

# This Week's Citation Classic®

Lang R E, Thölken H, Ganten D, Luft F C, Ruskoaho H & Unger T. Atrial natriuretic factor—a circulating hormone stimulated by volume loading. *Nature* 314:264-6, 1985. [German Institute for High Blood Pressure Research, Heidelberg, and Department of Pharmacology, University of Heidelberg, FRG]

This paper demonstrates that atrial natriuretic peptide is a true hormone, released from the heart in response to atrial distention, which circulates in blood at levels controlled by the intravascular volume. [The SC<sup>®</sup> indicates that this paper has been cited in more than 1,025 publications.]

## The Heart of the Matter

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By 1983, the primary sequence of atrial natriuretic peptide (ANP) had been published, the cDNA of pre-pro-ANP cloned, and binding sites for ANP identified. But it was still unknown whether the peptide was a local factor or a true hormone that circulates in blood.

At that time, I was working as a senior scientist in the group of Detlev Ganten at the Department of Pharmacology and the German Institute for High Blood Pressure Research in Heidelberg. Having spent many years in clinical and experimental endocrinology, I was fascinated by the revolutionary idea the heart may not just be a pump but could also produce a hormone to control its own load.

As soon as synthetic ANP became commercially available, I started the immunization of rabbits which were extremely cooperative in producing excellent antibodies within just a few months. The subsequent work would not have proceeded so quickly without the coincidence of several favorable factors. Besides my experience in developing radioimmunoassays for the determination of plasma hormones, these were the availability of an isolated heart preparation I was then using in my studies on the regulation of neuropeptide release from cardiac nerves; the arrival of Heikki Ruskoaho, a Humboldt Fellow from the University of Oulu in Finland, who soon got ad-

dicted to the Langendorff heart preparation; and Detlev Ganten, who provided us with all of the support we needed.

In a series of experiments in the living rat and the isolated heart, we discovered ANP-like immunoreactive material in plasma, which markedly increased in response to volume expansion and behaved chromatographically similar to the material eluting from the perfused heart.<sup>1</sup> In the isolated heart, ANP release could be stimulated by increasing right atrial transmural pressure. This suggests that ANP release is not reflexively mediated but relies on the distention of ANP-producing atrial muscle cells.

Subsequently, we have worked to elucidate the mechanism underlying the transformation of mechanically induced stretch into hormone secretion—a savory question for the physiologist's palate, but one that remains unanswered. Early experiments by Ruskoaho, in my laboratory, in which ANP secretion was stimulated by phorbol esters, pointed to a possible role of protein kinase C activation.<sup>2</sup> Later we found that metabolites of the phosphatidylinositolphosphate pathway accumulate in atria exposed to repetitive stretching, which would be consistent with stretch-induced activation of phospholipase C. This evidence, however, is indirect and requires further confirmation.

Our studies in humans, originally planned to run parallel to the animal experiments, have been delayed. This was because our original antibodies, raised at a time when the synthetic human peptide was not yet on the market, only poorly cross-reacted with human ANP. Nevertheless, after the successful immunization against the human sequence, we were still among the first to demonstrate that ANP was elevated in states characterized by an expanded plasma volume. Such states include end stage renal failure and various forms of cardiac diseases, adding further support to the contention that atrial stretch is the principal stimulus of ANP release.<sup>3,4,5</sup>

1. Ruskoaho H, Tholken H & Lang R E. Increase in atrial pressure releases atrial natriuretic peptide from isolated perfused rat hearts. *Eur. J Physiol.* 407:170-4, 1986.
2. Ruskoaho H, Toth M & Lang R E. Atrial natriuretic peptide secretion: synergistic effect of phorbol ester and A23187. *Biochem. Biophys. Res. Commun.* 133:581-ti, 1985.
3. Kascher W, Tulassay T & Lang R E. Atrial natriuretic peptide in plasma of volume-overloaded children with chronic renal failure. *Lancet* 2:303-5, 1985. (Cited 230 times.)
4. Weidmann P, Haslir L, Gnadinger M P, Lang R E, Uehlinger D E, Shaw S, Rascher W & Reubi F C. Blood levels and renal effects of atrial natriuretic peptide in normal man. *J. Clin. Invest* 77:734-42, 1986. (Cited 235 times.)
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Received October 15, 1992