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Identification and Characterization of Corticotropin Releasing Hormone (CRH) Type 1 System in Human Pancreatic Neuroendocrine Tumors

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Background: Neuroendocrine peptide hormone corticotropin-releasing hormone (CRH) plays an important role in integrating stress response to restore central and peripheral homeostasis. Potential risk factors for pancreatic endocrine tumor (PET) development are closely associated with chronic stress-induced metabolic disorders and inflammation. This study aims to determine if a local pancreatic CRH system exists in normal versus tumor tissues, and to characterize the function of CRH and urocortin (Ucn) peptides in human carcinoid BON cells and pancreatic cancer (PaCa) cells that are capable of CRH receptor-mediated cell signaling and hormone secretion.

Methods: Expression of CRH ligand, receptors and binding protein was determined by RT-PCR and qPCR using specific primers in Pancreatic Cancer and Disease Tissue Arrays (Origene) and PaCa cells. Tryptophan hydroxylyase 1 (TPH1) was measured as a marker for 5-HT producing PET. CRH receptor and binding proteins were examined by Western blot probed with specific antibodies. Protein lysates from BON and PaCa cells after CRH/Ucn treatment (10^{-10}-10^{-6} M, 30 min) were examined for phospho-ERK1/2, p38, CREB and AKT. Immunofluorecent staining was performed on cells and tissue sections were immunostained with CRHR antibodies.

Results: CRHR and CRHBP with multiple splice variants were detected in human pancreatic cancer tissues and cell lines. CRH and Ucn3, CRHR1a and 1c isoforms and CRHBP were predominantly expressed in the endocrine tumors in which 6/13 also express TPH1 above the normal value. CRH and Ucn-1 stimulated ERK1/2, p38 and CREB, but inhibit AKT phosphorylation via CRHR1 on the BON and PaCa cells.

Conclusion: Our data show that PET expresses a functional CRH type 1 system, in comparison to normally low or absent in ductal adenocarcinoma tissue. The finding of TPH1 expression in more than 40% of the PET suggests that a nascent CRH-5-HT axis may exist to amply CRH stress signals within and outside the endocrine pancreas.