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Orphan neuropeptides and receptors: Novel therapeutic targets

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Abstract

Neuropeptides are the largest class of intercellular signaling molecules, contributing to a wide variety of physiological processes. Neuropeptide receptors are therapeutic targets for a broad range of drugs, including medications to treat pain, addiction, sleep disorders, and nausea. In addition to >100 peptides with known functions, many peptides have been identified in mammalian brain for which the cognate receptors have not been identified. Similarly, dozens of "orphan" G protein-coupled receptors have been identified in the mammalian genome. While it would seem straightforward to match the orphan peptides and receptors, this is not always easily accomplished. In this review we focus on peptides named PEN and big LEN, which are among the most abundant neuropeptides in mouse brain, and their recently identified receptors: GPR83 and GPR171. These receptors are co-expressed in some brain regions and are able to interact. Because PEN and big LEN are produced from the same precursor protein and co-secreted, the interaction of GPR83 and GPR171 is physiologically relevant. In addition to interactions of these two peptides/receptors, PEN and LEN are co-localized with neuropeptide Y and Agouti-related peptide in neurons that regulate feeding. In this review, using these peptide receptors as an example, we highlight the multiple modes of regulation of receptors and present the emerging