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CORRESPONDENCE

Does angiotensin II cross the blood–brain barrier?

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There is a growing recognition that angiotensin II (Ang II) acts as a central, rather than just a peripheral, effector of cardiovascular autonomic function. A large number of studies, including one from the authors in the December edition of *Hypertension Research*,[1] corroborate the importance of the central renin-angiotensin system in cardiovascular homeostasis. In conjunction with this study, Paton *et al.*[2] have shown that Ang II type 1 receptors exist within the nucleus tractus solitarius (NTS) and that Ang II injected intraparenchymally into the NTS depresses the cardiac component of the baroreceptor reflex in rats.

The main remaining controversy stems from a wide claimed notion that Ang II does not cross the blood–brain barrier (BBB). Is that really so?

The authors justly communicate that the subfornical organ in the brain can detect increases in the plasma concentration of Ang II because of the lack of a BBB (circumventricular organ). It is true that Ang II induces signals from the subfornical organ to the paraventricular nucleus neurons in the hypothalamus, thus activating the rostral ventrolateral medulary (RVLM) neurons and peripheral sympathetic nerves, and raising the blood pressure. Therefore, 'the subfornical organ can translate the elevated plasma Ang II into an increase in peripheral sympathetic nerve activity via the paraventricular nucleus and RVLM neurons.' However, the authors realize that this route of signaling through the subfornical organ cannot explain the potential of Ang II action in its fullness. The authors then speculate that local astrocytes create Ang II, which then stimulates the RVLM neurons.

However, the last speculation from the authors is disputable. From an evolutionary point of view, it does not seem economical to 'invent' cells in the brain that will produce Ang II, in the setting of a general abundance of Ang II in the peripheral circulation. What seems like a more plausible explanation for the presence of Ang II in the brain-specific regions (NST and RVLM) is the attenuation of the BBB permeability for Ang II in and around these regions.

In rats in which the subfornical region had been removed surgically, circulating Ang II continued to depress baroreflex function through NTS inhibition, but this was prevented by AT1 receptor antagonism confined to NTS.[3] Thus, it is plausible that circulating Ang II can exert actions on RVLM and NTS neurons, even bypassing the subfornical organ.

Moreover, Fleegal-DeMotta *et al.*[4] show that Ang II directly regulates endothelial cell function at the BBB, which causes increased radioactive albumin permeability.

Finally, it has been shown that Ang II itself undergoes AT1 receptor-mediated transcytosis in the BBB endothelial cells.[5] These studies suggest that the Ang II molecule is probably too large to cross through tight junctions, but AT1 receptor-mediated trancytosis of Ang II at the BBB is likely to happen and contributes to the regulation of central cardiovascular autonomic function.

The question whether Ang II crosses the BBB becomes significant when contemplating mechanisms of autonomic nervous/cardiovascular system disorders. In disorders, such as multiple system atrophy (MSA) or vasovagal syncope, abnormalities of neurocardiogenic regulation are the culprit and Ang II is likely to be the key player. Two possible scenarios are as follows:

In a person prone to vasovagal syncope, who is experiencing a bout of hypotension, the periphery produces more Ang II to counteract a drop in the blood pressure. The person is also hyperventilating (common accompanying sign of vasovagal syncope) and the brain senses the drop in PCO2 and runs into syncope before seizure happens. The brain does this by not allowing Ang II produced in the periphery to cross the BBB, thus keeping the working of NTS unopposed; RVLM excitatory signals do not reach IML neurons, the heart rate and blood pressure go down and the person faints.

In neurodegenerative diseases, such as MSA, people who are prone to orthostatic hypotension due to autonomic impairment are diagnostically challenged on a tilt table test. During orthostatic challenge, the periphery will start producing Ang II, but a diseased brain will not propel enough Ang II through the BBB to excite RVLM and deactivate nucleus tractus solitarii. Consequently, the MSA person will lose the capacity to buffer acute changes in the blood pressure and either faint or present with orthostatic symptoms.

Future studies are warranted to elucidate the role of Ang II in disorders of cardiovascular autonomic regulation, with the potential for bringing new therapies for autonomic disorders.

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