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Functional Analysis of Novel Bioactive Peptides on the Salt and Water Regulation

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Summary

The discovery of novel neuropeptides opens avenues to delineate unidentified neural functions and to develop new drugs. We analyzed peptides secreted from human medullary thyroid carcinoma TT cells that produces amidated peptides, and have identified two novel amidated peptides, designated neuroendocrine regulatory peptide (NERP) -1 and NERP-2（J Biol Chem, 282, 26354-60, 2007）. NERP-1 and NERP-2 are 25 and 38 amino acids long, respectively, and are derived from distinct regions of the neurosecretory protein VGF. RP-HPLC coupled with radioimmunoassay analysis of hypothalamus extract demonstrated the endogenous presence of NERP-1 and NERP-2 in the rat. Ir- NERPs were highly abundant in the rat hypothalamus, especially in the SON and PVN. Immunofluorescence microscopy showed that NERPs frequently colocalized with vasopressin, but rarely with oxytocin. Within the PVN, immunostaining of NERPs was detected in both magnocellular and parvocellular divisions. Immunogold electron microscopy revealed the colocalization of NERPs with vasopressin in storage granules. VGF mRNA levels in both the PVN and SON were upregulated upon water deprivation in rats, accompanied by the upregulation of vasopressin mRNA levels. Icv injection of hypertonic NaCl or AII increased plasma vasopressin levels in rats. This stimulation was dose-dependently suppressed by icv injection of NERP-1 before injection of the vasopressin secretagogues. Similar effects were observed with NERP-2, but its potency was weaker than that of NERP-1. Neither non-amidated NERP-1 (NERP-1-Gly) nor non-amidated NERP-2 (NERP-2-Gly) suppressed vasopressin secretion. Icv administration of anti-NERP-1 IgG or anti-NERP-2 IgG significantly reversed plasma vasopressin suppression induced by acute water loading, suggesting that NERPs function as endogenous peptides to regulate vasopressin secretion. Further studies of NERPs and their receptors will pave the way for elucidating unknown regulatory mechanisms as well as developing novel therapeutics for inappropriate secretion of vasopressin.