Editorial Comment

The Brain Kallikrein-Kinin System
A Possible Role in Blood Pressure Regulation

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During the last decade, the actions of central nervous system peptides on blood pressure and volume homeostasis have been the subject of intense investigation. There is evidence that central mechanisms of cardiovascular control could be modulated by brain peptides. Kinins are biologically active peptides released from kininogen by either glandular or plasma kallikrein. Kinins in the central nervous system, released by glandular (tissue) kallikrein, may act at or near their site of origin. Components of the kallikrein-kinin system are found in a variety of tissues, among them the central nervous system. An enzyme that has the physical and chemical characteristics of glandular kallikrein has been identified in the rat brain. Kininogenase activity and immunoreactive glandular kallikrein have been shown to be similarly distributed within the brain. The presence of a messenger RNA (mRNA) coding for tissue kallikrein has been documented in both whole brain and discrete regions therein. Thus, the presence of mRNA functionally able to direct kallikrein synthesis, immunoreactive kallikrein, and kinin-forming activity in the brain indicates that the kallikrein-kinin system is present there as well.

The effects of a neuropeptide on the heart and blood pressure after central administration suggest a possible function of the endogenous system. Injections of bradykinin into the intracerebral ventricles as well as discrete areas that include the hypothalamic nuclei increase blood pressure and heart rate. By themselves, however, these data do not prove that the endogenous brain kallikrein-kinin system plays a role in modulating cardiovascular homeostasis.

The recent availability of a competitive bradykinin receptor antagonist allows us to study the effects of blocking brain kinins on cardiovascular homeostasis. The work of Madeddu et al provides evidence that under some experimental conditions, endogenous brain kinins are responsible for changes in blood pressure. It has been known for some time that components of the kallikrein-kinin system are responsible for blocking the response to CEI.

This cannot be due to blockade of angiotensin II formation, which would result in decreased, not increased, blood pressure; however, it could be due to increased brain concentration of kinins. The peptide/dipeptide hydrolase known as angiotensin converting enzyme (ACE) is of paramount importance as a kinin-degrading enzyme. Therefore, inhibition of ACE may increase brain kinin concentrations enough to modify cardiovascular parameters.

If this hypothesis is correct, a specific kinin receptor antagonist should block the cardiovascular response. Madeddu et al showed that the hypertensive response to intracerebroventricular injection of captopril, a CEI in SHR, is completely blocked by simultaneous administration of a kinin receptor antagonist. Unless the antagonist interacts with other neuropeptide receptors, these data indicate that in SHR brain kinins can be important for cardiovascular regulation. Madeddu et al also include data indicating that the antagonist does not block the blood pressure response to a series of compounds; thus, it is unlikely that nonspecific actions are responsible for blocking the response to CEI. The compounds tested for interaction with the kinin antagonist should have included vasopressin, as some kinin analogues have been shown to block vasopressin-induced contraction of uterine smooth muscle.

Intracerebral administration of the kinin antagonist in SHR or normal Wistar-Kyoto (WKY) rats does not modify basal blood pressure, suggesting that kinins in the cerebrospinal fluid or ventricular walls do not normally contribute to its regulation. However, we have found that the accelerated heart rate of 14-week-old awake SHR is decreased by acute intracerebroventricular administration of kinin antagonist. SHR exhibit an exaggerated hypertensive response to intracerebroventricular kinins; combined with data implying that brain kinins mediate the hypertensive response to intracerebroventricular captopril and the accelerated heart rate in SHR, this indicates that the brain kallikrein-kinin system is hyperactive and functionally important in this experimental hypertensive model. It remains to be determined where in the brain kinins exert their tonic action in SHR and which mechanisms mediate the final cardiovascular responses. It would also be interesting to determine the cardiovascular effects of long-term central administration of the kinin antag-

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onist, as its lack of effect on normal blood pressure regulation in acute experiments may be due to low concentrations in deeper areas of the brain. During acute administration, only circumventricular areas are exposed to effective concentrations of the antagonist.

A puzzling aspect of the data of Madeddu et al. is the extent of the hypertensive response to captopril in SHR (~44 mm Hg). What changes in brain kinin concentration would account for this response? Unfortunately, they did not report the concentration of bradykinin required to induce a 45 mm Hg increase in SHR when given intracerebroventricularly. It would be of interest to determine whether brain kinins increase after CEI administration, and, if so, how much. Also, they used a single high dose of captopril, in excess of that generally accepted for 100% kininase inhibition. It would be informative to obtain a captopril dose–response curve in SHR as was done in WKY rats. After inhibition of kininase II reaches 100%, blood pressure response to captopril should plateau. Lack of a plateau may suggest that the action of CEI is not entirely explained by increased brain kinins.

Although these data indicate a possible functional role of brain kinins in SHR, they could also play a role in other models. Maneuvers that increase the activity of the brain kallikrein-kinin system are also accompanied by hypertension and tachycardia. Evidence has been provided from Privitera’s group using dogs that when endogenous brain kinin activity is raised, blood pressure and heart rate increase as a consequence. These data suggest that the difference between SHR and normal rats may merely be one of degree. Brain kinin concentrations or sensitivity to kinins may be at a subthreshold level in normal rats, but if they are activated, cardiovascular homeostasis could be influenced. In young SHR, the activity of the brain kallikrein-kinin system or sensitivity to brain kinins appears to be high enough to play a role in cardiovascular homeostasis. It would be of interest to learn whether this system plays a role in the pathogenesis or maintenance of some forms of hypertension.

Most, if not all, of the studies on brain kallikrein and kinins have been done in experimental animals. It is not known what effects (if any) administration of CEI to patients has on brain kinins. It would be of interest to determine whether the response to CEI is influenced by changes in brain kinins, particularly in patients who fail to respond to these drugs.

Advances in our understanding of the role of the central nervous kallikrein-kinin system in hypertensive states, either in humans or animal models, have been slow in coming. The availability of a kinin receptor antagonist of reasonable specificity will help clarify their significance.

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