THE BRAIN RENIN-ANGIOTENSIN SYSTEM AND SALT-SENSITIVE HYPERTENSION

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Summary. An intrinsic tissue renin-angiotensin system (RAS) has been described in the brain. This review provides an overview of the localization of the enzymes, peptides, and receptors of the brain RAS and the organization of angiotensinergic pathways involved in cardiovascular regulation. Centrally administered exogenous angiotensin (Ang) II increases sympathetic neuronal activity, decreases the gain of the baroreflex, and induces vasopressin release. Ang II generated by the brain can cause similar changes through effects in nuclei from the forebrain to the brainstem. In salt-sensitive hypertension, both brain ouabain-like compounds ("ouabain") and the brain RAS appear to play an essential role. Both central and high sodium intake activate brain "ouabain" followed by stimulation of the brain RAS and sympathoexcitatory and hypertensive responses. The actual pathways involved have not yet been established, but appear to involve the ventral anteroventral third ventricle region, the anterior hypothalamic area, and the paraventricular nucleus of the hypothalamus.

INTRODUCTION

In 1961, Bickerton and Buckley first reported that circulating Angiotensin (Ang) II is able to act on the central nervous system to increase blood pressure [1]. Since then a number of Ang II sensitive sites in the brain have been demonstrated. Moreover, besides the classical circulatory renin-angiotensin system (RAS), intrinsic tissue RASs have emerged, including that in the heart and brain. The brain RAS and central actions of the circulatory RAS are involved in central cardiovascular regulation and body fluid homeostasis, cyclicity of reproductive hormones, sexual behavior, and perhaps neuronal development and differentiation, and learning and
memory [2–4]. This review (1) provides an overview of the localization of the brain RAS and the organization of angiotensinergic pathways, and (2) describes the role of brain Ang II in salt-sensitive hypertension.

LOCALIZATION OF THE BRAIN RAS

All components of the RAS have been identified in brain tissue, including angiotensinogen, the precursor for angiotensins, the protease renin, which cleaves angiotensinogen to the decapeptide Ang I; and the angiotensin-converting enzyme (ACE), which converts Ang I to the octapeptide Ang II. Expression of the mRNA for angiotensinogen, renin and ACE has been demonstrated in the brain of several species, including rats, and is consistent with the concept of a local brain RAS [5,6]. Incubation of brain homogenates with renin generates Ang I, implying that the precursor angiotensinogen is present locally [7]. In addition angiotensinogen has been identified immunohistochemically [8]. Following initial reports on central renin activity [7,9], the presence of brain renin that is independent of circulating renin, distinct from other proteases, active in vivo and inhibited by renin specific antibodies was confirmed [10,11]. Brain ACE is similar to peripheral ACE with respect to molecular weight, optimum pH, chloride dependency, and inhibition by various inhibitors [12]. However, ACE isozymes with different molecular weights have been demonstrated in the brain [13,14]. Brain ACE is ubiquitous in distribution and, like that of peripheral sources, is nonspecific in action, i.e., in addition to converting Ang I to Ang II, ACE of central origin degrades kinins and neuropeptides such as substance P.

Four main angiotensin receptor subtypes have been described [15,16]. Three of these—namely, the AT₁, AT₂, and AT₄ receptors—are distributed in the brain as well as in peripheral tissue. Central areas involved in cardiovascular regulation, body fluid homeostasis, and neuroendocrine function exhibit a predominance of AT₁ receptors [17–19], which bind Ang II with high affinity.

Angiotensinogen, detected immunocytochemically, is predominantly located in astrocytes and ependymal cells [20], and angiotensinogen mRNA detected by in situ hybridization is localized mainly in astrocytes [21]. However, angiotensinogen immunoreactive neurons have also been identified [22], and the presence of angiotensinogen has been demonstrated in CSF as well [23]. The site of synthesis of brain angiotensins is as yet unresolved. Bunnemann et al. [21] suggested that angiotensinogen may be produced in astrocytes and converted to Ang I by renin in the extracellular fluid or alternatively may be taken up by neurons and converted intraneuronally. Renin and ACE activity have been colocalized in synaptosomes, supporting the concept of intraneuronal synthesis [24]. However, renin has also been detected in oligodendrocytes, and ACE has been detected extracellularly [2,25]. After conversion of Ang I to Ang II by ACE, Ang II is further acted on by aminopeptidases to form the heptapeptide Ang III, which is converted to the hexapeptide Ang IV. Ang II is the first biologically active molecule in this cascade and acts as a neurotransmitter/neuromodulator. An alternate pathway exists whereby