Inflammation and Neurogenic Hypertension
A New Role for the Circumventricular Organs?

Eric Lazartigues

The brain renin–angiotensin system (RAS) plays a critical role in maintaining blood pressure regulation and volume homeostasis. Components of the RAS, including angiotensinogen, renin, angiotensin (Ang)-converting enzymes, and Ang receptors, are expressed in various nuclei located between the anteroventral region of the third ventricle (AV3V) and the brain stem. Accordingly, formation of the various Ang peptides, notably Ang II and Ang(1-7) can take place in the brain, independently of the endocrine RAS, and participate in the regulation of water intake, salt appetite, cardiac baroreflex and autonomic functions. Upregulation of Ang II type 1 (AT1) receptors in these nuclei has been shown to reduce baroreflex sensitivity and increase sympathetic tone, thus contributing to the development and maintenance of hypertension and heart failure, ultimately leading to end-organ damage. On the other hand, treatment with ACE inhibitors and Ang receptor blockers can prevent RAS overactivity and restore a normal cardiovascular function. In addition to Ang II generated in the brain, blood-borne Ang peptides can also enter the central nervous system via the circumventricular organs (CVOs) and contribute to the regulation of blood pressure and volume homeostasis.

The CVOs are represented by the OVLT (organum vasculosum of the lamina terminalis), the subfornical organ (SFO), the median eminence and the neurohypophysis, all surrounding the hypothalamus, the pineal gland located between the thalamic bodies, and the area postrema on the floor of the fourth ventricle. Because of their lack of blood–brain barrier, the CVOs represent “windows” to the central nervous system, allowing small molecules to enter the brain. These areas have previously been shown to be pivotal brain regions required for the Ang II–mediated pressor and water intake responses. Indeed, lesions of the SFO in dogs and rats prevented water intake and sodium appetite but also the development of hypertension induced by chronic administration of intravenous Ang II. Similarly, ablation of the area postrema attenuated the hypertension resulting from increased in blood borne Ang II. However, ablation of either SFO or area postrema failed to prevent non-renin-dependent hypertension. Altogether these studies provided evidence for a major new paradigm: the brain was required to mediate several forms of Ang II–induced hypertension. These findings were later extended to other brain regions inside the blood–brain barrier and it is now well accepted that an overactive brain RAS is critical for the development and maintenance of neurogenic hypertension.

In the last decade, increasing evidence have shown the participation of Ang II in the inflammatory process and suggested that hypertension might be an inflammatory disease. In this issue of Circulation Research, Marvar et al followed up on these observations and asked whether there is a central element in Ang II–induced inflammation in hypertension. To test this hypothesis, the authors used AV3V lesions, a procedure resulting in the destruction of part of the lamina terminalis and previously reported to prevent Ang II–mediated pressor and drinking responses. Interestingly, the authors report that destruction of the AV3V not only prevented elevation of blood pressure but also activation of T cells and vascular infiltration of leukocytes. Using pharmacological and genetic tools, they elegantly dissected the possible mechanisms for these responses and describe a feed-forward process in which the central pressor effects of Ang II lead to activation of T cells, which, in turn, promotes vascular inflammation. Some of the major findings from Marvar et al are the observations that superoxide and inflammatory cells were reduced in the vasculature of AV3V-lesioned mice receiving Ang II infusion. These data suggest that the octapeptide does not produce these responses through a direct effect on the vasculature but instead needs to interact with brain regions to promote inflammation and oxidative stress. Although it might seem like a totally new concept, this could be partially explained by the dose of Ang II infused. Indeed, in this study, mice received a dose of 490 ng · kg⁻¹ · min for 2 weeks, considered to be a subpressor dose and an experimental model for neurogenic hypertension. The main characteristic of this approach is that, at this dose, Ang II does not produce a direct vascular response but a slow-developing increase in blood pressure resulting from activation of the brain RAS. As a result, increased sympathetic tone would lead to norepinephrine release, contributing to vascular oxidative stress and inflammation. Although higher doses of Ang II may not have produced the same results, the current approach is considered to be more relevant to human essential hypertension.

The role of the CVOs in the immune response has been previously reviewed in the context of neurological disorders and shown to be primary sites for activation of macrophages and microglia. After previously showing that T cells are necessary for the development of certain forms of hypertension and that deletion of SOD3 in the SFO of transgenic mice, some CVOs express the coreceptors for immune cells, such as the chemokine receptors CCR2 and CCR5, and have been shown to be sites of leukocyte infiltration. Ablation of CVOs, leading to a reduction of leukocyte infiltration, has been shown to prevent the development of hypertension in these models. Therefore, the CVOs are key sites for immune cell infiltration and may be relevant in the development of hypertension.

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From the Department of Pharmacology & Experimental Therapeutics and Cardiovascular Center of Excellence, Louisiana State University Health Sciences Center, New Orleans.
Correspondence to Eric Lazartigues, PhD, Louisiana State University Health Sciences Center, School of Medicine, Department of Pharmacology and Experimental Therapeutics, 1901 Perdido St, New Orleans, LA 70112. E-mail elazar@lsuhsc.edu
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mice was responsible for an increase in baseline blood pressure and Ang II–mediated pressor response18 (although extracellular SOD failed to prevent hypertension in nontransgenic mice19), Marvar et al13 are the first to establish a link between CVOs, inflammation, and hypertension. This study clearly suggests a major role for the CVOs and particularly the SFO. It is important to note that AV3V lesion, although destroying the OVLT, does not physically affect the structure of the SFO. However, it is likely to destroy the axons of neurons projecting from the SFO to downstream nuclei, such as the paraventricular nucleus, and therefore impair the transmission of signal to these nuclei.

Although we used to think of the CVOs as open doors or windows to the central nervous system, the study by Marvar et al13 shows us that immune cells are waiting at these doors, ready to be activated by small peptides, like Ang II, and contribute to the development of neurogenic hypertension. Although some questions remain on the role of other CVOs, such as the area postrema, and the participation of signaling pathways (tumor necrosis factor-α, nuclear factor κB) contributing to the immune response in these regions, Marvar et al are leading the way for researchers who now should consider hypertension not only as a renovascular pathology but also as a neurological and immunologic disease.

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None.

References

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Non-standard Abbreviations and Acronyms

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ang</td>
<td>angiotensin</td>
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<tr>
<td>CVO</td>
<td>circumventricular organ</td>
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<tr>
<td>OVLT</td>
<td>organum vasculosum of the lamina terminalis</td>
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<tr>
<td>RAS</td>
<td>renin–angiotensin system</td>
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<td>SFO</td>
<td>subfornical organ</td>
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