This Week's Citation Classic®

CC/NUMBER 18
MAY 5, 1986

Erdös E G. Angiotensin I converting enzyme. *Circ. Res.* **36**:247-55, 1975.
[University of Texas Health Science Center, Depts. Pharmacology and Internal Medicine, Dallas, TX]

This article summarizes the background and research work on the angiotensin I converting enzyme done in my laboratory and elsewhere. [The *SCI*® indicates that this paper has been cited in over 215 publications.]

Ervin G. Erdös
Departments of Anesthesiology and Pharmacology
College of Medicine
University of Illinois
Chicago, IL 60680

December 31, 1985

The surprising aspect of this article is not the popularity of its subject, but that it appeared at all. When I wrote it at the request of a great editor, Robert Berne, I did not know that he would send it to 10 reviewers. Most of them tried to correct errors in the manuscript, but some used the opportunity to offer a free psychoanalysis of the writer and tried to improve his character instead of the style or content of the article. I literally threw the manuscript into a drawer designated as its final resting place. That it appeared in print at all was due to the urging of Berne.

The roots of the work went back quite a few years, first to the Mellon Institute (Carnegie-Mellon University). At that time (1960) synthetic bradykinin had just become available. Since previous active preparations were frequently about as homogeneous as a slice of liverwurst, we grabbed the opportunity and the peptide and found that human plasma inactivates it by the release of a single arginine,[1] through the action of the newly discovered carboxypeptidase N (kininase I).

While continuing the studies at the University of Oklahoma with H.Y.T. Yang, we looked for the kininase in tissues. Kidney extracts rapidly inactivated kinins, and after some initial purification we detected an enzyme, designated kininase II, in the particulate fraction that released a carboxyl-terminal dipeptide (Phe-Arg) instead of a single amino acid. This was reported at international meetings in 1965-1966. (Then, the only other peptidase that released carboxyl-terminal dipeptides was one from horse plasma, which converted angiotensin I to II.[2])

At first the idea that a single enzyme could both inactivate a potent hypotensive peptide (bradykinin) and release a powerful hypertensive peptide (angiotensin II) appeared to be perfect nonsense. However, the identity of this kininase II with the angiotensin I converting enzyme was shown after partial purification and after employing several substrates and inhibitors.[3] During this time, Vane and his colleagues drew attention to the lung as a metabolic organ involved in avidly metabolizing circulating vasoactive substances including bradykinin and angiotensin I,[4] but the metabolism of the two peptides was attributed to two different enzymes.

Subsequent research[5] suggested the close similarity or identity of the plasma, kidney, and lung enzymes. We coined the unfortunate name, dipeptidyl carboxypeptidase,[3] and, although this term is wrong, it has been widely used in the literature. The synthesis of specific inhibitors of converting enzyme and their introduction into clinical medicine to combat hypertension and congestive heart failure resulted in an ever-increasing number of publications.

Recent experiments with homogeneous human enzyme surprised us because converting enzyme cleaved substrates more promiscuously than first thought. It releases not only dipeptides with a free carboxyl terminus but also protected di- and tripeptides and, as R. Skidgel and I observed recently, even an amino-terminal tripeptide, at least *in vitro*.[6] Converting enzyme, alias kininase II, alias dipeptidyl carboxypeptidase, is still waiting for a definitive descriptive name.

1. **Erdös E G.** Enzymes that inactivate polypeptides. (Brodie B B & Erdös E G, eds.) *Metabolic factors controlling duration of drug action*. Oxford: Pergamon Press, 1962. p. 159-78. (Cited 40 times.)
2. **Skeggs L T, Kahn J R & Shumway N P.** Preparation and function of the hypertensin-converting enzyme. *J. Exp. Med.* **103**:295-9, 1956. (Cited 375 times.)
3. **Yang H Y T, Erdös E G & Levin Y.** A dipeptidyl carboxypeptidase that converts angiotensin I and inactivates bradykinin. *Biochim. Biophys. Acta* **214**:374-6, 1970. (Cited 155 times.)
4. **Vane J R.** The release and fate of vasoactive hormones in the circulation. *Brit. J. Pharmacol.* **35**:209-42, 1969. (Cited 590 times.)
5. **Oshima G, Gecse A & Erdös E G.** Angiotensin I converting enzyme of the kidney cortex. *Biochim. Biophys. Acta* **350**:26-37, 1974. (Cited 105 times.)
6. **Skidgel R A & Erdös E G.** Novel activity of human angiotensin I converting enzyme: release of the NH_2- and COOH-terminal tripeptides from the luteinizing hormone-releasing hormone. *Proc. Nat. Acad. Sci. US* **82**:1025-9, 1985.