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Regulation of Corticotropin Releasing Hormone (CRH) and Urocortin Family Peptide Expression in Human Carcinoid BON Cells

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Background: CRH plays a key role in integrating stress responses. While CRH neurons in the HPA-axis are well characterized, peripheral expression and function of CRH system are less clear. Understanding the neuroendocrine CRH system will be of clinical relevance in stress-related neuroendocrine tumors.

Aim: This study was to determine 1) if CRH and urocortin (Ucn) peptides are expressed and 2) how CRH and Ucn mRNA and peptides are regulated in response to stress hormones in human carcinoid BON cells.

Methods: BON-4N cells were treated with dexamethasone (Dex, 1-100 nM), 5-HT (0.1-10 μ M) and forskolin (Fsk, 1-100 μ M) for 1 h for hormone release, and 3-7 days for expression studies. BON-4N was also transfected with human neurogenin (NEUROG)-1 or NEUROG-3 (wild-type, R93L and R107S mutants) for 7 days to modify its growth and differentiation processes. CRH and urocortin transcripts were analyzed by RT-PCR and qPCR. ProCRH and CRH peptide were detected by Western blot and RIA, respectively.

Results: BON-4N cells differentially expressed multiple CRH mRNA transcripts in basal and stimulated states. Fsk (10-100 μ M) induced CRH and Ucn-1 mRNA increases by 2-5-fold, but reduced Ucn-2 and Ucn-3 expression. ProCRH and CRH were increased in Fsk-stimulated BON-4N cells. Dex at 10-100 nM, inhibited basal and stimulated CRH/Ucn-1 mRNA expression (>50 %). In contrast, 5-HT increased CRH transcripts after 3 days but shown no effects after 7 days. NEUROG-3 induced CRH and Ucn-1, but not Ucn-2 expression. NEUROG3 mutants or NEUROG1 did not show similar effects.

Conclusion: CRH gene expression is regulated by glucocorticoids, 5-HT and cAMP activators in BON-4N cells. Ectopic expression of NEUROG-3 changed the CRH/Ucn expression profile to a well differentiated 5-HT producing cell phenotype. Thus hormonally and transcriptionally modified BON-4N cells will be useful to unveil the molecular mechanisms underlying CRH gene regulation in neuroendocrine tumors under stress.