Brain Angiotensin II
New Insights Into Its Role in Sympathetic Regulation
Irving H. Zucker

Since its discovery, the renin-angiotensin II system (RAS) has intrigued physiologists and clinicians. Angiotensin II (Ang II), an ancient peptide, evolved to carry out a variety of biological functions, in order to meet the needs of diverse organisms. The negative feedback nature of the RAS enables it to participate in hemodynamic, endocrine, neural, behavioral, and excretory functions. It is truly a peptide to which the survival of most species is closely linked.

Over the past 20 years, blockade of the RAS has become a prime target for pharmacotherapy in a variety of diseases, especially hypertension and heart failure. Blockade of Ang I conversion to Ang II or blockade of the Ang II type I receptor (AT1) has been used to treat hypertension and heart failure. Administration of these agents is effective in ameliorating disease and enhancing survival, even in patients without augmented levels of circulating Ang II. This observation has led investigators to focus on the tissue RAS as a mechanism by which organ function is both controlled and, in disease states, impaired. Although the kidney is the only organ that stores renin in granular form, the components of the RAS have been found in tissues from several other organs. These include the heart, liver, lung, and brain. The regulation of the RAS system in the brain is especially intriguing because Ang II can act as both a neurotransmitter and a vasoconstrictor.

It has been known for some time that the brain expresses the genes that code for angiotensinogen, renin, converting enzyme, and all of the subtypes of the AT1 and AT2 receptors. The actions of Ang II in the central nervous system include promotion of thirst behavior and salt appetite, the regulation of vasopressin secretion, the regulation of sympathetic outflow, and modulation of the sensitivity of the arterial baroreflex, as well as many other important cardiovascular reflexes (Figure). The modulation of sympathetic outflow is a critical regulatory action of central Ang II because both chronic heart failure and some forms of hypertension are characterized by sympathoexcitation. The precise nature by which the brain RAS participates in the regulation of sympathetic outflow is still not completely understood. A major step forward in our understanding of the role of the RAS in blood pressure regulation has come from the study of Lazartigues et al reported in this issue of Circulation Research. These investigators developed a new and novel transgenic mouse that selectively overexpresses brain AT1a receptors. To develop this model, they took advantage of splicing the gene for the AT1a receptor with that of the neuron-specific enolase (NSE). The resulting animals (NSE-AT1) overexpressed the AT1 receptor in neurons in a wide variety of brain areas but not in glial cells or peripheral tissues (except for the adrenal medulla). Interestingly, these animals had normal resting arterial blood pressure, a finding not predicted based on other experiments in which arterial pressure was lowered in hypertensive animals by blockade or genetic manipulation of the central RAS. Although the arterial pressure of the NSE-AT1 was normal, these animals responded with an exaggerated increase in arterial pressure after central administration of Ang II. These two observations are important because they strongly suggest that overexpression of AT1a receptors in normal animals does not alter arterial pressure and, most likely, sympathetic outflow. These data also relate to the issue of baroreflex resetting, which has been shown to be influenced by nonpressor doses of Ang II. In order to minimize decreases in baroreflex sensitivity after an increase in arterial pressure, the baroreflex operating point may shift closer to the elevated pressure. The study by Lazartigues et al adds support for the notion that central AT1 receptors may participate in the resetting process.

The role of Ang II in the sympathoexcitatory process of disease states such as chronic heart failure has been an active area of investigation. For instance, it has been shown that central and peripheral administration of the AT1 receptor antagonist losartan enhances baroreflex sensitivity, which may contribute to sympathoinhibition. In addition, it appears that central Ang II participates in the sympathoexcitatory process of the heart failure state by virtue of sensitization of reflexes that are sympathoexcitatory in nature, such as the cardiac sympathetic afferent reflex. This reflex too can be normalized by blockade of the AT1 receptor in the brain or more specifically in discrete regions of the central nervous system such as the paraventricular nucleus.

The genetic manipulation of the AT1 receptor offers a unique opportunity to develop new therapeutic strategies in the treatment of hypertension, heart failure, and other states characterized by sympathoexcitation. The strategy described in the article of Lazartigues et al is but one possibility. Another method to implicate overexpression or hyperactivity of the AT1 receptor in disease states is the use of antisense oligonucleotide administration to reduce transcription of the mRNA for the AT1 receptor in both hypertension and heart failure. These studies point to a potential pivotal role of...
The RAS in the brain has been shown to modulate both sympathoinhibitory and sympathoexcitatory reflexes. In addition to an intrinsic RAS, circulating Ang II may gain access to the brain through areas with weak or no blood brain barriers. Ang II via stimulation of the AT₁ receptor in the brain may reduce arterial baroreflex and cardiopulmonary reflex sensitivity and contribute to baroreflex resetting. At the same time, Ang II augments excitatory reflexes. Both of these actions of central Ang II may lead to increases in sympathetic outflow in such disease states as heart failure and hypertension.

References


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