Is There a Brain Renin-Angiotensin System?

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SINCE THE original demonstration by Bickerton and Buckley1 that angiotensin II acts directly on the central nervous system to increase arterial pressure, it has become clear that the peptide has several central actions. These include stimulation of drinking as well as increased secretion of antidiuretic hormone (ADH) and of adrenocorticotropic hormone (ACTH) (for reviews see Ferrario et al.2 and Severs et al.3-4). Initially, it seemed unlikely that these effects represented physiological actions of circulating angiotensin II since the peptide is polar and apparently does not cross the blood-brain barrier. However, it was subsequently demonstrated that the receptors for at least some of the central actions of angiotensin are in areas that are outside the blood-brain barrier and, therefore, accessible to blood-borne angiotensin. These include the area postrema (pressor effect),7 the subfornical organ (dipsogenic action),6 the median eminence (ACTH secretion),7 and the pituitary (ACTH and ADH secretion).8-9 On the other hand, there appear to be other angiotensin receptors in areas that are inside the blood-brain barrier; these receptors may be activated by administration of angiotensin directly into the cerebral ventricles or by ionotophoretic application, but not by injecting angiotensin into the blood supply of the brain. Examples of such areas include the subnucleus medialis (pressor effect)10,11 and the supraoptic nucleus (ADH secretion).12

At present, the significance of the angiotensin receptors that are inside the blood-brain barrier is not clear. However, a possibility that has aroused considerable interest during recent years is that angiotensin is actually synthesized within the central nervous system and is, therefore, available to interact with brain angiotensin receptors. This proposal originated in 1971 with the observations by Ganten et al.13 and Fischer-Ferraro et al.14 that the components required for the generation of angiotensin II are present within the brain. These observations have been confirmed by other investigators15-19 and it is now frequently assumed that there is a functional brain renin-angiotensin system. Indeed, it has been proposed that such a system participates in the control of water intake, blood pressure, ADH secretion, and a variety of other physiological functions.16,19-21

The purpose of this review is to summarize the current knowledge concerning the properties of the components of the renin-angiotensin system in the brain and to critically evaluate the evidence that these interact to form a functional system which is involved in physiological regulation.

Components Required for the Generation of Angiotensin II

The pathway of angiotensin formation and metabolism in the peripheral circulation is summarized in Figure 1. There is evidence that the three components required for the formation of angiotensin II, viz., renin substrate, renin, and converting enzyme, are present in the central nervous system.

RENIN

Renin activity has been detected in extracts of dog,13,16,22 rat,17 and human18 brain. The renin activity does not appear to be of renal origin since renal renin does not cross the blood-brain barrier and, furthermore, brain renin activity does not decrease following bilateral nephrectomy.13 Brain renin activity (per g of tissue) is approximately 1/100th that in the renal cortex but is higher than plasma renin activity.13 It is present in all brain regions that have been studied. The activity varies little from region to region although the pinacl, the pituitary, and the cerebellum appear to have higher activities.17,18,22

The enzyme responsible for the renin activity in brain extracts clearly differs from renal renin. Although the pH optimum (4.5-5.0) is only slightly lower than that of renal renin, the activity of the brain enzyme decreases markedly above pH 5.0 so that at pH 7.4, there is no measurable activity;13,18,22 renal renin is, of course, active at pH 7.4. Both the brain and renal enzymes hydrolyze the synthetic tetradecapeptide renin substrate, but the affinity of the brain enzyme for this substrate appears to be greater than that of renal renin.13,18 The enzyme with renin activity extracted from rat and dog brain is active against hog or dog plasma renin substrate (at pH 5.5),13,17,22 whereas the enzyme extracted from human brain has negligible activity against human renin substrate.18

In a recent investigation in this laboratory,22 the enzyme with renin activity in dog brain was partially purified and its enzymology examined. Using ammonium sulfate frac-
tionation, Sephadex G-100 chromatography, and concentration by dialysis at pH 3.5, a 100-fold purification of the enzyme was accomplished. Of considerable interest was the concomitant purification of the lysosomal protease cathepsin D, the activity of which was also increased 100-fold by these procedures. Sephadex gel chromatography and isoelectric focusing of the purified material failed to separate the renin activity from the cathepsin activity. Both enzyme activities were undetectable above pH 6.0 and were irreversibly inhibited by pepstatin. These data indicate that cathepsin D may be responsible for the renin activity observed in brain extracts. It is noteworthy that pepsin, an acid protease with a substrate specificity similar to that of cathepsin D, can hydrolyze renin substrate at the same bond as renin to form angiotensin I. The question of whether the brain enzyme does actually produce angiotensin in vivo is discussed later.

**RENIN SUBSTRATE**

Ganten et al. reported that renin substrate is present in dog brain in a concentration of approximately 2 pmol/g. This concentration is very low compared to the concentration of renin substrate in dog plasma (670 ± 45 pmol/ml). However, injection of renin into the cerebral ventricles produces a variety of effects which appear to be mediated by angiotensin II (see below). This observation, which indicates that there is a substantial pool of renin substrate within the central nervous system that is readily accessible to centrally administered renin, led to the discovery of renin substrate in cerebrospinal fluid. In the dog, the cerebrospinal fluid renin substrate concentration is 158 ± 26 pmol/ml, a value approximately one-fifth the corresponding plasma renin substrate concentration. However, because the total protein concentration in cerebrospinal fluid is much less than that in plasma, the ratio of renin substrate to total protein is 15 times higher in cerebrospinal fluid than in plasma. Printz and Lewicki recently reported that renin substrate is present in rabbit brain in a concentration averaging 201 pmol/g of tissue. This was not due to contamination of the brain homogenates with blood.

At present, the origin of the renin substrate in the central nervous system is not known. One possibility is that it is derived from the plasma renin substrate pool in the normal process of cerebrospinal fluid formation. Consistent with this proposal is the finding that there are no apparent differences between the molecular weights or electrophoretic characteristics of brain and plasma renin substrate. On the other hand, the concentration of renin substrate in cerebrospinal fluid appears to be regulated independently of that in plasma, since elevation of plasma renin substrate concentration by bilateral nephrectomy or treatment with dexamethasone fails to alter the concentration of renin substrate in cerebrospinal fluid. Additional investigation is required to determine the source of the renin substrate in the central nervous system.

**CONVERTING ENZYME**

Angiotensin converting enzyme activity has been measured in the brain; this is not surprising since the enzyme activity is ubiquitous, having been found in every tissue so far examined. The converting enzyme activity of whole brain is low compared to the lung, which is the major site of conversion of plasma angiotensin I; however, it is distributed unevenly throughout the brain, with higher concentrations in the corpus striatum, the cerebellum, and the pituitary of the rat and in the caudate nucleus of the human. There is no detectable converting enzyme activity in cerebrospinal fluid. At present, the significance of this distribution is not clear. The converting enzyme of brain resembles that of peripheral tissues in that it requires chloride ion and is inhibited by ethylenediaminetetraacetic acid (EDTA), o-phenanthroline, and the nonapeptide SQ 20881.

Brain converting enzyme is active in vivo as well as in vitro. For example, angiotensin I has marked dipsogetic activity when injected centrally and this is blocked by central administration of SQ 20881. In addition, angiotensin I stimulates vasopressin release by incubated rat neurohypophyses and, again, this effect is blocked by SQ 20881.

**Effects of Central Administration of Renin and Renin Substrate**

The findings summarized above indicate that all of the components required for the generation of angiotensin II are present in the brain; however, it is not clear if the components interact in vivo to form a functional renin-angiotensin system. One approach to this problem is to determine whether renin elicits a physiological response when administered centrally. Since all of the known actions of renin are mediated via the formation of angiotensin, the finding that renin elicits responses when administered centrally would indicate that there is a reaction...
involving the exogenous renin, brain renin substrate, and converting enzyme which results in the formation of angiotensin in quantities sufficient to elicit a biological response. Similarly, the finding that central administration of renin substrate produces physiological effects would constitute evidence for the existence of renin activity in the brain under physiological conditions.

It is now clear that renin has a variety of actions when administered centrally. Epstein et al. first reported that renin is a potent dipsojen when injected intracranially in rats. Furthermore, the effect could be blocked by pepstatin, SQ 20881, or saralasin, a competitive antagonist of angiotensin II, suggesting that it was mediated via the pathway of angiotensin formation shown in Figure 1. These findings have since been extended to the cat and dog. Renin also produces a prolonged increase in arterial pressure when injected into the 3rd ventricle of the dog. The pressor effect is blocked by saralasin, indicating that it is mediated via the formation of angiotensin II. Intraventricular renin increases the secretion of ADH in the dog and in the rat and this effect is also mediated by angiotensin II. Finally, intraventricular renin increases the secretion of ACTH and decreases peripheral plasma renin activity; the latter effect probably results from the accompanying increase in plasma vasopressin concentration and/or blood pressure since both of these factors are known to inhibit renin secretion.

Measurement of cerebrospinal fluid angiotensin II concentration following central administration of renin has provided additional evidence that the effects described above are mediated via the formation of angiotensin II. Five minutes after injecting renin into the 3rd ventricle of dogs, angiotensin II could be readily detected in cisterna magna cerebrospinal fluid; concentrations ranging from 1.5-4.3 pmol/ml were observed 60 minutes after the injection. Taken together, the data indicate that there is an in vivo reaction involving injected renin, brain renin substrate, and converting enzyme which results in the formation of biologically active concentrations of angiotensin II.

These experiments do not, however, demonstrate endogenous brain renin activity in vivo. To address this question, the effects of central administration of renin substrate have been investigated. Such an approach requires that the concentration of renin substrate in the brain be rate limiting; this may be a reasonable assumption since, as described above, the concentration of renin substrate in the central nervous system is lower than in plasma where the concentration of renin substrate is in fact rate limiting. The first studies of this type used the synthetic tetradecapeptide substrate. Epstein et al. observed that intracranial injection of tetradecapeptide stimulated drinking in rats. The response was reduced by pepstatin and markedly attenuated by SQ 20881 or saralasin. It was, therefore, concluded that the drinking response to the tetradecapeptide was mediated via the pathway of angiotensin II formation shown in Figure 1.

The results of such studies should, however, be interpreted with caution because it is apparent that there are marked differences between the properties of the tetradecapeptide substrate and the native protein substrate. For example, Skeggs et al. have described an enzyme that hydrolyzes the tetradecapeptide at pH 7.5 to form angiotensin I, but which is inactive against plasma renin substrate at that pH. This enzyme, which they termed pseudorenin, was found in plasma as well as in every one of 13 tissues examined. The brain was not examined but it is worth noting that the enzyme with renin activity in human brain also hydrolyzes the tetradecapeptide but not human plasma renin substrate. Converting enzyme is also capable of forming angiotensin I and II from the tetradecapeptide substrate but not directly from natural substrate. For these reasons, Dorer et al. have warned against the use of the tetradecapeptide for the detection or assay of renin activity. Finally, the tetradecapeptide, but not natural substrate, possesses intrinsic biological activity.

Measurement of Angiotensin in the Brain

A further essential test of the hypothesis that angiotensin is generated locally within the central nervous system is to determine whether or not angiotensin is present in the brain. The detection and assay of angiotensin I and II in cerebrospinal fluid and brain extracts have been attempted by a number of investigators but extremely variable results have been obtained. Bioassay, radioimmunoassay, and immunohistochemical techniques have been employed.

CEREBROSPINAL FLUID

Finkielman et al. reported finding a high concentration of a pressor peptide pharmacologically similar to angiotensin I in the cerebrospinal fluid of hypertensive patients; this observation was not, however, confirmed by radioimmunoassay. Ganten et al. reported that angiotensin II, as measured by radioimmunoassay, is present in rat cerebrospinal fluid in a concentration of 169 fmol/ml. A lower value, 90 fmol/ml, was reported by Simpson et al. who used the Schwarz/Mann angiotensin II radioimmunoassay kit. Simpson et al. also reported that cerebrospinal fluid angiotensin II concentration increased in rats following nephrectomy, but Hutchinson et al. were unable to detect any difference between “brain angiotensin II secretion rate” in intact or nephrectomized rats. Other values reported for cerebrospinal fluid angiotensin II concentration include 37 fmol/ml in the human and 30-120 fmol/ml in the sheep. It should be noted that in all of these studies, the identity of the material being measured was not established beyond the fact that it reacted with angiotensin II antibodies. In this laboratory, angiotensin II has not been detected in the cerebrospinal fluid of the dog. Thus, although some preliminary data indicate that angiotensin II may be present in low concentration in the cerebrospinal fluid of some species, additional measurements and further characterization are clearly in order.

BRAIN

In their original reports, Ganten et al. and Fischer-Ferraro et al. reported that a pressor peptide resembling angiotensin I was present in high concentration in extracts of dog brain. The pressor activity observed by Ganten et al. could be suppressed by angiotensin I antibodies but not by angiotensin II antibodies. Recently, Horvath et al. have confirmed that a pressor peptide is present in...
extracts of dog brain; pressor activity was also found in extracts of rat and rabbit brain. However, their findings raised serious doubts that this material was angiotensin I or II. For example, the pressor activity of the material was not neutralized by antibodies to either angiotensin I or II or by saralasin. Moreover, radioimmunoassay of the same samples failed to detect significant amounts of angiotensin I or II.

Recently, there have been reports that high concentrations of angiotensin I, as measured by radioimmunoassay, are present in extracts of rat brain. Slavin reported a value of 60 pmol/g and Changaris et al. reported values ranging from 6–63 pmol/g. In this laboratory, high concentrations of apparent angiotensin I and II immunoreactivity were observed in extracts of dog brain. However, the material did not appear to be angiotensin since it was nondialyzable, did not adsorb to Fuller’s earth or Dowex, and was destroyed by acidification and boiling. Gel filtration studies indicated that the molecular weight of the material was well in excess of that of synthetic angiotensin I.

Recent studies indicate that the apparent angiotensin immunoreactivity in extracts of dog brain may be an artifact caused by angiotensinase activity. It appears that angiotensinases in brain extracts destroy the I-labeled angiotensin used in the angiotensin radioimmunoassay and thus reduce the amount of labeled angiotensin available for binding to the antibody; the reduced binding could be erroneously interpreted as displacement of I-labeled angiotensin by angiotensin. The evidence is as follows. (1) A number of enzymes capable of degrading angiotensin I and II are known to be present in the brain. (2) In the radioimmunoassay of angiotensin I and II, preincubation of I-labeled angiotensin I or II with brain extract abolishes subsequent binding of the labeled angiotensin to angiotensin antisera. (3) This effect can be almost completely abolished by a mixture of angiotensinase inhibitors. (4) The apparent angiotensin immunoreactivity in brain extracts is markedly reduced by the addition of angiotensinase inhibitors to the radioimmunoassay system.

This artifact probably accounts for the high angiotensin I values reported by Slavin and by Changaris et al. who both used mild extraction procedures similar to the one employed in this laboratory. It is significant that other investigators, who have used more elaborate extraction procedures which would have eliminated angiotensinase, have failed to detect significant amounts of angiotensin immunoreactivity in rat, rabbit, or dog brain. Thus, radioimmunoassay measurements have failed to provide convincing evidence for the presence of angiotensin in the brain.

An alternative technique for the detection of angiotensin, which is also subject to problems of specificity, is immunohistochemistry. Using an immunofluorescence technique, Fuxe et al. observed angiotensin II positive fluorescence in nerve terminals in the brain and spinal cord of the rat. Nahmod et al. who used a similar technique, also observed angiotensin II, but not angiotensin I, positive fluorescence in rat brain. In contrast, Changaris et al. who used the peroxidase-antiperoxidase technique, found angiotensin I positive staining in brain areas which included the subfornical organ and the pars intermedia.

In summary, the results of bioassay and radioimmunoassay measurements have not provided convincing evidence that either angiotensin I or II is produced within the brain. The positive evidence provided by immunohistochemical studies is of considerable potential importance, but additional studies using different antibodies are required to confirm these findings.

**Effect of Central Administration of Agents which Block the Renin-Angiotensin System**

Agents which block the formation or actions of angiotensin have been used successfully to evaluate the role of the renal renin-angiotensin system in the regulation of aldosterone secretion and arterial pressure. Injection of such agents into the central nervous system might also be expected to reveal any actions of angiotensin II formed within the brain. Angiotensin antagonists administered in this fashion may also block some of the central effects of blood-borne angiotensin II, and this must be taken into account in the interpretation of such experiments.

The effects of intraventricular administration of saralasin or SQ 20881 on water intake have been studied in rats and in dogs. Summy-Long and Severs reported that intraventricular injection of saralasin or SQ 20881 did not reduce the drinking produced in rats by relative cellular dehydration (hypertonic NaCl injection) or by hypovolemia (hyperoncotic polyethylene glycol administration). Similarly, Lehr et al. observed that intraventricular administration of SQ 20881 in rats did not modify the drinking response to either isoproterenol administration or cava ligation. Others have reported that the drinking response to injection of isoproterenol is blocked by intraventricular saralasin; this presumably results from blockade of circulating angiotensin II since the effect is also abolished by nephrectomy. In this laboratory, intraventricular administration of saralasin, in doses which block the dipsogenic action of intraventricular renin, failed to modify the drinking response to 24-hour water deprivation. On the other hand, Malvin et al. reported that the drinking response to water deprivation in rats was reduced or delayed when saralasin was infused into a lateral ventricle. This effect may have been due to blockade of circulating angiotensin II since it is known that plasma renin levels increase during water deprivation.

The effect on blood pressure of intraventricular saralasin has been studied in a number of situations. There is general agreement that it has no effect on the blood pressure of normal animals. Saralasin also appears to be without effect when administered centrally in sodium-deficient dogs, but lowers blood pressure when infused intravenously. In spontaneously hypertensive rats, it has been reported that central administration of saralasin produces a fall in blood pressure. Interestingly, a similar effect was produced by perfusing the ventricular system with artificial cerebrospinal fluid, an observation which raises questions as to the specificity of the hypotensive effect observed with saralasin. It has also been reported that the concentration of angiotensin II in the cerebrospi-
nal fluid of spontaneously hypertensive rats is approximately 50% higher than in normotensive rats, and it was suggested that this may be a causative factor in the hypertension.3-20 This mechanism seems unlikely, however, since intraventricular infusion of angiotensin II in normotensive rats, at rates calculated to be 1 thousand to 1 million times the values claimed to be the "brain angiotensin II secretion rate," failed to increase blood pressure to the levels observed in the spontaneously hypertensive animals.48

The effects of central administration of other angiotensin antagonists on blood pressure in the spontaneously hypertensive rat have also been investigated, but conflicting results have been obtained. For example, Sweet et al.72 reported that [Sar1, Ile8]angiotensin II reduced blood pressure in the mature spontaneously hypertensive rat, but was ineffective in young animals. In contrast, Vogel et al.73 observed that [succinamoyl'-Val^phe nylglycine']angiotensin II decreased blood pressure in 10-week-old hypertensive rats, whereas it increased blood pressure in rats 14 weeks of age. Furthermore, Elghozi et al.74 reported that neither [Sar1, Ile8]angiotensin II nor [Sar1, Thr8]angiotensin II decreased blood pressure in spontaneously hypertensive rats.

Recently it was reported that an angiotensin antagonist lowered blood pressure when administered centrally to rats with renal hypertension; the same doses of the antagonist were without effect when injected intravenously.75 Intraventricular injection of [Sar1, Ile8]angiotensin II has also been reported to lower blood pressure in rats with malignant hypertension.76 However, central administration of pepstatin or SQ 20881 failed to lower blood pressure, suggesting that the effectiveness of the antagonist was due to blockade of peripherally, rather than centrally, generated angiotensin. It appears that this is the case since bilateral nephrectomy also lowered blood pressure in these animals and abolished the blood pressure lowering action of the antagonist.78

In summary, the data concerning the effects of central administration of agents which block the renin-angiotensin system are either negative, inconclusive, or conflicting and do not constitute convincing evidence for the existence of a brain renin-angiotensin system.

Concluding Remarks

The aim of this brief review has been to evaluate the proposal that the brain contains an intrinsic renin-angiotensin system which is active in vivo and involved in physiological regulation. Some of the currently available evidence is consistent with this proposal but a number of problems exist and at the present it would seem premature to conclude that there is a functional brain renin-angiotensin system.

Perhaps the best evidence for the proposal is that substances capable of forming angiotensin II are present in the central nervous system, and that angiotensin II is formed in biologically active concentrations when exogenous renin is injected into the cerebral ventricles. However, it has not been satisfactorily demonstrated that the brain enzyme which has renin activity at low pH in vitro (probably cathepsin D) also functions as an angiotensin-forming enzyme in vivo. Experiments utilizing the synthetic tetradecapeptide substrate to detect renin activity are not conclusive because there are marked differences between the properties of this substrate and the natural substrate. Several investigators have attempted to demonstrate the presence of angiotensin in the brain but, in general, the results have not been convincing. Specific problems that have been encountered are nonspecificity of bioassay methods and destruction of labeled hormone by angiotensinase activity in the course of radioimmunoassay procedures. Positive results have recently been obtained using immunohistochemistry but additional work is required. Finally, approaches utilizing central administration of agents which block the renin-angiotensin system have not provided convincing evidence for the existence of a brain renin-angiotensin system.

Nevertheless, the possibility still remains that there is an intrinsic brain renin-angiotensin system. Of considerable interest is the observation that renin substrate is present in cerebrospinal fluid and in brain tissue. Further investigation is required to determine the origin, nature, and distribution of this material. Such information will help to answer the question, "Is there a brain renin-angiotensin system?"

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