Role of the organum vasculosum of the lamina terminalis for the chronic cardiovascular effects produced by endogenous and exogenous ANG II in conscious rats

Alexandre A. Vieira, David B. Nahey, and John P. Collister

Department of Veterinary and Biomedical Science, College of Veterinary Medicine, University of Minnesota, St. Paul, Minnesota

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The hormone ANG II has been shown to activate important pressor mechanisms in the brain (11, 21, 24). Recent results have shown that circulating (both endogenous and exogenous) ANG II acts at one of the central circumventricular organs (CVOs), the subfornical organ (SFO), to modulate chronic blood pressure regulation. However, at the forebrain, another CVO that is likely a key area for the chronic cardiovascular control is the organum vasculosum of the lamina terminalis (OVLT). In the present study, we tested the hypothesis that the OVLT mediates the hypertension or the hypotension produced by chronic infusion of ANG II or losartan (AT1 antagonist), respectively. Six days after sham or OVLT electrolytic lesion, male Sprague-Dawley rats (280–320 g, n = 6 per group) were instrumented with intravenous catheters and radiotelemetric blood pressure transducers. Following another week of recovery, rats were given 3 days of saline control infusion (7 ml/day) and then infused with ANG II (10 ng·kg⁻¹·min⁻¹) or losartan (10 mg·kg⁻¹·day⁻¹) for 10 days, followed by 3 recovery days. Twenty-four-hour average measurements of mean arterial pressure (MAP) and heart rate (HR) were measured during this protocol. Further analyses compared with rats with lesions of the entire AV3V region abolishes several hypertensive responses that depend on increases of sympathetic activity, including ANG II-dependent hypertension (5–8, 15, 27, 28, 35, 36).

However, the AV3V electrolytic lesion is not selective to only one area, as it contains not only the OVLT but also the AV3V region. Electrolytic lesions of the entire AV3V region abolish several hypertensive responses that depend on increases of sympathetic activity, including ANG II-dependent hypertension (5–8, 15, 27, 28, 35, 36).

Materials and Methods

Animals. Male Sprague-Dawley rats (Charles River Laboratories) weighing 280–320 g were used in all experiments. All procedures were conducted under Institutional Animal Care and Use Committee approval at the University of Minnesota (protocol no. 0908A70384).

Lesion of the OVLT. Rats were randomly selected for either sham or OVLT lesion. Rats were anesthetized with intraperitoneal pentobarbital sodium (65 mg/kg body wt) and intraperitoneal atropine (0.2 mg/kg body wt) and placed in a stereotaxic frame (model no. 900; David Kopf Instruments). Bregma and lambda were positioned at the same horizontal level. A tungsten wire electrode (0.008 in. of diameter) bared at the tip (0.5 mm) was inserted into the brain using the following coordinates: +0.6 mm from bregma, on the midline and 8.0 mm below the dura mater. Electrolytic lesions were performed using a cathode current (0.5 mA for 20 s). A clip attached to the tail was used as the indifferent electrode. Sham-lesioned rats underwent the same surgical procedures, with the exception that ventral coordinates...
were 4.0 mm less to avoid possible damage at the OVLT tissue, and no current was passed.

**Implant of the telemetric transducer.** Six days after sham or OVLT lesion, telemetric transducers (model no.TA11PA-C40; Data Sciences International) were implanted for continuous, 24-h sampling (500 Hz for 10 s/min) of mean arterial pressure (MAP) and heart rate (HR), as described previously (9, 10, 19). After the implant of the transducer, rats were instrumented with femoral venous catheters for continuous intravenous infusion and acute injections. The catheter was tunneled subcutaneously and passed through a rubber harness (Harvard Apparatus), and a flexible spring on the back of the rat to allow access in unrestrained, freely moving rats. A hydraulic swivel was used to connect the catheter to an infusion pump.

During recovery from surgery, every rat received an intramuscular antibiotic injection of 2.5 mg gentamycin and a subcutaneous injection of the analgesic butorphanol (0.075 mg). The rats were housed individually in metabolic cages (Nalgene) with the swivel mounted above in a controlled environment (temperature 23°C, with a 12:12-h light-dark cycle with lights on at 7:00 AM). A 0.4% NaCl diet (Research Diets) and distilled water were available during the entire experimental protocol. During the first 3 days of recovery from surgery, each rat received daily prophylactic intravenous antibiotics consisting of 15 mg ampicillin and also, a continuous intravenous infusion of 0.9% sterile NaCl.

**Histology.** At the end of the experiments, rats were deeply anesthetized with an overdose of pentobarbital sodium and perfused transcardially with 4% paraformaldehyde in PBS. The brains were frozen, cut coronally (50-μm sections), stained with cresyl violet stain, and analyzed by light microscopy to confirm the site of the OVLT lesions.

**Statistical analysis.** The results are reported as means ± SE. One- or two-way ANOVA combined with a Student-Newman-Keuls tests were used for comparisons. Differences were considered significant at $P < 0.05$.

**Experimental protocol.** For the rats that received infusion of ANG II (ANG II group), the experimental protocol started 3 days after the recovery period from surgery (implant of the telemetric transducer). Control period measurements were made during the first 3 days of continuous intravenous infusion of 0.9% sterile NaCl. After this control period (3 days), ANG II (10 ng·kg⁻¹·min⁻¹, dissolved in 0.9% sterile NaCl) was infused intravenously for 10 days in sham (n = 6) and OVLT lesioned rats (n = 6) to produce hypotension. After 10 days of intravenous ANG II, we measured three further recovery days similar to the control period with intravenous infusion of 0.9% sterile NaCl.

To understand the contribution of sympathetic vasomotor tone in the cardiovascular responses produced by ANG II, we measured the pressor response to 30 ng of ANG II on the first control day and changes in baseline MAP in both sham and OVLT lesioned rats.

Additionally, to test the vascular responsiveness in sham and OVLT lesioned rats, we injected both groups of the rats (ANG II and losartan) with 1 pressor dose of the $\alpha$-1 adrenergic agonist, phenylephrine (0.75 μg/kg) at day 2 (control period).

Infusions (ANG II or Losartan) were administered at a rate of 7 ml/24 h through a 0.2-μm syringe filter. Daily measurements of MAP, HR, food intake, water intake, urine output, as well as urinary sodium were recorded during the entire experimental protocol (16 days). Sodium intake was calculated as the sum of sodium received in the daily infusion (1 mmol/day iv), plus the product of food intake and the sodium content on the food (0.4% NaCl, 0.07 mmol/g). Urinary sodium content was measured with an ion-specific electrode (Nova Biomedical). Urinary sodium excretion was calculated as the product of urine flow rate and urinary sodium concentration.

We measured food and water intake, as well as changes in body weight during the immediate first 5 days after sham or OVLT lesion.

### RESULTS

**Histology.** Figure 1 illustrates representative coronal forebrain sections from sham and OVLT lesioned rats. The OVLT is a small area located at the anterior wall of the 3rd ventricle and ventral from the brain surface. It is the most anterior part of the AV3V region and encompasses different portions that begin immediately below the final portion of the diagonal band resting dorsally from the optic chiasm and ending before the complete union of the anterior commissure. After histological analyses, six rats per group were observed to have more than 90% lesion of the OVLT without damage in the other periventricular tissues or the ventral part of the median preoptic nucleus. These rats were included in the present results.

**OVLT lesion prevented ANG II-induced hypertension.** Three initial days of saline infusion (control period) did not produce changes in baseline MAP in both sham and OVLT lesioned rats.

**Fig. 1.** Photomicrographs of consecutive forebrain slices (50 μm) showing the portions of the organum vasculosum of the lamina terminalis (OVLT) in the Sham group of rats (A: circles), one example of one representative OVLT lesion from one studied rat (B; arrows), as well as a schematic drawing (C) showing places that were considered good OVLT lesion (black line) and places considered incomplete and/or misplaced OVLT lesions (gray circles). Scale bar = 500 μm; DBB, diagonal band; MnPO, Median preoptic nucleus; ac, anterior commissure.
Chronic infusion of ANG II (10 ng·kg\(^{-1}\)·min\(^{-1}\)) produced a slow and significant increase of MAP in sham but not in OVLT lesioned rats (total average during 10 days: 113.2 ± 0.2 and 103.2 ± 1.2 mmHg, respectively). By day 9 of ANG II infusion, MAP had increased 16 ± 4 mmHg in sham rats but only 4 ± 1 mmHg in OVLT lesioned rats (P = 0.010, Fig. 2). Additionally, during the recovery period (saline infusion), MAP in both sham and OVLT lesioned rats equally returned to the initial baseline control values (Fig. 2).

Three initial days of saline infusion (control period) did not produce changes in baseline HR in both sham and OVLT lesioned rats (total average during 3 days: 439 ± 6 and 437 ± 5 bpm, respectively). There were no differences in HR between sham and OVLT lesioned rats throughout the entire experimental protocol [F (1,15) = 1.03; P > 0.05] (Fig. 2).

OVLT lesion produced no change in the pressor (27 ± 1 vs. sham: 29 ± 2 mmHg, P > 0.05) and bradycardic (−34 ± 4 vs. Sham: −38 ± 3 bpm, P > 0.05) responses produced by intravenous phenylephrine (0.75 µg/kg).

**OVLT lesion did not prevent losartan-induced hypotension.** Three initial days of saline infusion (control period) did not produce changes in baseline MAP in both sham and OVLT lesioned rats (total average during 3 days: 103.9 ± 0.2 and 100.9 ± 1.2 mmHg, respectively). Chronic infusion of losartan (10 mg·kg\(^{-1}\)·day\(^{-1}\)) produced the same level of hypotension in both sham and OVLT lesioned rats (total average during 10 days: 78.3 ± 3 and 77.4 ± 3 mmHg), respectively (Fig. 3). Additionally, during the recovery period (saline infusion), MAP in both sham and OVLT lesioned rats equally started to return to the initial baseline control [F (1,15) = 0.242; P > 0.05] (Fig. 3).

**Fig. 2.** Average 24-h mean arterial pressure and heart rate recorded during saline infusion (3 days of control and recovery period) and 10 days of ANG II infusion (10 ng·kg\(^{-1}\)·min\(^{-1}\)) in conscious sham or OVLT lesioned rats. *P < 0.05 vs. control.

**Fig. 3.** Average 24-h mean arterial pressure and heart rate recorded during saline infusion (3 days of control and recovery period) and 10 days of losartan infusion (10 mg·kg\(^{-1}\)·day\(^{-1}\)) in conscious sham or OVLT lesioned rats. +P < 0.05 vs. control.

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Three initial days of saline infusion (control period) did not produce changes in baseline HR in both sham and OVLT lesioned rats (total average during 3 days: 450 ± 11 and 452 ± 3 bpm, respectively). There were no differences in HR between sham and OVLT lesioned rats throughout the entire experimental protocol [F(1,15) = 0.73; P > 0.05] (Fig. 3).

The pressor response to intravenous injection of ANG II (30 ng/kg) in the control period (25 ± 2 mmHg) was abolished during infusion of losartan (3 ± 2 mmHg, P < 0.05). OVLT lesion produced no change in the pressor (28 ± 1 vs. Sham group: 27 ± 1 mmHg, P > 0.05) and bradycardic (−37 ± 3 vs. Sham: −34 ± 2 bpm, P > 0.05) responses produced by intravenous phenylephrine (0.75 μg/kg).

Water and sodium balance responses. During the experimental protocol (16 days), the overall statistic did not show differences in daily water intake between groups of sham and OVLT lesioned rats that received ANG II or losartan (P > 0.05). There were no differences also in daily urinary output (P > 0.05) and water balance (P > 0.05), (Fig. 4).

Regarding the measurements of sodium parameters, during the experimental protocol (16 days), the overall statistic for sodium intake showed differences between the OVLT lesioned rats belonging to the group that received infusion of ANG II vs. sham and OVLT lesioned rats that received infusion of losartan (P < 0.05). However, comparisons for factors (group within days) showed these differences only at days 2, 6, and 13. In spite of this, there were no differences in sodium excretion (P > 0.05) and sodium balance (P > 0.05) throughout the protocol (Fig. 5).

Assessment of sympathetic tone in sham and OVLT lesioned rats. In sham rats, injection of hexamethonium produced a greater decrease in MAP during infusion of ANG II vs. infusion of saline (P < 0.05, Fig. 6). In OVLT lesioned rats, injection of hexamethonium produced the same level of decrease in MAP during infusion of ANG II vs. infusion of saline (P > 0.05). The decreases in MAP in sham rats were greater (P < 0.05) than in OVLT lesioned rats in both periods, during infusion of ANG II or saline, (Fig. 6). There was no change in HR between groups (data not shown).

Intake during the first 5 days after sham or OVLT lesion. After 1 day of slightly decreased water intake, which was greater in OVLT lesioned rats (in both groups), we did not observe any changes in water intake and food intake (Table 1), as well as any decrease in body weight 5 days after sham or OVLT lesion.

DISCUSSION

The CVOs play an important role in cardiovascular regulation. Characteristic to CVO, there is an incomplete blood-brain barrier, and this allows these areas to detect acute and chronic alterations in plasma osmolality, as well as changing concentrations of circulating chemical substances, such as the hormone ANG II (24, 25).

Recent results from our laboratory have demonstrated that both endogenous and exogenous circulating ANG II act at one of the CVOs, the SFO, to modulate chronic blood pressure regulation. In these studies, both the hypertension and hypotension produced by chronic exogenous (intravenous) infusion of ANG II or losartan (ANG II receptor antagonist, subtype AT1), respectively, were markedly attenuated in SFO lesioned rats (10). However, at the forebrain, another important CVO is the OVLT, an important nucleus belonging to the preoptic periventricular tissue surrounding the anteroventral third ventricle (AV3V region), and an important site of action of circulating ANG II (24, 26).
There is much evidence that the AV3V region plays important roles in cardiovascular regulation and the control of fluid-electrolyte balance (5–8). Studies have shown that lesions of the entire AV3V region, that include the OVLT as well as specific tissues, such as the periventricular tissues surrounding the 3rd ventricle and the ventral part of the median preoptic nucleus, impair the development of several forms of experimental hypertension and pressor responses that have been linked to increases of sympathetic activity, including ANG II-dependent hypertension (5–8, 27, 28, 35, 36).

The aforementioned area known as the OVLT is located ventrally from the brain surface and encompasses the most anterior wall of the 3rd ventricle (20). The present results have shown that electrolytic lesion of the OVLT itself blocked the hypertension produced by 10 days of intravenous infusion of ANG II but not the hypotension produced by 10 days of intravenous infusion of losartan. These results suggest that in

Table 1. Changes in WI and FI during control condition and during the first 5 days of sham or OVLT lesion

<table>
<thead>
<tr>
<th>ANG II Group</th>
<th>Control</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham WI, ml</td>
<td>±27</td>
<td>±23*</td>
<td>±28</td>
<td>±29</td>
<td>±29</td>
<td>±28</td>
</tr>
<tr>
<td>Sham FI, g</td>
<td>±25</td>
<td>±14*</td>
<td>±22</td>
<td>±25</td>
<td>±25</td>
<td>±25</td>
</tr>
<tr>
<td>OVLTx WI, ml</td>
<td>±26</td>
<td>±13*†</td>
<td>±25</td>
<td>±28</td>
<td>±30</td>
<td>±33</td>
</tr>
<tr>
<td>OVLTx FI, g</td>
<td>±26</td>
<td>±12*</td>
<td>±20</td>
<td>±24</td>
<td>±25</td>
<td>±25</td>
</tr>
<tr>
<td>Losartan WI, ml</td>
<td>±28</td>
<td>±21*</td>
<td>±26</td>
<td>±29</td>
<td>±28</td>
<td>±30</td>
</tr>
<tr>
<td>Losartan FI, g</td>
<td>±24</td>
<td>±12*</td>
<td>±23</td>
<td>±25</td>
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<td>±28</td>
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<tr>
<td>OVLTx WI, ml</td>
<td>±29</td>
<td>±13*†</td>
<td>±24</td>
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<td>OVLTx FI, g</td>
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<td>±24</td>
</tr>
</tbody>
</table>

WI, water intake; FI, food intake; OVLT, organum vasculosum of the lamina terminalis, OVLTx, OVLT lesion. *P < 0.05 vs. control; †P < 0.05 vs. Sham within the day 1; n = 6 per group.
conscious rats, ANG II does not act at the OVLT to maintain baseline mean arterial pressure (MAP). However, the increases of MAP produced by elevations of plasma ANG II are highly dependent on the integrity of ANG II receptors in the OVLT.

Importantly, it has already been demonstrated that the vasoconstrictive effects produced by stimulation of the entire AV3V region have origins in the OVLT (23) that, in turn, is activated after elevation of central osmolality (33) increasing sympathetic activity (34). Recent results in anesthetized rats (1) drinking 0.9% NaCl have suggested that neurons from forebrain areas, such as OVLT influence the excitability of the rostral ventrolateral medulla (RVLM), one of the most important areas for the cardiovascular control (17, 18). Our results suggest that like increases in central osmolality, increased plasma ANG II is sensed by the OVLT, and this activation also is important for chronic cardiovascular regulation. Also, because OVLT cells are responsive to increases in central osmolality (33, 34), as well as ANG II (4, 32), it is likely that the OVLT is a crucial site in the forebrain that contributes to hypertension induced by a combination of salt and ANG II, a currently well-reviewed concept in the field of neurogenic hypertension (29).

However, using this model of hypertension, we have found in the past that the integrity of another CVO, the SFO is also necessary for the full hypertension produced by chronic infusion of ANG II (19). Although a conclusive mechanism by which this occurs is still unclear, we can suggest that the hypertension produced by chronic infusion of ANG II is dependent on the normal activity of the forebrain CVOs. In other words, in conscious rats, a disturbance of any component of the CVOs of the lamina terminalis is sufficient to at least attenuate the hypertension produced by chronic infusion of the present dose of ANG II. Because there are reciprocal and important excitatory projections for the cardiovascular regulation between forebrain CVOs (20, 24, 26, 38), one possibility is that individual lesions might impair possible positive feedback between them, facilitating and maintaining the increase of sympathetic activity and blood pressure after ANG II infusion.

We do know that even in this model (salt replete), the chronic hypertension induced by infusion of ANG II is likely dependent on increases of sympathetic activity (19). In the present study, we also assessed and confirmed this contribution of sympathetic vasomotor tone in chronic ANG II-induced hypertension. In sham rats, our results demonstrated that the hypotension produced by infusion of the ganglionic blocker hexamethonium, was greater during chronic infusion of ANG II when compared with infusion of saline. However, additionally, our data demonstrated that during both periods (saline and ANG II infusion), hexamethonium produced a greater hypotensive response in sham vs. OVLT lesioned rats, suggesting an attenuation of sympathetic tone in OVLT lesioned rats during both control condition (saline infusion) and elevation of ANG II.

Furthermore, we also know that plasma ANG II can act on AT1 receptors located in the CVOs and that these signals can reach different downstream projected areas such as the paraventricular nucleus of hypothalamus (directly or via the median preoptic nucleus), producing, in turn, signals modifying sympathetic activity and blood pressure (2, 3, 24–26, 30, 32, 38). Also, there is much evidence that forebrain areas, indeed, have an important role on cardiovascular regulation and sympathetic activity (1, 7, 8, 35, 36). As such, recent results in conscious rats have shown that the integrity of the forebrain angiotensinergic mechanisms, as well as the integrity of the AV3V region is important for the pressor response produced by glutamatergic activation into the brain stem areas, such as the nucleus of the solitary tract and RVLM (35–37). These studies support the idea that at least in conscious rats, the OVLT is necessary to the normal activity of brain stem areas to increase blood pressure after increases of plasma ANG II. A suggestion is that in sham rats, ANG II could be acting chronically in CVO’s activating signals to increase MAP, and these signals, in turn, would be facilitated by excitatory projections from the OVLT indirectly and/or directly to the brain stem.

One question that remains unclear from the present study is related to the complete blockade of the hypertension in the OVLT lesioned rats. For example, as previously mentioned, in other studies from our laboratory, we have seen attenuated hypertensive effects of ANG II in animals with lesions of either the median preoptic nucleus (MnPO) or SFO (19, 30).

Studies have shown that the way by which ANG II produces increases in blood pressure involves a fast component that is dependent on its peripheral actions and later a slower component that likely depends on central mechanisms (12, 14, 16). We recognize the possibility of peripheral action of ANG II contributing to the increase of blood pressure, but this effect would probably be seen during the first days after infusion (22). In the present study, we did not see a significant increase in blood pressure during the first days of ANG II infusion, especially in OVLT lesioned rats (unlike previous studies with SFO lesioned rats in our lab). However, it is possible that lesion of the OVLT might impair both (the fast and the slow) component of the ANG II-induced hypertension, and this impairment is not due to any deficits in the vascular reactivity because the pressor responses to intravenous phenylephrine were not different between sham and OVLT lesioned rats.

The other major result from the present study is that the integrity of the ANG II receptors in the OVLT is not important for the hypertension produced by chronic infusion of losartan. Infusion of losartan produced the same level of hypotension in sham and OVLT lesioned rats. This result is different when compared with SFO and MnPO lesioned rats. Electrolytic lesion of the SFO attenuated while electrolytic lesion of the MnPO increased the hypotension produced by losartan infusion (9, 31). Our initial hypothesis would have predicted an attenuation of the hypotensive response to losartan, as we have observed in the past in SFO lesioned rats (9). For this reason, we can suggest that in conscious rats, the OVLT does not participate in the central neural circuitry mediating the hypotension produced by losartan infusion. In other words, under normal conditions, it seems that ANG II does not act in the OVLT to maintain baseline MAP. However, in situations in which circulating ANG II is elevated, contributing to increases of MAP, the integrity of the OVLT is essential.

In the present study, in both groups of rats (rats that received intravenously infusion of ANG II or losartan), lesions of the OVLT, by itself, did not produce any impairment on water and sodium balances. However, we observed some differences in the measurements of sodium intake between groups (ANG II and losartan infusion) on days 2, 6, and 13. This can be explained because of greater oscillations in the food intake observed on some days, including the aforementioned, in rats receiving infusion of ANG II when compared with rats receiving infusion of losartan. As mentioned in MATERIALS AND
METHODS, the measurements of sodium intake were made from the sum of sodium received in the daily infusion (1 mmol/day iv), plus the product of food intake and the sodium content on the food (0.4% NaCl, 0.07 mmol/g).

Importantly, we started to measure water and sodium intake only 24 h after infusion. For this reason, in rats receiving infusion of ANG II, we cannot discard the possibility of increases in water and sodium intake in the first minutes, as well as in the first hours (13). However, the known dipsogenic effect could be masked in our 24-h measurements, but certainly, there was no difference between sodium and water intake between the groups during this chronic experiment.

Moreover, because our experimental protocol began several days after the OVLT lesion, we did examine the acute effects of OVLT lesion on sodium and water homeostasis to compare its effect to those in rats with acute lesions of the entire AV3V region (6, 7). Lesions of the entire AV3V region that include the OVLT, produce several disruptions on HB, including abrupt adipsia and severe weight loss, which causes death if not subsequently treated correctly (6, 7). The most critical period is during the first week after the AV3V lesion. Importantly, our results have shown that a sole lesion of the OVLT, in contrast to the entire AV3V lesion, does not produce any loss of body weight nor severe changes in sodium and water homeostasis. OVLT lesioned and sham rats were similar in sodium and water balance at the start of the experimental protocol. As noted, this result is important, showing the failure of the OVLT lesion to produce impairment on HB to verify that the results observed on the attenuated hypertensive response were not related to any initial or ongoing disruption of HB. Indeed, these observations support our histological verifications that the OVLT lesion in the present study is truly distinct from previous studies involving entire AV3V lesions. Moreover, additional and important information from the present study is that the known disturbance of water intake produced in rats with entire AV3V lesions (6, 7) is not related to the loss of the OVLT function by itself.

The present result has established that the OVLT, a band of tissue within the AV3V region, as a necessary central site of ANG II-mediated chronic hypertension. Finally, the present study provides critical insight to our overall understanding of the mechanisms, whereby lesions of entire AV3V region promote impairment of experimental hypertension.

Perspectives and Significance

The OVLT is a CVO that houses receptors for ANG II (2, 25) and is also very sensitive to increases of osmolality (33, 34). Excesses of plasma sodium and increases of ANG II is a dangerous combination that can result in hypertension (29). However, the mechanisms by which this combination leads to hypertension is still not fully resolved. Is it possible that the OVLT has an additional role in the salt sensitivity of ANG II-induced hypertension? For this reason, additional future studies in OVLT lesioned rats consuming a diet rich in salt combined with ANG II are critical to our overall understanding of the relationship between salt, ANG II, and hypertension.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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