## THE DIFFERING ENDOCRINOLOGY OF MID GUT AND LUNG NEUROENDOCRINE TUMOURS

Keith D Buchanan, Colin F Johnston and Christopher Shaw

Wellcome Research Laboratories, Department of Medicine, The Queen's University of Belfast, Belfast, BT12 6BJ, N Ireland

The clinical syndromes of neuroendocrine tumours (NETs) of the mid gut (MG) and of the lung (L) have overlapping features ie flushing and diarrhoea, but also unique features to each ie heart disease in MGs and lacrimation, salivation and facial oedema in Ls. To discover if this can be explained by differing peptide hormone profiles frozen tumour tissue was extracted and assayed for peptide hormone content. Plasma from L and MG NETs with liver metastases was also analysed. The following peptide hormones were assayed:- pancreastatin (PST), neurokinin A (NKA), substance P (SP), gastrin releasing peptide (GRP) and calcitonin gene-related peptide (CGRP).

In the tissues, 91% of L NETs (n=23) contained PST and 100% of MG NETs (n=19). PST was also elevated in the circulation of 78% MG NETs (n=18) and 100% of L NETs (n=6). MG NETs but not L NETs contained NKA (100%) and SP (100%), whereas L NETs and not MG NETs contained CGRP (57%) and GRP (62%). Plasma levels of NKA (94%) and SP (57%) were elevated in MG NETs but not L NETs. Conversely plasma levels of CGRP (20%) and GRP (67%) were elevated in L NETs but not MG NETs.

In conclusion L NETs and MG NETs have overlapping but also distinct endocrinology, and should be considered as different endocrine tumours.

## Structural requirements for tyrosine sulfation of progastrin and its biological effects

*Jens R. Bundgaard, Jens Vuust[#] and Jens F. Rehfeld*

*Dept. of Clin. Biochem., National University Hospital, Copenhagen, Denmark.*
*[#] Lab. of Molecular Biology, Statens Serum Institut, Copenhagen, Denmark.*

Tyrosine sulfation is a widespread modification of proteins transported through the secretory pathways and it is catalyzed by a tyrosylprotein sulfotransferase located in the TGN. A consensus for tyrosine sulfation sites has been proposed, based on the primary sequences of proteins with known sulfated tyrosyl residues. However, a number of proteins are tyrosine sulfated at sites deviating from the general consensus. Among these are gastrin and some other members of the gastrin/CCK family. We have established a transient expression system for mutational analysis of progastrin processing and are utilizing this system for examination of the involvement of tyrosine sulfation in progastrin processing. Using site directed mutagenesis we have altered the structure around the sulfation site and determined the effect of sulfation of progastrin. We find that although an important determinant of sulfation is the presence of an acidic residue N-terminally (position -1) to the tyrosine, sulfation also depends on residues in other specific positions. For instance, the -3 position appears to be important whereas the nature of the residue in the -2 position appears insignificant. Hence, our study provides a useful extension of the present consensus for future predictions of sulfation sites.
Several different functions of tyrosine sulfation have been reported. Many of these suggest that sulfation enhances different types of protein-protein interactions. We have shown that sulfation increases proteolytic processing at the Lys-Lys cleavage site leading to gastrin-17. Moreover, sulfation affects the half life of gastrin and we will present data suggesting an effect on C-terminal amidation.