

**Bickerton R K & Buckley J P.** Evidence for a central mechanism in angiotensin induced hypertension. *Proc. Soc. Exp. Biol. Med.* 106:834-6, 1961.

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This publication reports the first evidence for a central mechanism in the pressor response produced by the parenteral administration of angiotensin II. Use of dog cross-circulation procedures in the administration of angiotensin II into the central circulation of a recipient animal evoked a pressor response that was independent of peripheral effects. The response appeared to result from increased sympathetic outflow from the central nervous system since it was prevented by the peripheral administration of dibenzylamine. [The *SCI*® indicates that this paper has been cited in over 370 publications.]

## Angiotensin in the Brain?

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This paper, which presents the first report of a centrally mediated effect of angiotensin II (ANGII), results from the doctoral research of RKB. The authors have collaborated, now as then, in preparing this commentary.

The demonstration of a central effect of ANGII was possible at that time because refinements in cross-circulation preparation had been made by both faculty and graduate students in the Department of Pharmacology, School of Pharmacy, University of Pittsburgh. Though not the major, or even primary, direction of the research, the data collected on ANGII have emerged as the most important. So many researchers at that time, including the authors, believed that ANGII was solely a peripherally acting peptide. Indeed, all data up to this report had confirmed the peripheral cardiovascular activity and had shown that the central nervous system (CNS) was not required for ANGII to induce a pressor response. Imagine, then, the feelings of a doctoral candidate, who, anticipating only confirmation of the peripheral effects at the end of an experiment performed for other purposes, injected ANGII into the recipient animal in a crossed-circulation preparation and observed indication of a centrally mediated pressor response.

Dr. R.P. Halliday (then a graduate student), who later confirmed and extended the original research,

was present; together we shared disbelief. The fact that the preparation had received other drugs and that the amount of leakage between head and body had not been determined allowed ready dismissal of a possible real effect. Though it was determined an hour or so later that there was no vascular leakage, the facts that other drugs had been administered, that the observation was at the end of an experiment, and that EVERYONE knew that ANGII did not have a central effect encouraged the students to question the result. However, the unexplained observation prompted experiments designed simply to test ANGII in preparations in which no other drugs had been previously administered. When the pressor effect in the recipient was again observed and the peripheral effect had also been replicated, the results were presented to others in the department.

Additional confirmatory experiments were performed, and some very preliminary investigations of the possible mechanisms of action suggested that ANGII increased sympathetic outflow from the CNS. These results were the subject of our paper. As we remember, the report was not met with universal acceptance but rather with a great deal of skepticism or outright disbelief. The confirmatory research of first Halliday<sup>1</sup> and then C.M. Ferrario<sup>2</sup> and many others established the fact that ANGII did indeed have a central locus of activity and confirmed that the central activity was not limited to the cardiovascular system. The report stimulated much research relating to the effect of ANGII (and other peptides) on the CNS, and, 15 years following the initial observation, an international symposium was held at the University of Houston.<sup>3</sup> Imagine, again, the feelings of an individual who was present and watched as one of the first slides projected was a photograph of an experiment first published in his doctoral dissertation some 15 years earlier. Imagine further, if you will, the feelings of that same individual who now writes comments on the paper for publication as a *Citation Classic*.

Though 28 years ago we believed the observation an important one, in retrospect it is important not for the observation itself but, perhaps, more for the further research it has stimulated. Over 40 papers have resulted from research in our laboratories on the central actions of ANGII and renin, including effects on midbrain structures, hemodynamic effects, and the development of experimental hypertension by chronically administering ANGII into cerebral ventricles of awake dogs.<sup>4</sup> It was most satisfying to see the publications from so many investigators throughout the world on the physiology, biochemistry, and molecular biology of angiotensin and renin in the brain, especially the identification of a brain renin-angiotensin system by D. Ganten *et al.*<sup>5</sup> There is no doubt today that ANGII does indeed have complex effects on the CNS.

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4. Jandhyala B S, Lokhandwala M F, Nandiwada P & Buckley J P. Circulatory effects of chronic administration of angiotensin II into the cerebral ventricles of dogs; studies on the development of an experimental model of hypertension. *Hypertension* 1:219-27, 1979. (Cited 20 times.)
5. Ganten D, Granger P, Ganten U, Boucher R & Genest J. An intrinsic renin-angiotensin system in the brain. (Genest J & Koiv E, eds.) *Hypertension* '72. Berlin, FRG: Springer-Verlag, 1972. p. 432-5.

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