Physiology

The expanding physiological roles of atrial natriuretic factor

from Philip Needleman

In 1981, A. de Bold and colleagues demonstrated profound excretion of sodium and water into the urine following injection of a cardiac atrial extract into rats. With the lightning pace of modern biomedical research it took just two years to describe the structure of a unique cardiac peptide and we are now in the position to begin clinical trials of a synthetic product. A recent meeting* was the first to bring together the investigators establishing the synthesis, processing, release, function and potential therapeutic use of the atrial peptide, especially the homeostatic regulation of fluid, salt and blood pressure. The start of clinical trials only five years after the first description of the activity from rat heart extract is a remarkable demonstration of the pace of modern biology.

Considerable effort has focused on the storage and processing of the hormone within cardiac tissue, and identification of the circulating form. The natriuretic vasodilator (variously termed atriopeptin, cardionatrin, auriculin, atrial natriuretic factor or peptide) is stored exclusively as a 126-amino-acid precursor in granules located in both the right and the left mammalian cardiac atrium (de Bold, Ontario; G. Thibault, Clinical Research Institute of Montreal, CRIM). Cultured fetal atrial myocytes store and release the intact prohormone into the medium (J. Seidman, Harvard). Blood levels of atrial peptide are elevated by intravenous volume overloading, vasoconstrictor agents, head-out water immersion (P. Needleman), morphine (J. Gutkowska, CRIM) and salt loading. There is a direct linear correlation between the elevated plasma atriopeptin levels stimulated by vasopressin in rats and the loss of atriopeptin precursor for the right, but not the left, atrium (Needleman). The mature 28 amino-acid carboxy terminus of the rat prohormone is the circulating form (Needleman Thibault) simultaneously accompanied by a high molecular mass amino-terminal fragment of the prohormone lacking the carboxy-terminal atriopeptin (Needleman). The intact prohormone has not been found in the blood of normal experimental animals or man, suggesting that the cleavage of the precursor that produces the mature hormone occurs at the time of release from the atrial granule. The cleavage enzyme responsible is a potential regulatory step and its cellular site and characteristics are one focus of current attention.

Immunocytochemical experiments confirm the presence of atriopeptin-like materials in the brain, especially the hypothalamus (D.M. Jacobowitz, National Institutes of Health). Chromatographic analysis of brain extracts show low levels of a peptide that co-migrates with atriopeptin-28 (the carboxy-terminus of the prohormone) (H. Imura, Kyoto; T. Inagami, Vanderbilt University). However, neuronal synthesis of atriopeptin or isolation and description of the messenger RNA for atriopeptin in brain has not been found. Autoradiographic experiments demonstrate the existence of specific, high-affinity receptors for atriopeptin in the brain (R. Quirion, CRIM) and incubation of isolated brain regions with the peptide gives elevated cyclic GMP production (Inagami), but there are only hints of cerebral functions for atriopeptin. Systemic injection of the peptide partially suppresses the drinking response and blood pressure elevation in rats produced by angiotensin (Inagami; Imura); the salt appetite and total fluid intake in spontaneous hypertensive rats (Imura); and vasopressin release (W.K. Samson, University of Texas). These experiments imply that atriopeptin has a central role in regulating body salt and fluid levels and peripheral blood pressure.

The availability of synthetic peptides rapidly led to investigation of receptor binding and analysis of the potential second messenger for atriopeptin. Down-regulation of atriopeptin receptor density is induced by pre-exposure to atriopeptin of cultured arterial smooth muscle cells or in blood vessels isolated from rats that were salt loaded and/or treated with mineralocorticoid (T. Schiffrin, CRIM). In fact, deoxycorticosterone acetate-salt hypertensive rats showed diminished sensitivity to the hypotensive effects of atriopeptin. The current best candidate for a second messenger appears to be cyclic GMP as stimulation of particulate guany-

* First International Symposium of Atrial Natruiretic Factor, Montreal, 10 – 11 March 1986, organized by M. Cantin.

25 years ago — Discovery of messenger RNA

AN UNSTABLE INTERMEDIATE CARRYING INFORMATION FROM GENES TO RIBOSOMES FOR PROTEIN SYNTHESIS

By Dr. S. BRENNER
Medical Research Council Unit for Molecular Biology, Cavendish Laboratory, University of Cambridge
Dr. F. JACOB
Institut Pasteur, Paris
AND
Dr. M. MESELSON
Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California

A LARGE amount of evidence suggests that genetic information for protein structure is encoded in deoxyribonucleic acid (DNA) while the actual assembling of amino-acids into proteins occurs in cytoplasmic ribonucleoprotein particles called ribosomes. The fact that proteins are not synthesized directly on genes demands the existence of an RNA is not the intermediate carrier of information from gene to protein, but rather that ribosomes are non-specialized structures which receive genetic information from the gene in the form of an unstable intermediate or 'messenger'. We present here the results of experiments on phage-infected bacteria which give direct support to this hypo-

UNSTABLE RIBONUCLEIC ACID REVEALED BY PULSE LABELLING OF *ESCHERICHIA COLI*

By Drs. FRANCOIS GROS and H. HIATT
The Institut Pasteur, Paris
Dr. WALTER GILBERT
Departments of Physics, Harvard University
AND
Dr. C. G. KURLAND, R. W. RISEBROUGH and Dr. J. D. WATSON
The Biological Laboratories, Harvard University

WHEN *Escherichia coli* cells are infected with *T* even bacteriophage particles, synthesis of host proteins stops[1], and much if not all new protein synthesis is phage specific[2]. This system thus provides an ideal model for observing the synthesis of new proteins following the introduction of specific

During these years, evidence[7] accumulated that the sites of much, if not all, protein synthesis are the ribosomal particles, and it was thought most likely that ribosomal RNA was genetically specific, with each ribosome possessing a base sequence which coded for a specific amino-acid sequence (one ribo-

From *Nature* **190**, 576; 13 May 1961 and **190**, 581; 13 May 1961.

©1986 Nature Publishing Group