



The TIP39–PTH2 receptor system: Unique peptidergic cell groups in the brainstem and their interactions with central regulatory mechanisms

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ABSTRACT

Tuberoinfundibular peptide of 39 residues (TIP39) is the recently purified endogenous ligand of the previously orphan G-protein coupled parathyroid hormone 2 receptor (PTH2R). The TIP39–PTH2R system is a unique neuropeptide–receptor system whose localization and functions in the central nervous system are different from any other neuropeptides. TIP39 is expressed in two brain regions, the subparafascicular area in the posterior thalamus, and the medial paralemniscal nucleus in the lateral pons. Subparafascicular TIP39 neurons seem to divide into a medial and a lateral cell population in the periventricular gray of the thalamus, and in the posterior intralaminar complex of the thalamus, respectively. Periventricular thalamic TIP39 neurons project mostly to limbic brain regions, the posterior intralaminar thalamic TIP39 neurons to neuroendocrine brain areas, and the medial paralemniscal TIP39 neurons to auditory and other brainstem regions, and the spinal cord. The widely distributed axon terminals of TIP39 neurons have a similar distribution as the PTH2R-containing neurons, and their fibers, providing the anatomical basis of a neuromodulatory action of TIP39. Initial functional studies implicated the TIP39–PTH2R system in nociceptive information processing in the spinal cord, in the regulation of different hypophysiotropic neurons in the hypothalamus, and in the modulation of affective behaviors. Recently developed novel experimental tools including mice with targeted mutations of the TIP39–PTH2R system and specific antagonists of the PTH2R will further facilitate the identification of the specific roles of TIP39 and the PTH2R.

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Abbreviations: ACTH, adrenocorticotropin; AVP, arginine-vasopressin; CGRP, calcitonin gene-related peptide; CRH, corticotropin releasing hormone; DRG, dorsal root ganglion; ED, embryonic day; GH, growth hormone; i.c.v., intracerebroventricular; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone; MPL, medial paralemniscal nucleus; PIL, posterior intralaminar complex of the thalamus; PND, postnatal day; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; PTH1R, PTH 1 receptor; PTH2R, PTH 2 receptor; PTH3R, PTH 3 receptor; PVG, periventricular gray of the thalamus; SPF, subparafascicular area; SPFP, parvicellular subparafascicular thalamic nucleus; TH, tyrosine hydroxylase; TIP39, tuberoinfundibular peptide of 39 residues; TIP39-KO, mice with targeted null mutation of the TIP39 gene; VGLUT, vesicular glutamate transporter; WT, wild type.

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1. Introduction

Tuberoinfundibular peptide of 39 residues (TIP39) was identified on the basis of its activation of the parathyroid hormone 2 receptor (PTH2R), a seven transmembrane domain G-protein coupled receptor (Usdin et al., 1999b). The distribution of TIP39 containing fibers and terminals is very similar to the distribution of PTH2R-containing neurons and neuronal fibers throughout the brain (Dobolyi et al., 2003b; Faber et al., 2007), and TIP39 is a potent and selective PTH2R agonist (Usdin, 2000). This functional and anatomical match suggests that TIP39 is the endogenous ligand of the PTH2R in the brain, and that they form a neuromodulator system. TIP39 neurons have a highly restricted localization. This pattern of synthesis by cells in a few discrete

areas and widespread, but still topographically organized, projections to several distant brain areas resembles several other recently developed neuropeptide systems including, for example, relaxins (Ma and Gundlach, 2007), orexins (Baumann and Bassetti, 2005), calcitonin-gene related peptide (van Rossum et al., 1997), prolactin-releasing peptide (Roland et al., 1999), kisspeptin (Mikkelsen and Simonneaux, 2009), and urocortins (Pan and Kastin, 2008). Based on the available data, however, the TIP39–PTH2R system is a unique neuropeptide–receptor system whose localization and functions in the central nervous system are different from any other neuropeptides.

TIP39 is a member of a small peptide family comprised of parathyroid hormone (PTH), parathyroid hormone-related peptide (PTHrP) and TIP39 (Usdin et al., 1999b). Mature PTH and PTHrP are

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