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Ferrario C M, Gildenberg P L & McCubbin J W. Cardiovascular effects of angiotensin mediated by the central nervous system. *Circ. Res.* 30:257-62, 1972.
[Research Division, Cleveland Clinic Foundation and Cleveland Clinic Educational Foundation, OH]

The data described in this article showed that angiotensin affects the central nervous system, resulting in increased arterial pressure and vascular resistance caused by sympathetic vasomotor discharge. The effect involves the area postrema, a fourth-ventricle circumventricular organ having a deficient blood-brain barrier. [The *SCI*® indicates that this paper has been cited in over 250 publications.]

Carlos M. Ferrario
Department of Cardiovascular Research
Cleveland Clinic Foundation
Cleveland, OH 44106-4775

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The discovery of neurogenic actions of angiotensin II (Ang II) is a fascinating aspect of hypertension research, since only with considerable travail were these findings eventually recognized as an important contribution to the understanding of mechanisms involved in the pathogenesis of arterial hypertension. It is now accepted that stimulatory actions of Ang II on brain mechanisms regulating blood pressure, water, and salt balance and secretion of hormones such as vasopressin and ACTH contribute to maintenance of homeostasis. Such was not always the case.

Following the synthesis of Ang II in 1957, studies of its physiological actions suggested that Ang II was not simply a powerful vasoconstricting agent but that it was almost ubiquitous in its action. In 1966, when I joined the laboratory of James McCubbin and Irvine H. Page at the Cleveland Clinic Foundation, they had just established that Ang II produced a hypertensive effect partly by augmenting peripheral sympathetic nerve activity.[1] Although Bickerton and Buckley[2] had shown previously that Ang II affects the central nervous system (CNS), the significance of their observations was missed by most investigators because the dosage used was far greater than amounts believed to be produced endogenously, and the hormone was thought too large to cross the blood-brain barrier.

Almost concurrently, C.J. Dickinson had forwarded the hypothesis that essential hypertension results from relative ischemia of central vasomotor centers due to increased cerebrovascular resistance produced by activation of the renal pressor system.[3] Attempts by Dickinson and McCubbin[4] failed to show that Ang II infusion into the hindbrain circulation of the anesthetized dog produced pressor responses different from those obtained by intravenous infusion. However, I had the opportunity to talk with Dickinson at the 1967 Physiological Congress in Washington, DC. That discussion greatly influenced my research.

We concluded that the failure to observe a central effect of Ang II was possibly due to the CNS-depressing effect of pentobarbital. By repeating those experiments and measuring responses to vertebral artery Ang II infusions, using dogs equipped with electromagnetic flowmeters and anesthetized with morphine-chloralose, we showed that infusion of small doses of Ang II (without effect when given intravenously) into the vertebral arteries produced a pressor response.[5] The dose-response curve suggested a neuronal effect, and additional experiments showed that the area postrema in the fourth ventricle was the angiotensin-sensitive structure mediating blood pressure increase via activation of central vasomotor sympathetic outflow.

I believe this paper is frequently cited because it provided the first comprehensive description of the direct action of Ang II on a brain structure highly sensitive to the hormone (area postrema), documented the mechanism of action, and proposed that the central effects of Ang II revealed a feedback link between the brain and the renal pressor system. (The fact that this controversial article was reviewed by *seven* referees foretold its future as an often-cited reference!)

Since 1972 we have affirmed area postrema involvement in the regulation of blood pressure and sympathetic nerve activity by many studies, including characterization of its anatomical and neurochemical substrate and the discovery that it functions in the tonic control of arterial pressure and the expression of the early phase of renovascular hypertension.[6] For this latter work I received the 1979 Harry Goldblatt Award from the American Heart Association, Council of High Blood Pressure Research.

1. **McCubbin J W & Page I H.** Neurogenic component of chronic renal hypertension. *Science* 139:210-15, 1963. (Cited 80 times.)
2. **Bickerton R K & Buckley J P.** Evidence for a central mechanism in angiotensin induced hypertension. *Proc. Soc. Exp. Biol. Med.* 106:834-6, 1961. (Cited 340 times.)
3. **Dickinson C J & Lawrence J R.** A slowly developing pressor response to small concentrations of angiotensin: its bearing on the pathogenesis of chronic renal hypertension. *Lancet* 1:1354-6, 1963. (Cited 85 times.)
4. **Dickinson C J & McCubbin J W.** *Neurogenic hypertension.* Oxford: Blackwell Scientific Publications, 1965. p. 158.
5. **Ferrario C M, Dickinson C J & McCubbin J W.** Central vasomotor stimulation by angiotensin. *Clin. Sci.* 39:239-45, 1970. (Cited 120 times.)
6. **Ferrario C M.** Neurogenic actions of angiotensin II. *Hypertension* 5(Suppl. V):V-73-V-79, 1983.

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