In the salt-loading group, V1A caused slight decreases in heart rate in both BHR and NCR, and CAP also caused a decrease in heart rate in BHR. The decrease in heart rate was enhanced after C6 treatment in both BHR and NCR, although it was significantly greater in the former. The results indicate that heart rate was enhanced by SNA only in salt-loaded BHR (Fig. 4, bottom).

**Depressor Effects of V1A after Salt Loading in Sympatho-Inhibited rats**

In the second series of experiments, in the control (no salt-loading) group, the hypotensive effect of V1A was augmented only in sympatho-inhibited BHR pretreated with C6 (closed bars) (Fig. 5, left). However, as shown in Fig. 3, there was no change in the magnitudes of the depressor effects of V1A after salt loading in either BHR or NCR. On the other hand, V1A induced a significantly greater increase in heart rate in sympatho-inhibited BHR than in sympatho-inhibited NCR, but the degrees of increase in heart rate were not different between the control group and salt-loading group (Fig. 5, right).

**Depressor Effects of CAP after Salt Loading in Sympatho-Inhibited rats**

After sympatho-inhibition in the control (no salt-loading) group, the depressor effects of CAP alone were not different between BHR and NCR. However, the depressor effect of CAP was attenuated in BHR after pretreatment with C6 plus V1A ($\Delta$MAP$_{\text{NCR}} = -15.9 \pm 1.7$ mmHg vs. $\Delta$MAP$_{\text{BHR}} = -7.5 \pm 1.5$ mmHg, $p < 0.01$) (Fig. 6, left). In contrast, the hypotensive effects of CAP were completely inhibited in both BHR and NCR after salt-diet loading (Fig. 6, right). These findings indicate that the renin-angiotensin system was inhibited completely by salt-diet loading in both rat groups.

**Discussion**

Enhanced SNA plays a dominant role in the maintenance of hypertension in SHR and in DOCA rats (16–20). In the present study, the C6-induced hypotension was markedly less in BHR than in SHR or in DOCA rats, and there were no significant differences in C6-induced hypotension between BHR and NCR (Fig. 2, left). These results indicate that SNA is weaker in BHR than in SHR or DOCA rats, whereas SNA in BHR is almost the same as that in NCR, although the decrease in heart rate was significantly greater in BHR than in NCR (Fig. 4, bottom). These findings indicate that SNA does not play a dominant role in the maintenance of hypertension in BHR, unlike in SHR or in DOCA rats.

The dose of AVP needed to produce an increase in AP is 10 to 100-fold higher than that required to produce maxi-
mum antidiuresis (7). Lohmeier et al. (21) reported that, when AVP was infused chronically in normotensive dogs, the AP of the animals increased transiently during the early stage of the infusion, and as the infusion continued, diuresis occurred, water retention decreased, and AP fell progressively. Thus, the vasoconstricting action of vasopressin has been regarded as a pharmacological property of little physiological importance (22). Some investigators also have reported that V1A had almost no effect in lowering AP in intact SHR (23) and that a nonpeptide V1A is relatively unimportant in the development and maintenance of hypertension in conscious SHR (12) and anesthetized DOCA rats (11). However, several lines of evidence show that vasopressin plays an important role in the development and maintenance of hypertension in SHR (24–28). Naitoh et al. (29) reported the involvement of vasopressin V1 receptor-mediated pressor action in the pathogenesis of hypertension in SHR. It has been shown that AVP also plays a major role as a pressor agent in both the pathogenesis and maintenance of hypertension in DOCA rats (3–8). Thus, it is uncertain whether the vasoconstrictive effect of endogenous vasopressin is enhanced in hypertensive animals under conditions in which sympathetic vasoconstrictor tone is intact. Iriuchijima has reported that pressor amounts of endogenous vasopressin are secreted only after inhibition of sympathetic activity in DOCA rats (30) but can be secreted in SHR after acute spinal transection or sinoaortic denervation (31). The latter findings are in sharp contrast to results in NCR (32) showing that the absence or marked abatement of both baroreceptor impulses and adrenomedullary secretion is necessary for secretion of vasopressin in pressor amounts. Therefore, we investigated the hypotensive effect of V1A during ganglionic blockade to elucidate the role of vasopressin in the regulation of AP in BHR. V1A alone induced a slight but significant decrease in MAP only in BHR (Fig. 2, right). In contrast, the depressor effect of V1A was remarkably greater after ganglionic blockade in BHR than after that in SHR, DOCA rats or NCR (Fig. 2, right). The present results indicate that inhibition of SNA easily enhances the secretion of endogenous vasopressin in BHR, i.e., a compensatory vasoconstrictor action of AVP occurs in BHR to maintain AP immediately after the inhibition of SNA.

There are several lines of evidence supporting the theory that the sympathetic nervous system plays a role in the genesis of NaCl-related hypertension, which in turn suggests that sodium retention and hypertension in salt-sensitive animals may be dependent on an increase in SNA or in the ratio of norepinephrine to dopamine secretion (33). A high-NaCl diet has also been shown to stimulate rather than suppress SNA in SHR and Dahl salt-sensitive rats (34–36). An increase in renal SNA could shift the pressure-natriuresis relation toward higher pressure and be responsible for the sodium retention (37–39). Another important finding in the present study is that BHR are salt-sensitive. Namely, BHR became hypertensive after loading with an 8% salt diet for 10 weeks, resulting in a MAP value of 164 ± 14.4 mmHg (Table 2). The acceleration of SNA rather than vasopressin seems to play a major role as a pressor agent in both the pathogenesis and maintenance of salt-sensitive hypertension in BHR, since the C6-induced depressor effect (Fig. 4, top) and the effect on heart rate (Fig. 4, bottom) were significantly enhanced in both rat groups after salt loading. However, there was no significant difference in the magnitudes of decrease in MAP between BHR and NCR. These findings indicate that SNA was enhanced by the high-salt intake in BHR as well as in NCR. In addition, the degree of hypotension induced by V1A was almost unchanged after salt loading, although the depressor effect of V1A was significantly greater.

Fig. 6. Changes in mean arterial pressure (MAP) in sympatho-inhibited normotensive control rats (NCR) without salt loading (open bars) and with salt loading (dotted bars) and in borderline hypertensive Hiroshima rats (BHR) without salt loading (closed bars) and with salt loading (oblique bars) about 10 min after injection of an angiotensin-converting enzyme inhibitor, captopril (CAP, 1 mg/kg, i.v.), alone and V1A (10 µg/kg, i.v.) plus CAP. Note that no change in MAP was induced by CAP injection in either salt-loaded NCR or BHR. Data are the means ± SEM of the number of rats shown in parentheses. *p < 0.05 vs. the value in NCR.
in BHR than in NCR (Fig. 5). These results suggest that most of the endogenous vasopressin is secreted easily after sympato-inhibition, resulting in the secretion of only a little additional endogenous vasopressin even after high-salt intake.

An increase in the plasma concentration of AVP was observed in Dahl salt-sensitive rats after high-NaCl intake, but V1A failed to lower the AP of this hypertensive strain (14, 40). Share and Crofton (14) found that the hypertensive action of V1A in Dahl salt-sensitive rats was prevented by a compensatory increase in renin secretion. In the present study, however, the pressor action of endogenous vasopressin after sympato-inhibition was activated almost equally with or without high-salt intake in BHR during angiotensin II activation. These findings show that even slight sodium-dependent V1 receptor activation is sufficient for regulation of AP in BHR. However, our results are not contradictory to those of a previous study showing that centrally released vasopressin is involved in mediation of the pressor effect exerted by centrally applied angiotensin II in renin transgenic hypertensive rats (15). On the other hand, Kubo et al. (41) reported that the pressor response to angiotensin II injected into the anterior hypothalamic preoptic area was blocked by intracerebroventricular injection of V1A in DOCA rats. The hypertensive effect induced by CAP in BHR was less when the rats were pretreated with a ganglionic blockade followed by V1A (Fig. 6, left). This reduced response to CAP in BHR may have been due to a decrease in the pressor action of angiotensin II during ablation of V1 receptor activation. In other words, endogenous vasopressin is necessary for angiotensin II receptor activation to elicit a pressor effect in BHR. In contrast, after treatment with C6 plus V1A, a subsequent injection of CAP produced no depressor effect in either NCR or BHR after salt loading, i.e., the CAP-induced hypertensive effect was completely inhibited in both rat groups after high-salt intake (Fig. 6, right).

In conclusion, SNA does not play a dominant role in the maintenance of hypertension in BHR, although it is enhanced by the high-salt intake in these rats. V1A-induced hypertension is induced in sympato-inhibited BHR even after high-salt intake, although there was a little change in the degree of this V1A-induced hypertension. These findings indicate that V1A-induced hypertension is almost independent of salt loading. Thus, some of the characteristics of BHR may render them a unique model for the study of hypertension mechanisms.

References


