REGULATION OF THE HYPOTHALMIC-PITUITARY-ADRENAL AXIS AND VASOPRESSIN SECRETION

Role of Angiotensin II

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INTRODUCTION

Angiotensin II (ANG II) has a number of actions in the central nervous system, including regulation of water intake, blood pressure and the secretion of pituitary hormones such as ACTH, prolactin and gonadotropins (1,2). With respect to ACTH, several in vitro studies in rodents and primates have shown that ANG II directly stimulates ACTH secretion and potentiates the stimulatory effect of corticotropin releasing hormone (CRH) through ANG II receptors in the pituitary corticotroph (3). However, the physiological importance of the direct pituitary action seen in vitro is not clear, and in most experimental conditions the stimulatory effect of ANG II on ACTH secretion in vivo appears to be mediated by central mechanisms (4). The stimulatory effect of peripherally administered ANG II on ACTH secretion is mediated, at least in part, by CRH, as demonstrated by the ability of CRH antiserum to block the effect (5), and by the transient increases in irCRH in the median eminence following ANG II administration (4). Circulating ANG II may centrally activate CRH release by acting directly on the median eminence or through the circumventricular organs, areas containing abundant ANG II receptors (2,6).

Although the above evidence indicates that ANG II is involved in regulating the HPA axis, the physiological role of the peptide in the responses to acute or chronic stress is not understood. It is possible that ANG II is involved in stress-specific responses of the HPA axis under different stressors. Activation of the magnocellular system following chronic osmotic stimulation inhibits the HPA axis, whereas repeated physical-psychological stress results in hyperresponsiveness to a novel stress, with or without desensitization of the response to the primary stimulus, depending on the stress paradigm (7). Thus, the question remains as to whether differential activation of ANG II receptors in the hypothalamic paraventricular nucleus (PVN) by various stressors influences the response of the CRH neuron.
ANG II is also involved in the central regulation of vasopressin (VP) secretion. I.c.v. injection of ANG II causes release of VP from the posterior pituitary lobe (1,2). At least part of the effects of ANG II on VP secretion are indirect, mediated through catecholamine release by activation of ANG II receptors located in afferent terminals innervating magnocellular PVN neurons (8,9). On the other hand, the presence of ANG II binding sites and AT₁ receptor mRNA in the magnocellular PVN (10), suggests that ANG II directly modulates the function of VP neurons.

**Ang II Receptor Binding and AT₁ Receptor mRNA in the PVN**

Autoradiographic analysis of the binding of $^{125}$I[Sar¹, Ile⁸]ANG II in serial coronal sections of the PVN reveals high density staining throughout the anteroposterior axis of the PVN, with localization in the periventricular and parvicellular pars (Figure 1). Periventricular binding was distinct in the most anterior sections, where light microscopic analysis of the stained sections showed few lateral parvicellular or magnocellular cells. Binding was also present in the magnocellular areas, but it was less well defined and of lower density. In addition, high binding is clearly present in nerve fibers associated with the dorsolateral area of the PVN, and in the median eminence (2,6,10). Binding of the radiolabeled ligand is completely inhibited by the AT₁ receptor antagonist, Losartan, indicating that ANG II receptors in the PVN are type I (AT₁).

The topographic distribution of AT₁ receptor mRNA is similar to that of the AT₁ receptor binding, with the highest levels in the periventricular and parvicellular portions of the PVN. Very low hybridization was found in the dorsolateral magnocellular region. No AT₁ receptor mRNA is observed in the median eminence (Figure 1) indicating that the receptors are likely associated with nerve terminals rather than glial cells. The demonstration of AT₁ receptor mRNA in CRH perikarya (see below) suggests that the nerve terminals containing ANG II receptors originate in CRH cells, and that these AT₁ receptors mediate the stimulatory effect of peripherally administered ANG II on the release of CRH into the pituitary portal circulation (5,11).