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Ventrolateral Medulla AT_1 Receptors Support Arterial Pressure in Dahl Salt-Sensitive Rats

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Abstract—The present study addresses the hypothesis that angiotensin type 1 receptors (AT_1Rs) in the rostral ventrolateral medulla (RVLM) contribute to the elevation of mean arterial pressure (MAP) in Dahl salt-sensitive (DS) rats fed a diet with a high NaCl content. Groups of DS or Dahl salt-resistant (DR) rats were fed diets containing either 0.3% NaCl (LNa) or 8% NaCl (HNa) for 3 weeks. Rats were anesthetized with α-chloralose, and the effects of microinjecting the AT_1R antagonist valsartan (Val) or angiotensin II (Ang II) into the RVLM on MAP were measured. Bilateral injection of 100 pmol Val into the RVLM reduced the elevated MAP in the DS-HNa rats by ≈35 mm Hg. In contrast, Val had no effect on MAP in DS-LNa rats. DR rats were normotensive on either diet; Val injection into the RVLM had no significant effect on MAP in DR-HNa rats but did evoke a small decrease in MAP in DR-LNa rats. Injection of Ang II into the RVLM increased arterial pressure in all groups, but the response was substantially larger in DS-HNa rats. Inhibition of neuronal function in the vicinity of the hypothalamic paraventricular nucleus, a possible source of innervation of the RVLM AT_1R, by local injection with muscimol also produced a substantial decrease in MAP in DS-HNa rats but not in DS-LNa rats or DR rats. Thus, RVLM AT_1Rs appear to contribute to salt-dependent hypertension in DS rats, and the paraventricular nucleus may be a source of this tonic activation. **(*Hypertension*. 2003; 41[part 2]:744-750.)**

Key Words: brain ■ hypertension, essential ■ hypothalamus ■ angiotensin ■ angiotensin antagonist

Angiotensin acting within the brain has repeatedly been implicated in the pathogenesis of hypertension. In many forms of experimental hypertension, interference with components of the renin-angiotensin system in the brain decreases arterial pressure (AP). For example, in spontaneously hypertensive rats (SHR), intracerebroventricular injection of antagonists of either angiotensin-converting enzyme or angiotensin type 1 receptors (AT_1Rs) decreases AP.[1–3] Furthermore, central injection with AT_1R or angiotensinogen antisense oligonucleotides also decreases AP in SHR but not in control normotensive rats.[4,5] These observations are not unique to the SHR model of hypertension, because similar findings of decreased AP after blockade of brain AT_1Rs have been reported for numerous models of hypertension,[6–8] including the Dahl-salt sensitive (DS) rat.[9–12] The DS model is particularly interesting in this regard because salt-dependent hypertension can be studied in comparison with normotensive rats with a similar genetic make-up.[13]

The site (or sites) at which angiotensin acts to maintain increased AP in hypertensive rats is not presently known. However, increasing evidence has focused attention on the rostral ventrolateral medulla (RVLM), a brain stem region essential for the maintenance of sympathetic vasomotor tone and the mediation of many neurally mediated cardiovascular reflexes.[14,15] Among areas of the brain thought to be involved in the control of AP, the RVLM has a high concentration of angiotensin receptors, predominantly of the AT_1 subtype.[16] Furthermore, injection of angiotensin II (Ang II) into the RVLM increases AP in rats[17–20] and other species.[21–23] This pressor action of Ang II in the RVLM is mediated by an action on AT_1Rs,[24] and the activity of RVLM spinal neurons is increased by stimulation of AT_1Rs.[25,26] In SHR and in the TGR(mREN2)27 transgenic rat model of renin-dependent hypertension, microinjection of an AT_1R antagonist into the RVLM decreased AP,[24,27,28] whereas these drugs had no effect on AP in normotensive rats.[24,29–32]

The RVLM may also be involved in the effects of changes in dietary salt intake on cardiovascular regulation. Although standard strains of laboratory rats are rather resistant to salt-induced hypertension, cardiovascular responses evoked by stimulation of the RVLM are increased by increases in dietary salt intake.[33,34] For example, the increase in AP elicited by injection into the RVLM of the neuroexcitatory substance glutamate is ≈50% larger in normotensive Sprague-Dawley rats fed a diet containing 8% NaCl compared with those fed standard laboratory rat chow containing 1% NaCl.[33] Dahl salt-resistant (DR) rats show this same potentiated glutamate response when fed a diet with a high

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NaCl content,[35] but DS rats do not show this salt-induced potentiation of the response to glutamate,[35,36] possibly because whatever mechanism is responsible for this effect of NaCl is already activated in DS rats and contributes to the larger response to glutamate observed in DS-LNa rats compared with DR-LNa rats.[35]

The present studies tested the hypothesis that activation of RVLM AT_1Rs contributes to the increased AP in DS rats fed a diet high in sodium. Furthermore, because innervation of the RVLM AT_1Rs appears to originate from the hypothalamic paraventricular nucleus (PVN),[29] we also examined the role of the PVN in the maintenance of resting AP in DS rats.

Methods

Six-week-old male DS and DR rats of the Iwai substrain (Seac Yoshitomi Ltd, Fukuoka, Japan) were housed in groups of 2 or 3 in hanging wire-mesh cages in temperature-controlled rooms with a 12-hour/12-hour light/dark cycle for at least 4 weeks before the experiments. All rats were initially fed a diet containing 0.3% NaCl (LNa diet; Oriental Yeast Co), and 3 weeks before the experiments, some DS and DR rats were switched to a diet containing 8% NaCl (HNa diet). Food and tap water were freely available.

At the time of the experiment, rats were anesthetized and prepared for measuring AP and heart rate (HR) and for injections into the RVLM and PVN as previously described.[24,35] Rats were initially anesthetized with halothane (2% in 100% O_2), and a cannula was inserted into the femoral artery for monitoring AP, mean AP (MAP), and HR; a cannula was also inserted into the femoral vein to allow for intravenous drug injections. The trachea was cannulated, and the rat was treated with tubocurarine (0.5 mg/kg IV, supplemented with 0.2 mg/kg every hour) and artificially ventilated. The rat was then injected with α-chloralose (70 mg/kg IV, supplemented with 20 mg/kg every hour), and halothane administration was terminated. In most experiments, the rat was then placed in a stereotactic frame with the incisor bar set at −11 mm, and the dorsal surface of the medulla was surgically exposed to allow for positioning of microinjection pipettes into the RVLM (with the pipette angled rostrally 20°, 1.8 mm rostral to the caudal tip of the area postrema, 1.8 mm lateral to the midline, 3.0 mm below the dorsal surface of the medulla). In animals receiving injections into the PVN, small holes were drilled into the skull to allow micropipette placement into the PVN (coordinates: 1.8 mm posterior and 0.5 mm lateral to bregma, 7.8 mm below the dura, with the incisor bar at −19 mm[29]). Drugs were microinjected into the brain in a 100-nL volume of artificial cerebrospinal fluid (aCSF) with the use of single-barrel glass micropipettes with tips of ≈50 um OD. Drugs injected were valsartan (Val, 100 pmol), Ang II (100 pmol), L-glutamate (1 nmol), bicuculline (100 pmol), and muscimol (100 pmol); drug doses were based on previous reports.[24] Val was provided by Novartis Pharma AG (Basel, Switzerland), whereas other drugs were obtained from Sigma Chemical Co (St. Louis, Mo).

In experiments involving RVLM injections, glutamate was first injected to verify that the coordinates had placed the pipette into a functional pressor site. Then, other injections were made through the same pipette by withdrawing the pipette, rinsing it thoroughly, filling it with a new drug solution, and reinserting it into the RVLM at the same coordinates. For bilateral injections, injections were made on 1 side, and then the pipette was moved to the contralateral side; the 2 injections were made ≈1 minute apart. For experiments in which injections were made into the RVLM, after the RVLM sites were verified with glutamate injections, each rat was then tested with Ang II unilaterally on each side and finally with bilateral injections of Val. For PVN experiments, rats were first tested with unilateral injections of bicuculline on each side and then bilateral injections of muscimol. In all experiments, baseline MAP was allowed to return to baseline and stabilize for at least 20 minutes before the next injection.

At the conclusion of most experiments, ≈10 nL of 1% fast green dye was injected at the coordinates used for the experiment. The brain was then removed, frozen, and cut into 30- or 50-μm sections for histological examination of the injection site. RVLM injection sites were similar to those that we have described previously.[37] No differences in localization of microinjection sites were noted between groups. A technical problem occurred in the processing of brains from the PVN injection experiment, and therefore, accurate assessment of the injection sites into the PVN is not available for many of these rats. Injections at the specified coordinates typically resulted in injections localized toward the medial aspect of the magnocellular subregion of the PVN.

All data are expressed as mean±SEM. Data were analyzed by 2-way ANOVA (substrain X diet) for each drug treatment and each variable. Statistical analyses were done using Systat 10 software (SPSS, Inc).

Results

Inhibition of AT_1Rs in the RVLM Decreases MAP in Dahl Hypertensive Rats

The key issue examined in these studies is whether the elevated blood pressure in DS rats consuming a diet with a high Na content (8% NaCl; HNa) is supported by activation of AT_1Rs in the RVLM. To address this issue, 100 pmol of the AT_1R antagonist Val was injected bilaterally into the RVLM of groups of chloralose-anesthetized DS and DR rats; this dose of Val had been shown previously to inhibit the effects of 100 pmol Ang II injected into the RVLM.[24] DS rats fed the HNa diet (DS-HNa rats) were hypertensive (Figure 1), whereas DS-LNa rats and DR rats on either diet were normotensive, as expected.[35] Bilateral injection of Val into the RVLM had no significant effect on MAP in DR-HNa or DS-LNa rats (Figures 1 and 2). In contrast, Val injected into the RVLM of hypertensive DS-HNa rats decreased MAP by 36±4 mm Hg ($n=6$; $P<0.05$; Figures 1 and 2). The decrease in MAP in response to Val in DS-HNa rats was slow to develop (onset, 1.3±2 minutes; latency to peak, 13.5±0.6 minutes) and lasted for 38±2 minutes. Injection of Val into the RVLM also produced a small decrease in DR-LNa rats (Figure 1). In the 5 DR-LNa rats receiving bilateral injections of Val into the RVLM, only 4 of these rats showed a decrease in MAP; in these 4 rats, the decrease in MAP was 16±4 mm Hg, with an onset latency of 1.5±0.5 minutes, a latency to peak of 6.2±08 minutes, and a duration of 13.4±2.9 minutes. Compared with the depressor response observed in DS-HNa rats, the response in DR-LNa rats was smaller ($P<0.05$) and briefer ($P<0.05$).

In addition to showing a depressor response to injection of Val into the RVLM, DS-HNa rats also displayed an exaggerated pressor response to injection of Ang II (100 pmol, unilateral) (Figure 3); injection of Ang II into the RVLM increased MAP in all groups, but the response was significantly larger in the DS-HNa rats than in each of the other groups. In marked contrast, injection of glutamate (1 nmol, unilateral) into the RVLM of DS rats elicited a large increase in MAP that was not significantly altered by diet (Figure 3), in agreement with prior observations.[35] Similar glutamate injections into DR rats elicited smaller pressor responses, which were significantly enhanced in the DR-HNa rats compared with the DR-LNa rats, as noted previously.[35] Thus, using the response to glutamate as the

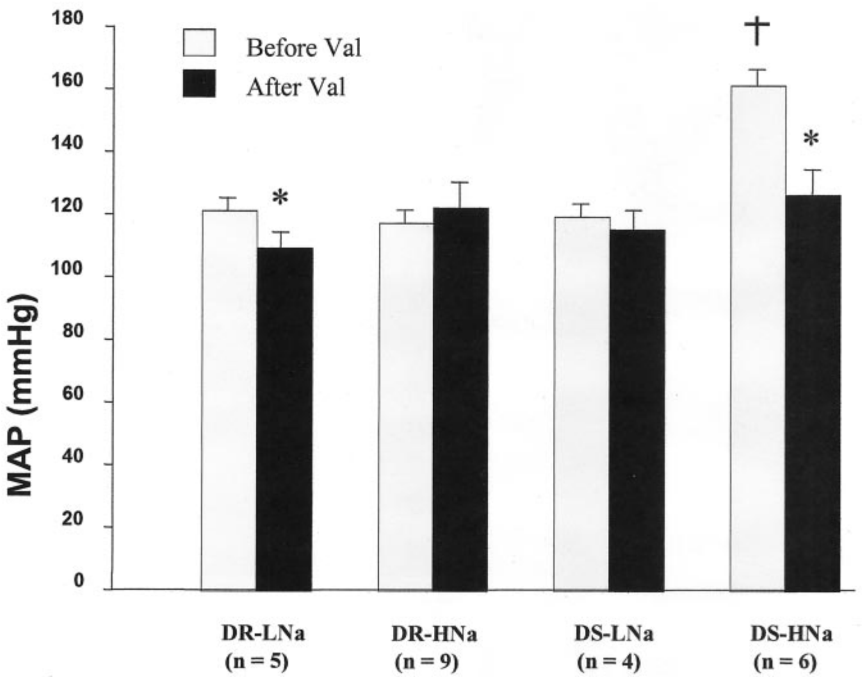

Figure 1. Effects of valsartan (Val) injected into the rostral ventrolateral medulla (RVLM) on arterial pressure (AP) in Dahl salt-sensitive (DS) and Dahl salt-resistant (DR) rats fed either 0.3% NaCl (LNa) or 8% NaCl (HNa) diets. Val (100 pmol, bilateral) was injected into the RVLM of chloralose-anesthetized DS or DR rats fed either the LNa or HNa diet. Values presented represent mean arterial pressure (MAP) just before injection (gray bars) and MAP at the maximal decrease in AP observed within 15 minutes after Val injection. *Significant decrease in MAP compared with before Val, $P<0.05$; the effect of Val in DS-HNa rats was greater than that observed in each of the other groups($P<0.05$). †Significant difference in baseline MAP from each of the other groups, $P<0.05$. Val decreased heart rate (HR) in DS-HNa rats (460±10; −28±3 bpm; $P<0.05$) and in DR-LNa rats (390±15; −10±3 bpm; $P<0.05$) but not in the other groups (DR-HNa: 397±20, 5±8; DS-LNa: 399±7, 4±8); baseline HR was higher in DS-HNa rats than in the other groups, and the response to Val was also greater ($P<0.05$).

standard for the effect of exciting the RVLM, HNa increased the relative effectiveness of Ang II in DS rats but substantially decreased it in DR rats.

Inhibition or Stimulation of the PVN Alters MAP in Dahl Hypertensive Rats

If RVLM AT_1R function is enhanced and tonically active in DS-HNa rats and the PVN is a potential source of angiotensin input to the RVLM,[29] then in DS-HNa rats, activation of the PVN should elicit an enhanced pressor response, and inhibition of the PVN should decrease MAP. This hypothesis was tested by activating the PVN by local injection of the γ-aminobutyric acid antagonist bicuculline (thereby disinhibiting this region) and by inhibiting the PVN by local injection of the γ-aminobutyric acid agonist muscimol. Unilateral injection of bicuculline targeted at the PVN increased MAP to a greater extent in DS-HNa rats than in DS-LNa rats (Figure 4). Conversely, the response to injection of bicuculline targeting the PVN was greater in DR-LNa rats compared with DR-HNa rats. Bilateral injection of muscimol targeting the PVN substantially decreased MAP in DS-HNa hypertensive rats but had little effect on MAP in the other 3 groups of rats (Figure 4). The time course of the fall in MAP in response to inhibition of the PVN in DS-HNa rats (onset, 1.4±0.4 minutes; latency to peak, 12.4±1.6 minutes; $n=4$) was similar to the gradual decrease in MAP observed after injection of Val into the RVLM.

Discussion

The key finding of the present studies is that injection of Val into the RVLM or injection of muscimol aimed at the PVN produced a significant decrease in MAP in DS-HNa hypertensive rats, whereas these treatments had little effect on MAP in DS-LNa normotensive rats. These results are similar to recent studies in SHR[24,27,38] and therefore extend the notion that tonic stimulation of RVLM AT_1Rs, possibly driven from the PVN, might be responsible for the increased activity of sympathetic vasomotor drive in hypertensive rats. Furthermore, interesting observations emerged regarding the effects of a high dietary NaCl intake in DR rats on cardiovascular responses mediated by the RVLM.

Role of RVLM AT_1Rs in Hypertension

Although injections of AT_1R antagonists into the RVLM have little effect on blood pressure or sympathetic nerve activity in normotensive rats on a standard laboratory diet containing approximately 1% NaCl,[17,20,29–32] they do decrease MAP and sympathetic activity in SHR[24,27] and in TGR(mREN2)27 hypertensive rats[28]; this now appears to be also true in another model of hypertension. The notion that tonic stimulation of RVLM AT_1Rs might increase sympathetic vasomotor tone is consistent with the observations that injection of Ang II into the RVLM increases sympathetic vasomotor tone and blood pressure in rats[17–20] and other species.[21–23] Moreover, AT_1Rs are present in the RVLM,[16] and stimulation of AT_1Rs on RVLM spinal neurons studied in vitro elicits an increase in the electrophysiological activity of these neurons.[25,26]

Not only are RVLM AT_1Rs tonically activated in hypertensive rats, as demonstrated by a decrease in blood pressure after administration of an AT_1R antagonist into this region, but also the response to stimulation of these receptors seems to be enhanced. Injection into the RVLM of 100 pmol Ang II, a dose shown previously to elicit maximal effects, elicited an increase in MAP that was >50% larger in hypertensive DS-HNa rats than in normotensive DS-LNa or DR rats. Similar enhancement of the response in DS-HNa rats has also been observed by using a submaximal dose of Ang II (10 pmol; authors' unpublished observations). We[24] and others[39] have observed a similar enhancement of responses to Ang II

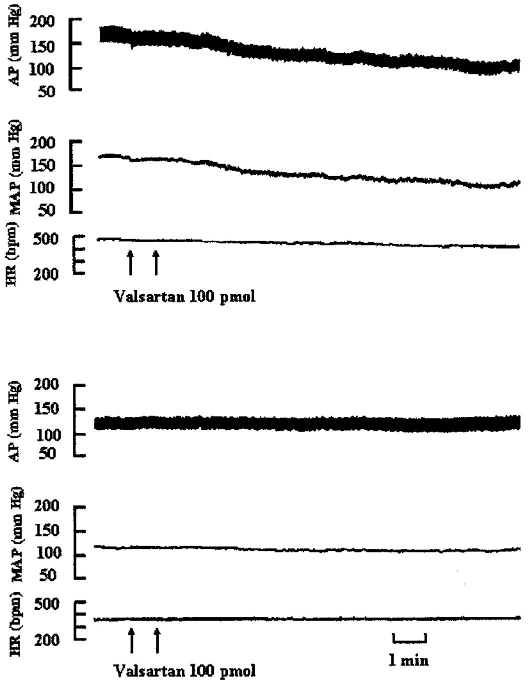

Figure 2. Representative polygraph records of the effects of valsartan (Val) injected into rostral ventrolateral medulla on arterial pressure (AP) and heart rate (HR) in Dahl salt-sensitive rats fed the high-sodium (*top*) or low-sodium (*bottom*) diet. Arrows indicate the times at which Val was injected, first on the left side and then on the right. These recordings are typical of the data included in Figure 1.

in SHR, although some others[17,18] have not observed this. Although changes downstream from the RVLM (eg, altered vascular responsiveness) might contribute to the enhanced response to Ang II in DS-HNa rats, the observation that glutamate injected into the RVLM elicits responses of similar magnitude in both hypertensive DS-HNa rats and normotensive DS-LNa rats argues strongly against this.

Input to the RVLM AT$_1$R appears to arise, at least in part, from the PVN. The strongest data in support of this hypothesis come from a study by Tagawa and Dampney[29] showing that the increase in MAP and sympathetic nerve activity resulting from disinhibition of the PVN by local injection of bicuculline was markedly reduced by prior injection of losartan into the RVLM. Anatomic evidence of angiotensin immunoreactive neurons in the PVN,[40,41] in the region that can be retrogradely labeled from the RVLM,[42] is consistent with this notion, although indirect pathways are also a possibility. If this putative PVN-to-RVLM angiotensinergic pathway is tonically active in hypertensive but not in normotensive rats and the response to Ang II at the level of the RVLM is enhanced in hypertensive rats, then the response to disinhibition of the PVN should be enhanced in hypertensive rats, and inhibition of the PVN should decrease AP. Such responses were observed in the present study and have been reported previously for SHR[24,38] and renal hypertensive rats.[43] Bilateral injection of muscimol targeting the PVN, with a dose of muscimol that had been shown previously to inhibit activity of this region,[44,45] decreased MAP by ≈35 mm Hg in DS-HNa rats. In contrast, injection of muscimol aimed at the PVN in normotensive DS-LNa rats and in DR rats had minimal effects on MAP. The finding that muscimol injections targeting the PVN had no substantial effect on MAP in normotensive rats is in agreement with previous studies,[44–46] although 2 studies using excessively higher doses of muscimol (>1 nmol) have reported decreases in MAP.[47,48] Thus, the PVN, by way of a tonically active angiotensin-mediated input to the RVLM, may contribute to the maintenance of baseline AP in the DS model of hypertension, as well as in other models.

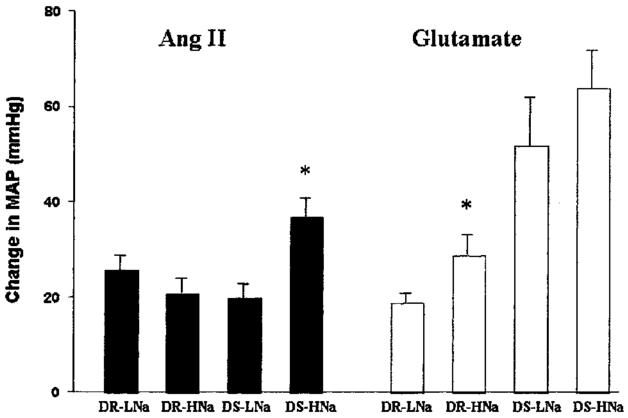

Figure 3. Responses to injection of glutamate and angiotensin II (Ang II) into the rostral ventrolateral medulla (RVLM) in Dahl salt-sensitive (DS) and Dahl salt-resistant (DR) rats. Glutamate (1 nmol) and Ang II (100 pmol) were injected unilaterally into the RVLM of DS and DR rats fed a diet containing either 0.3% NaCl (LNa) or 8% NaCl (HNa). Values are expressed as the maximal change in mean arterial pressure or heart rate (HR). Glutamate and Ang II significantly ($P<0.05$) increased MAP in all groups. *Significant difference ($P<0.05$) between the same strain on different diets. Glutamate-evoked responses were larger in the DS rats than the DR rats ($P<0.05$). HR increased in response to Ang II in all groups, although the responses were larger in DS-HNa rats (24±2 bpm) and DR-LNa rats (25±4 bpm) than in DS-LNa rats (14±2 bpm) and DR-HNa rats (11±3). In DS rats on either diet, the response to glutamate was variable and not statistically significant, whereas glutamate significantly increased HR in DR-LNa (31±3 bpm) and DR-HNa (29±8 bpm) rats.

Interestingly, the response to blockade of RVLM AT$_1$Rs or neuronal activity in the vicinity of the PVN in hypertensive DS-HNa rats has a gradual onset; a similar time course of these responses has also been observed in SHR.[24] The similar gradual time course of the 2 responses is consistent with a common mechanism and also with the time course of the action of Ang II on RVLM spinal neurons studied in vitro.[26] Thus, it appears that in SHR and DS-HNa hypertensive rats, removing excitation of AT$_1$Rs in the RVLM results in a slowly developing disexcitation of RVLM sympathoexcitatory neurons.

We have previously reported that injection of the excitatory amino acid antagonist kynurenic acid into the RVLM decreases MAP in hypertensive DS-HNa rats.[35] Although the relation between this response and the response to injection of Val into the RVLM is not clear at present, experiments in SHR suggest that the 2 responses might be fully independent. Specifically, similar responses to both kynurenic acid and Val have been observed in SHR, and the responses are additive,[35] suggesting that they are mediated by distinct mechanisms.

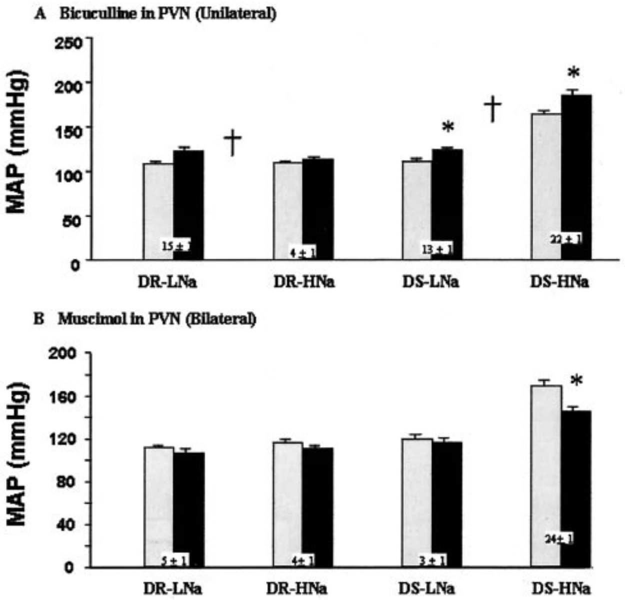

Figure 4. Effects of bicuculline (*top*) or muscimol (*bottom*) injected into the vicinity of the hypothalamic paraventricular nucleus (PVN) on arterial pressure (AP) in Dahl salt-sensitive (DS) and Dahl salt-resistant (DR) rats fed either 0.3% NaCl (LNa) or 8% NaCl (HNa) diets. Groups of DS and DR rats fed either the LNa or HNa diet (4 to 6 rats per group) had bicuculline (100 pmol, unilateral) injected into the PVN. After the effects of bicuculline had worn off (at least 1 hour), muscimol (100 pmol) was injected bilaterally into the PVN. Values show mean arterial pressure (MAP) just before injection (gray bars) and maximal response of MAP after injection of drug (black bars). Values inside the bars represent the change in MAP. *Significant change in MAP after drug injection. †Significant difference in response between rats of the same strain on the different diets, $P<0.05$. Bicuculline produced a significant increase in heart rate in DS-HNa rats (+17±4 bpm, $P<0.05$) and in DR-LNa rats (+22±4 bpm, $P<0.05$). Muscimol produced a small decrease in heart rate in DS-HNa rats only (−12±4 bpm, $P<0.05$).

Thus, both increased excitatory amino acid input and angiotensin-mediated input to the RVLM may contribute to the increase in MAP in DS-HNa rats.

Changes in Dietary NaCl Influence RVLM-Evoked Responses in Normotensive Rats

Altering the dietary NaCl intake of DR rats did not alter baseline MAP, but it did affect the responses to injection of test agents into the RVLM and PVN. As we have noted previously,[35] injection of glutamate into the RVLM produces a substantially larger increase in MAP in DR-HNa rats compared with DR-LNa rats. Such an effect of dietary salt on responses to injection of glutamate and other substances into the RVLM has been noted previously in other Sprague-Dawley substrains[33,34] and appears to result from increased responsiveness of RVLM neurons. Surprisingly, in the present study, the pressor response to Ang II injected into the RVLM was not enhanced in DR-HNa rats; indeed, when considered relative to the pressor response evoked by glutamate, the response to Ang II in DR-HNa rats was actually reduced compared with that in DR-LNa rats. This observation is interesting for 2 reasons. The demonstration that only certain pressor responses evoked from the RVLM are enhanced by elevated dietary NaCl intake provides strong support for the notion that this effect of high NaCl on RVLM-evoked responses is not simply a reflection of altered peripheral circulatory control (eg, altered vascular responsiveness). More important, it suggests that changing dietary salt intake selectively alters Ang II–mediated mechanisms in the RVLM. DiBona and Jones[32] noted that injection of the AT1R antagonists candesartan and losartan into the RVLM decreased renal sympathetic nerve activity and, to a small extent, AP in rats on a low salt diet compared with a high dietary salt intake. Similarly, in the present study, it was observed that Val injected into the RVLM decreased MAP in DR-LNa rats but not DR-HNa rats. Furthermore, DiBona and Jones[49] reported that disinhibition of the PVN with bicuculline elicits a larger increase in renal sympathetic nerve activity in normotensive Sprague-Dawley rats on a low dietary salt intake compared with a high dietary salt intake; though a similar trend was observed with AP, the responses were small and not statistically different. In the present study, we did observe that in DR rats the pressor response to injection of bicuculline into the PVN was significantly greater in rats fed the LNa diet compared with the HNa diet. DiBona and Jones[49,50] suggested that low sodium intake, which is associated with increased activity of the renal renin-angiotensin system, similarly activates a brain renin-angiotensin system, resulting in increased responsiveness of the RLVM to drugs that act on the renin-angiotensin system. However, evidence that a brain renin-angiotensin system responds in a parallel manner to the renal renin-angiotensin system in normal rats is lacking. In DR rats, it has been reported that brain AT_1Rs are increased in DS-HNa rats, possibly more so than in DR-HNa rats,[51] which may partially explain the larger response to injection of Ang II into the RVLM of DS-HNa rats. DS-HNa rats also appear to have an increased angiotensin-converting enzyme activity in the hypothalamus and pons (the only areas examined),[10] although this was not accompanied by detectable changes in Ang II.[10] Clearly, the alterations in brain renin-angiotensin system function in normotensive and hypertensive rats in response to changes in dietary salt intake are not fully understood.

Summary and Conclusions

In summary, tonic activation of RVLM AT_1Rs appears to contribute to the maintenance of elevated AP in the Dahl model of salt-sensitive hypertension. The observation that inhibition of neuronal function in the vicinity of the PVN also decreases AP in hypertensive DS rats is consistent with the notion that the increased activity of RVLM vasomotor neurons is driven by a PVN-to-RVLM pathway. These data provide initial support for the hypothesis that a PVN-to-RVLM pathway, exciting RVLM vasomotor neurons by activating AT_1Rs, may play an important role in salt-sensitive hypertension. Furthermore, observations in normotensive DR rats suggest that changes in dietary salt intake may selectively alter responsiveness of RVLM neurons to angiotensin.

Perspective

Salt-sensitive hypertension appears to have a strong neurogenic component. Although the source of increased sympathetic vasomotor tone in models of salt-sensitive hypertension is not known, the RVLM is a likely candidate for the presympathetic site providing the increased drive of sympathetic vasomotor tone. The present studies in DS rats showing a large decrease in MAP caused by blocking RVLM AT_1Rs suggest this mechanism as a possible neural substrate for our beginning to understand the sympathetic hyperactivity in salt-sensitive hypertension and suggest a mechanism by which AT_1R antagonists might act to lower AP in salt-sensitive hypertension.

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