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Neural Mechanisms by which Gravitational Stimuli and Stress Affect the Secretion of Renin and Other Hormones

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Description of Research

The NASA grant which supports this research was activated August 1, 1983. It was initially administered from NASA Headquarters, but has now been transferred to NASA-Ames Research Center and given a new number effective February 1, 1987. The long-term goal of the research is delineation of the neural pathways and transmitters that mediate changes in the secretion of renin and other hormones concerned with regulation of salt and water balance in response to gravitational and other stimuli. Evidence from this laboratory indicates that stimulation of serotonergic neurons on the dorsal raphe nucleus of the midbrain increases renin secretion, and that these neurons project to the mediobasal hypothalamus (Karteszi, et al., Neuroendocrinology 34:323-326, 1982). The initial goal of determining how the message got from the hypothalamus to the renin-secreting cells in the kidney was accomplished by pharmacological experiments demonstrating that the pathway was sympathetic (Alper and Ganong, 1984; see publication list). The present goal is to determine by the production of discrete lesions the parts of the hypothalamus and brainstem that are involved in serotonin-mediated increases in renin secretion. In addition, we want to determine the role of the brain in the renin responses to other stimuli. Therefore, we have developed and standardized a variety of stimuli which act in different ways to increase renin secretion. These include: 1) administration of the serotonin-releasing drug p-chloroamphetamine (PCA); 2) the pyschological stress of immobilization; 3) the postural stress of 45° head-up tilt; 4) the volume depletion stress of a low sodium diet; and 5) the acute volume stress of nonhypotensive hemorrhage.

Accomplishments

Major accomplishments, particularly in the past year, include the following observations:

1) Like the PCA response, the renin responses to immobilization and head-up tilt were shown to be blocked by the ß-adrenergic blocking drug propranolol, indicating that the final common pathway from the spinal cord to the renin-secreting cells in the kidney is sympathetic in all three situations.

2) Although the increase in renin secretion produced by PCA was abolished by lesions of the dorsal raphe nucleus, the response to immobilization, head-

up tilt, and a low sodium diet was not. Therefore, these latter stimuli do not act by increasing the discharge of the serotonergic neurons in the dorsal raphe nucleus.

3) Bilateral lesions of the paraventricular nuclei reduced or abolished the increase in plasma renin activity (PRA) produced by PCA, immobilization, head-up tilt, and a low sodium diet. However, paraventricular lesions also produced a marked, reproducible decline in the plasma concentration of renin substrate. Since substrate is rate limiting for the generation of angiotensin I in plasma, we remeasured generation of angiotensin I after adding exogenous renin substrate, thus measuring plasma renin concentration (PRC). Like the PRA response, the PRC response to PCA was also abolished by paraventricular lesions. However, the PRC response to immoblization, head-up tilt, and a low sodium diet was normal. Consequently, it appears that the renin-stimulating serotonergic neurons in the dorsal raphe nucleus project to the paraventricular nuclei, but that immoblization, head-up tilt, and a low sodium diet do not act via the paraventricular nuclei.

4) The PRA response to nonhypotensive hemorrhage was normal in rats with bilateral paraventricular lesions, but the PRC response was much greater than normal. Thus, it appears that the body compensates for the deficient production of angiotensin I (and, consequently, of angiotensin II) by producing a stronger stimulation of renin secretion with this particular stress when there are lesions of the paraventricular nuclei.

5) Bilateral lesions of the ventromedial nuclei abolished the PRA response to PCA, immobilization, head-up tilt, and a low sodium diet without producing any change in plasma substrate concentration (Gotoh, et al., 1987). Thus, it appears that the ventromedial nuclei are nodal points in the neural pathways responsible for the increase in renin secretion produced by a variety of different stimuli. We will soon embark on experiments to determine whether these nuclei mediate responses to multiple stimuli or exert some sort of overall tonic effect on the responsiveness of the juxtaglomerular cells.

6) Confirming others, we found that paraventricular lesions block the ACTH response to stress but do not decrease resting plasma ACTH. Since adrenal glucocorticoids, estrogens, and thyroid hormones all stimulate the secretion of renin substrate by the liver, it seems likely that the effects of paraventricular lesions on substrate are due to endocrine changes. The paraventricular nuclei are involved in the regulation of TSH as well as ACTH secretion, and hypophysectomy has been shown by us to produce a decrease in renin substrate (Alper, et al., 1986). In preliminary experiments, the time course of the decline of substrate produced by paraventricular lesions paralleled that produced by hypophysectomy. However, this experiment needs to be confirmed, expanded, and supplemented with hormone replacement experiments. This will be an important goal of the research during the coming year.

7) To see if vasopressin-secreting efferents from the hypothalamus to the cardiovascular regulatory areas in the brainstem and spinal cord are involved in the regulation of renin secretion, the renin secretory responses to the stimuli we have been employing were tested in Brattleboro rats that were

unable to produce vasopressin in their brains. Responses to all the stresses were greater than normal. Conversely, intraventricular injection of vasopressin appeared in very preliminary experiments to inhibit renin secretion and intraventricular administration of an oxytocin agonist appeared to stimulate renin secretion. Further experiments of this type are planned.

8) Blood pressure, heart rate, and vasopressin responses to head-up tilt have been measured in addition to renin during the past year. There were no differences in blood pressure and heart rate between rats with lesions of the paraventricular nuclei and controls. In very preliminary experiments with vasopressin and renin antagonists, it appeared that it was primarily the renin- angiotensin system rather than vasopressin that maintained blood pressure during head-up tilt.

9) Additional data were obtained in the previously described collaborative experiment with Keil at NASA-Ames in which ACTH, corticosterone, PRA, and vasopressin levels are being measured with long-term head-down suspension in rats.

Significance of These Accomplishments

The experiments with PCA have now demonstrated that there is a serotonergic pathway which projects from the dorsal raphe nuclei to the paraventricular nuclei and the ventromedial nuclei of the hypothalamus; that the projection from the paraventricular nuclei to the brainstem and spinal cord may be oxytocinergic, although this point needs additional research; and that the pathway from the spinal cord to the renin secreting cells is sympathetic. The demonstration that paraventricular lesions lower circulating renin substrate is important because it raises the possibility that substrate secretion is under neural control, either via the pituitary or by direct neural pathways. If the endocrine pathways prove to be key, this once again demonstrates the importance of neuroendocrine mechanisms in the maintanence of cardiovascular homeostasis. The discovery that lesions of the ventromedial nuclei appear to abolish the increase in renin secretion produced by many different stimuli without affecting the concentration of renin substrate in the plasma makes the position of the hypothalamus in the regulation of fluid and electrolyte balance more prominent than previously suspected.

Publications:

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