Neuroendocrine Components in the Regulation of Blood Pressure and Renin Secretion

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NEURALLY regulated variables that affect blood pressure include not only the rate of discharge in vasomotor and cardiac nerves, but the rate of secretion of adrenocorticotrophic hormone (ACTH), growth hormone, vasopressin, and renin. Adrenocorticotrophic hormone produces hypertension in sheep and some humans, and plays a significant role in the regulation of aldosterone secretion. Growth hormone does not appear to stimulate renin or aldosterone secretion, despite some claims to the contrary, but it does help maintain the sensitivity of the zona glomerulosa to stimuli that increase aldosterone secretion. Vasopressin occupies a pivotal position in water and secondarily in electrolyte homeostasis, and there is some evidence that its secretion is inappropriately high in renal and deoxycorticosterone-salt hypertension. The relation of renin to hypertension is apparent. This paper is concerned primarily with the interactions between the nervous system and the renin-angiotensin system, with comments about vasopressin as it relates to renin. The secretion of vasopressin, ACTH and growth hormone are also discussed as they relate to the function of α-adrenergic receptors in the brain.

It is worth noting that the interactions between the nervous system and the renin-angiotensin system are multiple and complex. Not only is sympathetic output one of the main regulators of the release of renin from the kidney, but the angiotensin II formed in the circulation by the action of renin and converting enzyme acts on the brain to increase water intake, increase the secretion of vasopressin and ACTH, and raise blood pressure. In addition, the brain may have a renin-angiotensin system of its own. In this paper, the “brain renin-angiotensin system” is briefly reviewed, the actions of angiotensin on the brain are analyzed, and the neural mechanisms regulating the secretion of renal renin are considered in detail.

The Brain Renin-Angiotensin System

The nature and physiological significance of the components of the renin-angiotensin system found in the brain have been reviewed and debated. Additional research will be needed to still the controversy and settle the questions that have been raised. However, a review of the literature makes a number of points stand out.

First, neither renin nor angiotensin II cross from the blood to the brain or cerebrospinal fluid (CSF) in more than trace amounts. The molecular weight of renin (40,000) is such that it would not be expected to cross the cerebral capillaries, and most if not all investigators find no measurable renin activity in CSF. Angiotensin II is a much smaller molecule, but most of the evidence indicates that it also fails to enter brain tissue or CSF. This conclusion is based on experiments in which systemically administered radio-labelled angiotensin II was not detected in CSF (Reid, unpublished), and studies in which CSF angiotensin concentration failed to change when plasma angiotensin was markedly increased.

Silver grains have been seen over the ventricular cavities in some studies employing radioautography following injection of radioactive angiotensin II systemically, but diffusion artifact was not ruled out and there was no proof that the radioactivity represented intact angiotensin. Phillips has argued that although there is no penetration of angiotensin II at resting levels, some peptide enters due to disruption of the blood-brain barrier when injected angiotensin II increases blood pressure more than 35 mm Hg. However, the significance of such entry, if it does occur, is questionable, and the evidence for it is indirect.
Second, many and perhaps all of the components of the renin-angiotensin system can be found in brain tissue and/or CSF. Two careful studies have demonstrated the presence in brain tissue of saturable binding sites with the characteristics of angiotensin II receptors. Angiotensinase activity is also found in brain, and there is angiotensinogen in brain and CSF. It is worth noting that the concentration of angiotensinogen in CSF is about 20% of the concentration in peripheral plasma (158 ± 26 pmol/ml vs 670 ± 45 pmol/ml), whereas the concentration of other proteins in CSF averages only 0.5% of their concentration in plasma. This suggests that angiotensinogen is formed in the brain, or that there is a highly unique transport system permitting selective access of this protein from the blood to the CSF. Converting enzyme is not present in CSF but is present in many parts of the brain with a high concentration in choroid plexus. Confirmation that these compounds are present and active in vivo comes from the demonstration that injections of renin into CSF generate abundant angiotensin II and produce the same pressor effect on blood pressure, water intake, vasopressin secretion and ACTH secretion as intravenous angiotensin II.

In addition, there is considerable angiotensin-generating activity in brain tissue, and according to some investigators, angiotensin I and II are present in brain tissue and CSF. Most of the current debate centers around the chemical nature of the angiotensin-generating activity and the true level of angiotensin I and angiotensin II in cerebral tissues and fluid.

Several reviews on the chemistry of "brain isorenin" have been published. Most investigators report that the angiotensin-generating activity in brain has an optimum pH of 4.5-5.0, and very little if any activity at pH 7.4. Day and Reid found that this brain activity copurified with the lysosomal hydrolase cathepsin D, and argued that all brain renin activity was due to cathepsin D. However, Hirose et al. report that they have separated a "brain renin" from the cathepsin D in brain tissue. Their enzyme was active at extracellular pH and was neutralized by antibodies to pure renal renin. Confirmation and extension of their findings would do much to establish the fact that a brain renin does indeed exist.

Table 1 provides a summary of reported values for angiotensins I, II and III in brain tissue and CSF. Most investigators report values that are low but above the sensitivity of the analytic methods employed. Some of the high values in brain may have been due to failure to adequately inhibit angiotensinases, with consequent degradation of the tracer and spuriously high values. However, some of the analyses were very carefully performed. The bioassay and immunoassay data for the presence of angiotensins have now been butressed by chromatographic evidence that the angiotensin in dog CSF is des-Asp-angiotensin II (angiotensin III). Additional evidence for the existence of angiotensin II in brain tissue is the demonstration of its existence by immunocytochemical methods. Its occurrence in neurons has now been reported in studies employing both the fluorescent and the peroxidase-
antiperoxidase (PAP) techniques. Not all investigators have been able to confirm these findings, and there is room for debate about the relative frequency of false positive and false negative results with immunocytochemistry. However, these studies plus the data cited in table 1 provide considerable evidence that there are angiotensins in the brain and CSF.

What is the function of the brain renin-angiotensin system, if indeed it does exist? Alterations in fluid and electrolyte balance generally fail to produce changes in the components of the renin-angiotensin system in the brain. However, the fact that circulating renin and angiotensin are concerned with volume homeostasis and fluid balance does not mean that the system in the brain subserves the same function. An attractive alternative function is modulation of the release and action of brain catecholamines. Angiotensin II is known to facilitate transmission in sympathetic ganglia, augment the postsynaptic effects of norepinephrine, and increase the amount of norepinephrine released by impulses in sympathetic noradrenergic neurons. There do not appear to be any published data on the effects of angiotensin II or III on catecholamine metabolism in the brain, but the subject merits exploration. There are extensive systems of catecholamine-containing neurons in the central nervous system, and angiotensins could play an important role in any or all of their multiple functions.

Effects of Circulating Angiotensin II on the Brain

It is now well established that circulating angiotensin II acts on the brain to increase fluid intake and raise blood pressure. In addition, there is evidence that circulating angiotensin II stimulates the secretion of vasopressin and ACTH. Angiotensin III has about half the dipsogenic activity of angiotensin II, and presumably has the other activities as well. The neurally mediated pressor effect may be due in part to increased secretion of vasopressin, but it is mainly due to increased sympathetic output; when angiotensin II is administered centrally, the pressor response is abolished by section of the spinal cord and not significantly reduced by hypophysectomy. In greyhound dogs, a decrease in vagal tone may also contribute. Since angiotensin II acts on the brain to increase sympathetic discharge and sympathetic discharge increases renin secretion, one would expect the neural action of angiotensin II to increase renin secretion. However, plasma renin activity is actually reduced because vasopressin secretion is increased, and vasopressin inhibits renin secretion.

Angiotensin II appears to produce a drinking response, an increase in blood pressure and an increase in vasopressin and ACTH secretion by acting on the circumventricular organs, a group of small, centrally located structures that unlike the rest of the brain have fenestrated capillaries. They are therefore “outside the blood-brain barrier” and freely permeable to substances in the general circulation. They include the neurohypophysis and adjacent median eminence, the organum vasculosum of the lamina terminalis (OVLT), the subfornical organ (SFO) and the area postrema (fig. 1). The subcommissural organ resembles the other areas in some ways but may have a different function because it lacks fenestrated capillaries. The circumventricular organs are in an excellent position to function as neurohemal organs (areas in which peptides secreted by neurons are transferred to the circulation), or as chemoreceptor zones (areas in which blood-born chemicals act on receptors that trigger changes in brain function). Oxytocin and vasopressin enter the general circulation in the neurohypophysis, and hypothalamic hypophysiotropic peptides enter the portal-hypophysial circulation in the median eminence. Lesions of the SFO abolish the drinking response to intravenous angiotensin II, and microinjection of small quantities of angiotensin II in the SFO produce drinking responses, and increase blood pressure. In addition, local application produces an increase in neuronal activity in the SFO, and this increase is prevented by saralasin. Lesions of the tissues around the anterior third ventricle, which destroy the OVLT, decrease the pressor and drinking responses to intravenous angiotensin II. Microinjection of angiotensin II into the preoptic recess of the third ventricle produces drinking responses and increases blood pressure, although there is some controversy about the threshold for such responses. It should be noted...
that the physical act of drinking increases blood pressure, and care must be taken in interpreting experiments that involve drinking and blood pressure unless the pressor response precedes the ingestion of fluid. In dogs, cats, and rabbits but not in rats, lesions of the area postrema reduce the pressor response to intravenous angiotensin II. There are as yet no published reports of the effects of lesions of the circumventricular organs on vasopressin responses to intravenous angiotensin II, but angiotensin II releases vasopressin from posterior pituitary tissue incubated in vitro. So does angiotensin I, and the response to angiotensin I is blocked by converting enzyme inhibitors, whereas the response to angiotensin II is not. Consequently, circulating angiotensin II may act directly on the posterior pituitary. The site at which angiotensin II acts to stimulate ACTH secretion is unknown, but the response could be due to vasopressin, since this posterior pituitary peptide has corticotropin releasing activity.

The pattern that emerges from the data summarized in the preceding paragraph is one of considerable overlap in the functions of the circumventricular organs, as well as some species variation. There are many gaps in our knowledge, but it seems possible that the SFO and OVLT both mediate pressor and drinking responses to intravenous angiotensin II. Embryologically, these two organs arise from the same general area, and there are neural pathways interconnecting them. In some species the area postrema also mediates pressor responses.

Injections of angiotensin II directly into the cerebral ventricles produce the same four responses produced by intravenous angiotensin II, i.e., drinking, increased blood pressure, and increased secretion of vasopressin and ACTH. The responses are also produced by intraventricular injection of renin. Responses to intraventricular angiotensin II and renin are blocked by saralasin, and the responses to renin are also inhibited by inhibitors of converting enzyme, indicating that they are due to the angiotensin II produced by the renin. Can these responses be explained by the diffusion of angiotensin II to the circumventricular organs, or is it necessary to postulate the existence of separate intracerebral angiotensin II receptors to explain them? Two kinds of evidence can be brought to bear on this question: the effect of lesions of the circumventricular organs on the responses to intraventricular angiotensin II and renin, and the effects of intraventricular saralasin on the responses produced by angiotensin II in the systemic circulation.

There are no data on the effects of lesions on the vasopressin and ACTH responses to intraventricular angiotensin II. In the case of drinking, lesions of the SFO decreased or abolished the dipsogenic effect of intraventricular angiotensin II. Drinking has also been reported to be reduced when access of intraventricularly injected angiotensin II to the OVLT is blocked. The situation with the pressor response is more complicated because of species differences. In rats, the pressor response to intraventricular angiotensin II has been reported to be abolished by maneuvers that prevent access of angiotensin II to the anterior third ventricular (AV3V) region and by AV3V lesions, whereas the area postrema does not appear to function as a receptor mediating pressor responses to angiotensin II in this species. In cats, injection of angiotensin II in the aqueduct of Sylvius at the level of the midbrain produced a large pressor response, but injection at a more caudal location in the aqueduct produced a small response. In addition, bilateral lesions of the subnucleus medialis in the periaqueductal gray of the midbrain markedly reduced the pressor response to intraventricular angiotensin II. In dogs, lesions of the area postrema abolished pressor responses to injections of angiotensin II in the vertebral artery without affecting the pressor response to intraventricular angiotensin II. This suggests that there may be a separate angiotensin II-sensitive site in the ventricular system of carnivores.

The other approach to this problem is determination of the effect of intraventricular saralasin on the responses to circulating angiotensin II. Blockade of a given response indicates that saralasin is reaching the receptors wherever they may be in the brain. If saralasin and related antagonists diffuse to the receptors, angiotensin II itself could probably reach them, since the antagonist and agonist molecules are about the same size. In dogs, the drinking response to systemic injection of isoproterenol has been reported to be abolished by intraventricular saralasin. The isoproterenol increases renin secretion, and the drinking is due to the resultant increase in circulating angiotensin II. In rats, the drinking response to systemic angiotensin II was abolished by injection of saralasin directly into the SFO, and by intraventricular saralasin, although the dose required in the latter situation was relatively large. Intraventricular saralasin lowered blood pressure in rats which had one-kidney Goldblatt hypertension with elevated plasma concentrations of renin and angiotensin II, whereas converting enzyme inhibitors failed to have any effect. Intraventricular saralasin also reduced the pressor response to intraventricular angiotensin II by 40%. A discordant note is the report by Mann et al. that showed intraventricular saralasin lowered blood pressure in rats with spontaneous hypertension (SHR) and normal plasma angiotensin II concentrations. Systemic saralasin was without effect in these animals, and nephrectomy did not modify the depressor response. However, there are differences of opinion about the effect of intraventricular saralasin in SHR rats and additional research is needed.

In their studies in dogs, Ramsay et al. found that intraventricular saralasin abolished the increase in vasopressin secretion produced by systemic administration of isoproterenol. Secretion of ACTH was not studied.

Thus, the data are as yet incomplete, and in the case of the pressor response to intraventricular angiotensin II in carnivores, there may be intracerebral angiotensin II receptors in addition to circumventricular...
organ. However, with this exception, current evidence suggests that angiotensin II in the spinal fluid can diffuse to the circumventricular organs responsible for the dipsogenic, pressor, and vasopressin responses to increased circulating angiotensin II, and it does not appear necessary to postulate separate intracerebral receptors. Of course, it is still possible that centrally generated angiotensin II acts on central receptors to produce effects such as modulation of the release and action of brain catecholamines.

**Central Nervous System Regulation of Renin Secretion**

Neural control of the secretion of renin from the kidneys is exerted primarily via the renal nerves, with an additional contribution by catecholamines from the adrenal medulla. The excitatory effects of norepinephrine and epinephrine are exerted via \( \beta \)-adrenergic receptors that are probably located on the membranes of the juxtaglomerular cells. There is in addition, an inhibition of renin secretion mediated by intrarenal \( \alpha \)-adrenergic receptors, but the physiological significance of this inhibition is uncertain. It is worth noting that changes in the pattern of discharge in vasomotor nerves to \( \alpha \)-adrenergic receptors in intrarenal or other vascular beds can bring about secondary changes in renin secretion via the arterial baroreceptor and macula densa mechanisms that also regulate renin secretion. The brain can also affect renin secretion by way of its control of vasopressin, since vasopressin inhibits renin secretion. An additional possible control is via ACTH, but we have been unable to confirm the claim of Hauger-Klevene and associates that ACTH increases renin secretion. Indeed, we found long-term ACTH treatment expanded ECF volume and decreased renin secretion.

Stimulation of the medulla, midbrain, pons, and posterior hypothalamus (Frankel, Ganong and Reid, unpublished observations) has been reported to produce an increase in renin secretion that is accompanied by an increase in blood pressure. At least in the case of the medulla and midbrain, the increase in blood pressure is due to diffuse sympathetic discharge, since the increase in renin secretion was abolished by renal denervation and by \( \beta \)-adrenergic blockade without significantly reducing the pressor response. Conversely, stimulation of the anterior hypothalamus lowered blood pressure and plasma renin activity.

It does not appear that neurally mediated increases in renin secretion are always associated with diffuse increases in sympathetic output. Stimulation of the renal nerves at certain frequencies increased renin secretion without producing renal vasoconstriction. In monkeys, stimulation of the amygdala and cingulate region produced increases in plasma renin activity without an increase in blood pressure. In addition, experiments with clonidine and tryptophan make it clear that separate brain mechanisms are involved.

Clonidine is an \( \alpha \)-adrenergic agonist that lowers blood pressure and depresses renin secretion. It penetrates brain tissue, where it appears to stimulate central \( \alpha \)-adrenergic receptors that in some way initiate a decrease in sympathetic output. Injections of phenoxybenzamine into the fourth ventricle block the depressor response. Clonidine also slows the heart, but it is uncertain whether this action is central or peripheral (see below).

Clonidine has additional central actions that are of neuroendocrinological interest. It stimulates growth hormone secretion, and this action is mediated via \( \alpha \)-adrenergic receptors because it is blocked by administration of phenoxybenzamine in the third ventricle. Other evidence indicates that increases in growth hormone secretion are produced by stimulation of \( \alpha \)-adrenergic receptors in the hypothalamus. Clonidine inhibits ACTH secretion, and this action is also blocked by administration of small doses of phenoxybenzamine but not its vehicle in the third ventricle. Other evidence indicates that stimulation of \( \alpha \)-adrenergic receptors in the hypothalamus inhibits ACTH secretion. Clonidine also inhibits vasopressin secretion, and other evidence indicates that vasopressin secretion is inhibited by stimulation of central \( \alpha \)-adrenergic receptors (Blair, Reid, Keil and Ganong, unpublished observations).

The decrease in renin secretion produced by clonidine is due to an action on the brain because it is produced by central administration of systemically ineffective doses, and it is neurally mediated because it is prevented by renal denervation, ganglionic blockade, and section of the spinal cord in the cervical region. In addition, perfusion of isolated rat kidneys with clonidine increases rather than decreases renin secretion (Fray, Reid and Ganong, unpublished observation). Where in the brain is clonidine acting to inhibit renin secretion, and how is the inhibition brought about?

The first question has been explored by Rudolph, who carefully analyzed the effects of intravertebral and intracarotid clonidine on renin secretion in pentobarbital anesthetized dogs. Rudolph demonstrated by injection of radiolabelled microspheres that the vertebral arteries in dogs supply the brain stem and hypothalamus. The carotid arteries also supply the hypothalamus and the cerebral cortex. Microspheres injected into one vertebral artery are found on both sides of the brain, whereas most of the spheres injected into one carotid artery remain on the injected side. These results generally confirm those of Wells and associates. Rudolph next placed an occluding clip on the basilar artery in the midpontine region and by injecting microspheres demonstrated that in such preparations the pons and medulla are perfused by the vertebral arteries, whereas the midbrain, hypothalamus and cortex are separately perfused by the carotid arteries. He also injected microspheres into the heart before and after clipping the basilar artery and demonstrated that there was no significant change in blood flow to the medulla, pons, midbrain and other parts of the brain. Thus, the clip did not produce any gross infarction of the brain stem.

Rudolph then compared the effects of intravenous clonidine to clonidine injections in the vertebral or
carotid arteries with and without a clip on the basilar artery. Intravenous clonidine in the dose employed (2 
\mu g/kg) had no effect on the secretion of ACTH or growth hormone, whereas injection of the same dose into both carotid or both vertebral arteries without a clip produced a decline in plasma ACTH and an increase in plasma growth hormone (fig. 2). When the clip was in place, responses were obtained only upon intracarotid injection. Thus, clonidine only affects growth hormone and ACTH secretion when injected into the blood perfusing the hypothalamus and cerebral cortex. On the basis of other data, it seems likely that its actual site of action is the hypothalamus. The effects of clonidine on blood pressure and heart rate are summarized in figure 3. Intravenous and intracarotid injections produced a small decline in blood pressure, but a large depressor response was only produced when the drug was injected into the blood perfusing the medulla and pons. The decrease in heart rate upon injection into the carotid and vertebral arteries was no greater than the decrease upon intravenous injection. Others have argued that the effect of clonidine on heart rate is due to an action on the hindbrain, but our data are more consistent with an effect outside the brain, presumably at the level of the heart itself. The data on renin secretion are surprising (fig. 4). Intravenous clonidine failed to affect plasma renin ac-
tivity, whereas injection into the vertebral or carotid arteries caused a significant decline; in confirmation of other data, these results indicate that the renin-lowering effect of clonidine is due to an action on the brain. However, there was no decline in plasma renin activity when clonidine was injected into either the carotid or vertebral arteries if the basilar artery was clipped. Even though the microsphere injection data showed no gross infarction, this result might be explained if the action of clonidine were on a small area in the pons or midbrain on the border between the areas perfused by the vertebral and carotid arteries in the clipped dogs. Because of its border position, this area might be poorly perfused by either blood supply. Since the effect of clonidine on renin secretion is mediated via the renal nerves, it may be relevant that large bilateral lesions of the ventral medulla in dogs have been reported to prevent clonidine from decreasing the discharge rate in splanchnic and renal nerves while leaving the depressor response intact. Alternatively, it may be necessary for clonidine to act on both the forebrain and the hindbrain to produce its renin-lowering effect. At any rate, the data demonstrate that clonidine exerts its effect on blood pressure at a site separate from the site or sites at which it acts to affect renin secretion. The renin-lowering site is also separate from the forebrain sites at which clonidine acts to affect the secretion of ACTH and growth hormone.

How does clonidine produce its renin-lowering effect? One possibility is stimulation of cerebral H2 receptors, since the H2 receptor blocking drug metiamide has been reported to reduce the depressor response to clonidine. However, H1 and H2 agonists failed to produce any change in plasma renin activity when administered directly into the third ventricle, even though clonidine lowered plasma renin activity when injected by this route in a dose of only 1 μg/kg.

Another possibility is an excitatory action on α-adrenergic receptors in the brain. Presumably most of these α receptors are associated with norepinephrine-secreting neurons, although there are also epinephrine-secreting neurons in the brain, and these latter neurons are known to be involved in blood pressure regulation. However, it has been difficult to abolish the renin-lowering effect of clonidine with α-adrenergic blocking drugs. Administration of phenoxybenzamine into the third ventricle had no effect on the renin-lowering action of intravenous clonidine, and administration of phenoxybenzamine into the fourth ventricle reduced but did not abolish the decrease in renin secretion. Injection of phentolamine and piperoxan into the third ventricle and phentolamine into the fourth ventricle had no effect on the response (Reid, Ganong and Chalett, unpublished observations).

In considering possible actions of drugs on α-adrenergic receptors, effects on pre- as well as postsynaptic receptors must be considered. In both the peripheral and the central nervous system, there are postsynaptic α-adrenergic receptors (α1 receptors) on which norepinephrine acts to produce direct effects, and there are α-adrenergic receptors on the terminals of presynaptic noradrenergic neurons (α2 receptors) that when stimulated decrease the release of endogenous norepinephrine. Clonidine is known to have a greater affinity for pre- than postsynaptic α-adrenergic receptors, whereas norepinephrine and epinephrine have an equal affinity for α1 and α2 receptors and phenylephrine and methoxamine have a greater affinity for α1 receptors. Evidence that the effects of clonidine on ACTH and growth hormone are due to an effect on postsynaptic rather than presynaptic receptors is provided by the observation that intraventricular norepinephrine stimulates growth hormone secretion. In addition, ACTH secretion is inhibited and growth hormone stimulated by L-dopa and by intraventricular tyramine, both of which release catecholamines from neurons in the brain (Ganong, Shackelford and Boryczka, unpublished observations). The depressor effect of clonidine is probably due to an effect on postsynaptic receptors, since it is also produced by intraventricular epinephrine and norepinephrine and by drugs that provoke the central release of endogenous catecholamines.

The evidence regarding the renin-inhibiting action of clonidine is not as clear-cut. On the one hand, Hausler has reported that even when catecholamines are depleted and presynaptic inhibition is therefore reduced or abolished, clonidine lowers the discharge rate in sympathetic nerves. When central
release of catecholamines was provoked by administration of L-dopa in the presence of the peripheral decarboxylase inhibitor carbidopa, renin secretion was decreased.\textsuperscript{108} No decrease was produced by L-dopa when central and peripheral decarboxylase were both inhibited by administration of benserazide.\textsuperscript{108} This decrease was neurally mediated because it was abolished by renal denervation\textsuperscript{108} and occurred in spite of a marked reduction in plasma vasopressin concentration by the combination of L-dopa and carbidopa (Blair, Reid, Keil and Ganong, unpublished observations).

On the other hand, we found that injection of norepinephrine directly into the third ventricle in many different doses increased rather than decreased renin secretion.\textsuperscript{104} This is in contrast to clonidine and oxymetazoline, which decreased renin secretion when administered in comparable doses by the same route (Nolan and Reid, unpublished observations).\textsuperscript{92} Increases rather than decreases were also produced by epinephrine, the norepinephrine precursor dopamine, and two drugs with predominantly postsynaptic \(\alpha\)-adrenergic activity,\textsuperscript{104} phentolamine and methoxamine.\textsuperscript{108} Thus, at least when administered directly into the third ventricle, drugs with the greatest affinity for presynaptic \(\alpha\)-adrenergic receptors decreased renin secretion, whereas drugs with the greatest affinity for postsynaptic receptors increased renin secretion. Additional research is clearly needed to settle whether the site of action of clonidine is pre- or postsynaptic as far as renin secretion is concerned. Another possibility is that clonidine acts on a different type of postsynaptic receptor than phentolamine.

Five-hydroxytryptophan (5-HTP), the immediate precursor of serotonin, increases renin secretion when injected in pentobarbital-anesthetized dogs.\textsuperscript{109} This compound displaces catecholamines and consequently can release them.\textsuperscript{108} However, our evidence indicates that its renin-stimulating effect is due to central release of serotonin rather than catecholamines.\textsuperscript{109} We found that the increase in plasma renin activity produced by 5-HTP was potentiated by carbidopa but abolished by benserazide, indicating that it was due to central release of serotonin rather than catecholamines.\textsuperscript{109} We found that the increase in plasma renin activity produced by 5-HTP was potentiated by carbidopa but abolished by benserazide, indicating that it was due to the central action of a decarboxylated derivative of 5-HTP (fig. 5). In addition, it was also abolished by metergoline, a drug that specifically blocks serotonin receptors.

If central release of serotonin increases renin secretion, one would expect that an increase would also be produced by tryptophan. This amino acid increases brain serotonin content without exerting any significant effect on catecholamine-secreting neurons.\textsuperscript{111} We found that tryptophan exerted a marked stimulatory effect on renin secretion (fig. 6). The effect was abolished on renal denervation. It was potentiated by carbidopa and reduced by benserazide, so it was presumably central in origin. Other studies indicate that serotonergic neurons play a role in the regulation of blood pressure and heart rate.\textsuperscript{112} However, the increase in renin secretion in our dogs occurred without

\begin{figure}
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\includegraphics[width=\textwidth]{figure5.png}
\caption{Effect of 5-hydroxytryptophan (5-HTP) on plasma renin activity, and modification of the 5-HTP response in the presence of peripheral and central inhibition of decarboxylase activity, and in the presence of blockade of serotonin receptors with metergoline.}
\end{figure}
Effect of tryptophan on plasma renin activity, and modification of the tryptophan response in the presence of peripheral and central inhibition of decarboxylase activity.

Summary

Components in the regulation of blood pressure that are under neuroendocrine control include the secretion of vasopressin, ACTH, growth hormone, and renin. Circulating angiotensin II affects brain function and there may be a separate renin-angiotensin system in the brain.

The brain renin-angiotensin system remains a controversial subject, and additional careful research is needed before its existence as a functional unit can be regarded as established. However, renin substrate, converting enzyme, angiotensin II receptors and angiotensinase are found in brain and/or cerebrospinal fluid. In addition, it seems likely that there are small amounts of angiotensins I, II and III in brain and cerebrospinal fluid, and a renin-like enzyme in brain tissue that is separate from cathepsin D has been tentatively identified.

Angiotensin II (and presumably angiotensin III) acts on the brain to increase water intake, raise blood pressure, and increase secretion of vasopressin and ACTH. Some and possibly all of these actions are mediated via the circumventricular organs, special highly permeable regions around the cerebral ventricles that function as neurohemal organs and chemoreceptor zones. Increases in blood pressure, water intake and the secretion of vasopressin and ACTH are also produced by intraventricular injections of angiotensin II and renin. There is considerable evidence that the responses are due to diffusion of angiotensin II from the ventricles to the circumventricular organs, rather than an action on separate intracerebral angiotensin receptors.

Catecholamines released from renal nerve endings and the adrenal medulla act on intrarenal \( \beta \)-adrenergic receptors to increase renin secretion. Stimulation of brain areas that cause a diffuse increase in sympathetic output increase renin secretion. However, it is possible to separate the brain areas concerned with the regulation of renin secretion from the areas that are more directly concerned with the regulation of blood pressure.

Clonidine inhibits renin secretion by an action on the brain. In dogs, this \( \alpha \)-agonist acts on the hypothalamus to increase the secretion of growth hormone and decrease the secretion of ACTH. It lowers blood pressure by an action on the pons and/or medulla. It acts at a different, as yet undefined, site to inhibit renin secretion, and it may have to act on both the forebrain and hindbrain to produce this effect.

The actions of clonidine on growth hormone secretion, ACTH secretion, and blood pressure are probably due to an action on intracerebral \( \alpha \)-adrenergic receptors because they are also produced by drugs that release catecholamines in the brain and by central injection of norepinephrine or epinephrine. Renin secretion is also inhibited by L-dopa when peripheral decarboxylation is prevented by carbidopa. However, clonidine and oxymetazoline decrease renin secretion when injected into the third ventricle, whereas norepinephrine, epinephrine, dopamine, phenylephrine and methoxamine increase renin secretion. This finding suggests that, at least in the region around the third ventricle, the action of clonidine on renin secretion may be presynaptic rather than postsynaptic.

Five-hydroxytryptophan increases renin secretion. The stimulating effect is potentiated by inhibition of peripheral decarboxylase, abolished by inhibition of peripheral and central decarboxylase, and blocked by the serotonin-receptor blocking drug, metergoline. Tryptophan also increases renin secretion and its effect is reduced by inhibition of central decarboxylase.
and abolished by renal denervation. This suggests that serotonergic neurons in the brain are part of a neural pathway with a selective excitatory effect on renin secretion. Clonidine may exert its inhibitory effect on renin secretion via this pathway, since there is some evidence that it acts by way of α-adrenergic receptors to inhibit serotonergic neurons.

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