Angiotensin Type 1A Receptors on Glial Cells in Rostral Ventrolateral Medulla and Hypertension

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During the 1970s and early 1980s, all the components of the renin–angiotensin system (RAS) were identified within the brain. Subsequent physiological studies have shown that angiotensin II (Ang II) can act at various sites within the brain stem and hypothalamus to regulate cardiovascular function and fluid and electrolyte balance. Further, there is increasing evidence that brain Ang II can contribute to increased sympathetic activity in hypertension and heart failure.

In recent years, a number of investigators have studied the physiological effects of alteration of the expression of genes encoding various components of the RAS. As reviewed recently by Davisson, early studies by Ganten and colleagues showed that transgenic rats containing the mouse renin (Ren-2) gene were hypertensive. Although there is an increased expression of Ang II in the hypothalamus and medulla oblongata of such animals, the extent to which the hypertension was caused by increased levels of central or peripheral Ang II was not clear. Later, with the development of new methods that enabled brain-selective expression of particular genes, transgenic mice in which the angiotensin type 1A (AT1A) receptors were overexpressed in the brain but not in peripheral tissues were produced. These animals exhibit exaggerated pressor responses to intracerebroventricular administration of Ang II, but have a normal resting arterial blood pressure. Thus, this indicates that an increased density of AT1A receptors alone is not sufficient to produce hypertension.

Other genetic models, however, have demonstrated that overactivity of the brain RAS can produce hypertension. In transgenic mice containing both the human angiotensinogen (hAGT) gene under the control of the human glial fibrillary acidic promoter and the human renin (hREN) gene, the resting blood pressure was increased. Because in these mice the hAGT gene was expressed only in the brain (mainly in glial cells, which are the primary source of brain AGT), this study indicated that increased production of Ang II derived from brain AGT can produce chronic hypertension. Furthermore, the hypertension in this transgenic model is corrected by intracerebroventricular injection of losartan, a specific antagonist of AT1 receptors, or by blockade of sympathetic ganglionic transmission. Thus, these results indicate that the hypertension is attributed to chronic activation of brain AT1 receptors, resulting in sympathetic overactivation. A recent study has also shown that, in a transgenic mouse in which genes for both hAGT and renin are overexpressed, ablation of the hAGT gene specifically in glial cells also abolishes the hypertension, such that the arterial pressure is reduced to a level not different from that in nontransgenic control mice.

The studies described above provide good evidence that increased production of Ang II derived specifically from AGT in glia is sufficient to result in sustained hypertension. The question then arises as to the specific location(s) within the brain at which Ang II produces this effect. AT1 receptors are known to be located in several sites in the brain stem and hypothalamus that are important in cardiovascular control. One site of particular interest is the rostral ventrolateral medulla (RVLM), which contains a group of sympathoexcitatory neurons that project directly to sympathetic preganglionic neurons in the spinal cord and which have a pivotal role in the tonic and phasic regulation of sympathetic vasomotor tone. Studies in a variety of species, including humans, have shown that this region contains a high density of AT1A receptors, and activation of these receptors by microinjection of Ang II results in an increase in blood pressure and sympathetic activity. These effects appear to be selective to sympathoexcitatory neurons in the RVLM, because Ang II has no effect on respiratory neurons that are also located in this region.

The role of endogenous Ang II in the RVLM in the regulation of sympathetic vasomotor activity is still unclear. Blockade of AT1 receptors bilaterally in the RVLM has little effect on arterial pressure or sympathetic activity in normotensive animals, although in spontaneously hypertensive rats, Dahl salt-sensitive hypertensive rats, and transgenic rats in which the renin gene is overexpressed in the brain, blockade of these receptors does cause a decrease in blood pressure, indicating that at least in these hypertensive models AT1 receptors in the RVLM do make a significant contribution to sympathetic vasomotor tone and resting arterial pressure.

The study by Allen et al published in this issue of Hypertension provides important new information concerning the role of AT1 receptors (specifically the AT1A subtype, which is the subtype that mediates the pressor effects of central Ang II) in the RVLM. By using adenoviruses encoding the wild-type AT1A receptor, or a constitutively active form of the receptor, the authors found that overexpression of the constitutively active, but not the wild-type, AT1A receptor in the RVLM resulted in an increase in blood pressure that was sustained for 3 to 4 days. This finding is interesting for several reasons. First, it shows for...
the first time that increased AT1A receptor activity in the RVLM alone will increase blood pressure for a period of several days. Second, consistent with previous studies showing that overexpression of AT1A receptors in the entire brain does not alter resting blood pressure,2 the study by Allen et al.8 shows that increased activity of AT1A receptors in the RVLM, not simply an increase in receptor density, is required to trigger the mechanisms leading to an increase in blood pressure. Finally, another very interesting observation is that the overexpression of the AT1A receptors appeared to be confined to non-neuronal, mainly glial cells in the RVLM. As the authors point out, the possibility cannot be ruled out that there was increased expression of these receptors also in neurons, which was too small to be detected. Nevertheless, this finding is consistent with previous studies, referred to above, which demonstrated that glia-specific overexpression of AGT in the brain, in the presence of increased renin activity, will also lead to hypertension.4,6 Allen et al.8 suggest that activation of AT1A receptors on glial cells may up regulate AGT synthesis in these cells, leading to increased Ang II synthesis and activation of RVLM sympathoexcitatory neurons. Clearly, however, the precise signaling pathway remains to be determined.

One unexplained aspect of the results is that the increase in blood pressure did not persist beyond 3 to 4 days, even though the increased AT1A receptor expression in the RVLM was sustained for at least 10 days. Whether this reflects an adaptive intracellular response that counters the effects triggered by increased constitutive activity of the AT1A receptors or other responses triggered by the increased blood pressure can also only be resolved by further studies. The rapidly advancing technology in this field2 should also enable future studies to determine the role in blood pressure regulation of AT1A receptors located specifically on neurons or endothelial cells within the RVLM. In particular, the method of RNA interference, which has been used recently to silence AT1A receptors in the subfornical organ and in the nucleus tractus solitarius/dorsal vagal nucleus,9 is likely to be an effective tool for such studies.

Although much has been learned of the mechanisms that subserve short-term regulation of blood pressure, much less is known about long-term regulation, largely because of the lack of appropriate methods. The study by Allen et al.8 together with other recent studies in which alterations of gene expression have been produced in selected regions or selected cell types,2,6 demonstrate the potential power of molecular genetic methods combined with integrative physiological studies in elucidating the mechanisms that underlie long-term changes in sympathetic activity and blood pressure.

References
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