Peptide function

Is chromogranin a prohormone?

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IN THE 4 December issue of *Nature*[1], K. Tatemoto and co-workers report the sequence of a newly discovered putative hormone, pancreastatin, which as its name implies inhibits insulin (and somatostatin) secretion from the endocrine pancreas. There is a striking structural similarity between pancreastatin and part of bovine chromogranin A, whose sequence was recently reported in *Nature*[2] by myself and collaborators, and independently in the *EMBO Journal* by Benedum *et al.*[3]. This similarity suggests that chromogranin A is a prohormone precursor for pancreastatin or a pancreastatin-like peptide. If so, Tatemoto and co-workers will have contributed decisively to the elucidation of a least one of the physiological functions of chromogranin A. Its role has eluded neuroendocrinologists since its discovery 20 years ago[4–7].

Chromogranin A is the chief representative of a family of acidic glycoproteins that are abundant throughout the neuroendocrine system[8–11]. Chromogranin A is about 10 per cent of the protein weight of catecholamine-secreting chromaffin cells of the adrenal medulla and is found, often with related proteins variously called chromogranins B and C and secretogranins I and II (ref. 12), in the brain, pituitary, retina, thymus, parathyroid, sympathetic nervous system, enteric nervous system, endocrine gut and endocrine pancreas[8–11]. It is from the last-named tissue that Tatemoto *et al.* isolated the 49-amino acid 'pancreastatin' whose structure and biological activity, together with the recently determined structure[2,3] of chromogranin A, may finally give a clue to the function of chromogranin A.

Pancreastatin, a potent inhibitor of insulin secretion from the isolated rat pancreas, is quite similar to residues 243–294 of bovine chromogranin A (residues 261–312 of prechromogranin A): 71 per cent of the amino-acid residues of the two peptides are identical (see figure). The similarity is even greater (80 per cent, with one gap) in the carboxy-terminal 41 amino acids of pancreastatin. This is significant in that all the biological activity of pancreastatin seems to be localized in the carboxy-terminal 17 amino acids of the peptide[1]. The next six nucleotides of bovine chromogranin A messenger RNA encode the dipeptide Gly–Lys, a potential processing signal for proteolytic cleavage and carboxy-terminal amidation, consistent with the isolation of pancreastatin as an amidated species. At the amino terminus, chromogranin A contains a lysine residue, which may be the amino-terminal processing signal for the formation of pancreastatin from a chromogranin A-like precursor in the rat.

There is chromogranin, as well as pancreastatin, immunoreactivity in the pancreas of several species, and both polypeptides are present in the brain[11,15], consistent with a precursor–product relationship between chromogranin A and pancreastatin. Whether or not pancreastatin is generated from chromogranin A or a chromogranin A-like precursor must await the sequencing of the porcine chromogranin A complementary DNA, now under way, or the demonstration of the analogous pancreastatin in the bovine pancreas.

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GWPQ--AP--AMDGAGKTGAEEAQPPEGKGAREHSRQEEEEETAGAPQGLFRG
KETQRAAPGWPEDGAGKMGAEEAKPPEGKGEWAHSRQEEEE-MARAPQVLFRGGK
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Top sequence, porcine pancreastatin; bottom sequence, bovine chromogranin A 243–296 (prechromogranin A 261–314)[2]. Single-letter code for amino acids. Stars, identical residues; dashes, gaps introduced into either sequence to maximize alignment; hash, conservative substitution.

Alternatively, the pancreastatin-like peptide potentially encoded by chromogranin A and pancreastatin itself could be related members of a larger, hitherto unidentified family of peptide hormones analogous to the secretin 'superfamily' of gut hormones[13]. Benedum *et al.*[3] have characterized a second bovine adrenomedullary messenger RNA encoding a chromogranin A identical in size and with 98 per cent of the peptide and 94 per cent of the nucleic acid sequences identical to the chromogranin messenger RNA characterized by us[2]. Eberwine *et al.*[14] report that sequences hybridizing to a pancreastatin-complementary oligonucleotide probe may be found in as many as five separate genes in the rat. These observations suggest that chromogranin A and pancreastatin are members of a peptide hormone superfamily. For the moment, both possibilities seem equally likely. Structural analysis of porcine chromogranin A or bovine pancreastatin is needed to distinguish between them.

Several additional questions must be answered to clarify the relationship between pancreastatin and chromogranin A. Does chromogranin A indeed generate a pancreastatin-like peptide in adrenal medulla, endocrine pancreas or any other tissue? Is native unprocessed chromogranin A itself a pancreastatin? These questions are crucial because the ubiquity of chromogranin A in the neuroendocrine system would suggest that the role of pancreastatin or pancreastatin-like molecules is not limited to the pancreas. In fact plasma levels of chromogranin A are sufficiently high[16] (about 3 nM) to stimulate pancreastatin receptors even if only a small percentage of plasma chromogranin was processed to a pancreastatin-like molecule, or if native chromogranin A had only a fraction of the pancreastatin potency of the peptide characterized by Tatemoto *et al.*. It is clearly necessary to establish that the molecule isolated by Tatemoto *et al.* is indeed the substance found at beta-cell and D-cell receptors *in vivo*. It will be of special interest to determine if amidation is necessary for biological activity, because amidation of other biologically active peptides such as enkephalins seems to oc-cur differentially in central and autonomic nervous tissue, and this differential post-translational modification may be relevant to different, as yet undiscovered hormonal functions of these molecules. In addition, there is precedent for cleavage at single basic amino-acid residues within the precursors of other biologically active secretory peptides[17] and thus pancreastatin residues 1–49, 14–49, 27–49, 31–49 and 36–49 (or chromogranin A 244–294, 248–294, 260–294, 267–294, 272–294, 279–294 and even 287–294) could be the actual biologically active peptide(s) produced by and secreted from any endocrine tissue.

In any event, the demonstration of biological activity for a chromogranin A-derived molecule would be a partial reward for the considerable efforts so far made to characterize and understand this ubiquitous but puzzling molecule. Further information validating or disproving a biosynthetic and/or genetic relationship between pancreastatin and chromogranin A, and linking chromogranin A to other endocrine functions, should accrue quickly.

Two of the authors of ref. 3 independently report the sequence similarity between chromogranin A and pancreastatin on page 305 of this issue[18]. □

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