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Review

Regulation of the hypothalamic Thyrotropin Releasing Hormone (TRH) neuron by neuronal and peripheral inputs

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ABSTRACT

The hypothalamic-pituitary-thyroid (HPT) axis plays a critical role in mediating changes in metabolism and thermogenesis. Thus, the central regulation of the thyroid axis by Thyrotropin Releasing Hormone (TRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) is of key importance for the normal function of the axis under different physiological conditions including cold stress and changes in nutritional status. Before the TRH peptide becomes biologically active, a series of tightly regulated processes occur including the proper folding of the prohormone for targeting to the secretory pathway, its post-translational processing, and targeting of the processed peptides to the secretory granules near the plasma membrane of the cell ready for secretion. Multiple inputs coming from the periphery or from neurons present in different areas of the brain including the hypothalamus are responsible for the activation or inhibition of the TRH neuron and in turn affect the output of TRH and the set point of the axis.

1. Introduction

The hypothalamic-pituitary-thyroid (HPT) axis plays an essential role in the maintenance of metabolic homeostasis in response to alterations in metabolism and external environment. Thyrotropin releasing hormone (TRH) produced in the parvocellular division of the hypothalamus is the key peptide hormone responsible for HPT regulation. TRH is synthesized from a larger inactive precursor (proTRH) by a series of post-translational modifications while transported through the regulated secretory pathway (RSP). These processing events are conducted by two members of the family of prohormone convertases (PCs), PC1/3 and secondarily by PC2 [183,184,227]. The intermediate products of processing generated by these enzymatic activities are further subjected to additional modifications by exopeptidases, such as carboxyl peptidase E and D (CPE, CPD), to remove the C-terminal basic amino acids [188]. TRH-gly, the immediate precursor to TRH (pGlu-His-Pro-NH_2; thyroliberin), is then amidated at its carboxyl terminus by the action of peptidylglycine α-amidating monooxygenase enzyme (PAM) [58,188,195] (see Fig. 1). Anatomically, a subgroup of TRH neurons (see Section 2) originating in the paraventricular nucleus of the hypothalamus (PVN) project their axon terminals to the median eminence (ME) where they are in close proximity to the capillaries of the hypophysial-portal system. TRH released in these capillaries stimulate the biosynthesis and secretion of thyroid stimulating hormone (TSH) from the pituitary [105,107], which in turn, stimulates biosynthesis of the thyroid hormones, thyroxine (T_4), and it modified product triiodothyronine (T_3) by the action of deiodinases [11]. The thyroid hormone regulates the

Abbreviations: TRH, Thyrotropin Releasing Hormone immunoreactive; PTU, propylthiouracil; HPT, hypothalamic-pituitary-thyroid; DVC, dorsal vagal complex; DMN, dorsal motor nucleus of the vagus; NTS, nucleus tractus solitaris; NPY, neuropeptide Y; NE, norepinephrine; GABA, g-aminobutyric acid; CPE/D, carboxypeptidase E/D; CSF, cerebrospinal fluid; PVN, periventricular nucleus of the hypothalamus; ICV, intracerebroventricular; SC, subcutaneous; IC, intracerebral; CNS, central nervous system; ME, median eminence; RER, rough endoplasmic reticulum; PCs, proconverting enzymes; RSP, regulated secretory pathway; GC, Golgi complex; SG, secretory granules; ISG, immature secretory granules; TGN, trans-Golgi network; ICC, immunocytochemistry; TRE, thyroid response element; CRE, cAMP response element; PAM, peptidylglycine α-amidating monooxygenase enzyme; TSH, thyroid stimulating hormone; T4, thyroxine; T3, triiodothyronine; UCPs, uncoupling proteins; BAT, brown adipose tissue; α-MSH, melanocortin stimulating hormone; AgRP, agouti-related peptide; ARC, arcuate nucleus of the hypothalamus; VMH, ventromedial hypothalamus; LH, lateral hypothalamus; ObRb, leptin receptor; MC3-R and MC4-R, melanocortin-3 and 4 receptors; STAT, signal transducer of activated transcription; JAK, Janus tyrosine kinases; ^{40}PGL^{42}, Pro-Gly-Leu; ICC, immunocytochemistry.

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transcription of important genes by binding to a family of nuclear receptors throughout the body, and is of critical significance to sustain protein synthesis and metabolic activity in peripheral tissues. The thyroid hormone also plays a pivotal role in the regulation of thermogenesis. Roughly 30% of resting energy expenditure is dependent upon thyroid hormone, and it is critical in facultative thermogenesis during cold exposure [241,242]. One mechanism by which thyroid hormone affects thermogenesis is by affecting

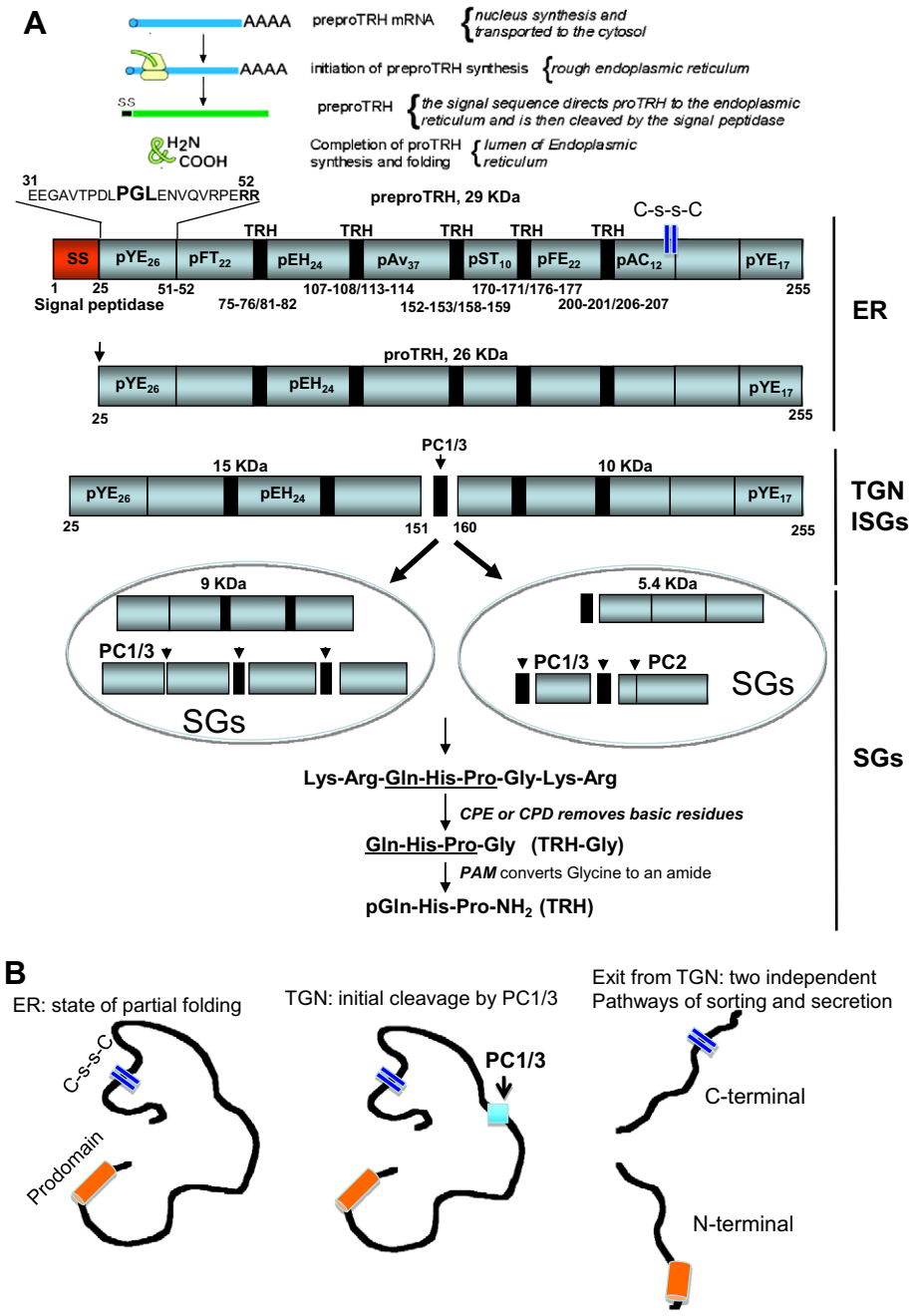

Fig. 1. Schematic representation of the biosynthesis and post-translational processing of rat proTRH. (A) Depicts the transcription and post-translational modifications in the rat proTRH composed of 231 amino acids. The signal sequence is cleaved from preproTRH upon delivery into the endoplasmic reticulum yielding proTRH. The conserved PGL sequence in the pYE26 peptide ensures the proper folding of proTRH within the lumen of the endoplasmic reticulum. The initial processing cleavage of proTRH by PC1/3 begins at the trans-Golgi network level generating an N-terminal and C-terminal intermediate forms. The intermediate forms of processed proTRH are then targeted to different secretory granules where processing continues by the action of the PCs, CPE/D and PAM until TRH and non-TRH peptides are formed. The vertical bars on the right indicate in which intracellular compartment proTRH is cleaved and further procesed. Numbers indicates the positions of paired basic residues. Non-TRH peptides are indicated in the proTRH molecule, and TRH is indicated by a black rectangle. Peptides are indicated as pXYZ nomenclature, where "p" means peptide, "X" is the first amino acid of each peptide, "Y" is the last one, and Z indicates the total number of amino acids in that given peptide. The non-TRH peptides are then targeted to different secretory granules ready for secretion. (B) Depicts the proposed model of the unfolding process for proTRH after its initial cleavage by PC1/3, exposing potential sorting signals responsible for the targeting to different granules. Thus far a disulfide sequence has been identified in proTRH as an important sorting signal for the correct targeting of peptides to secretory granules. SS: signal sequence; ER: endoplasmic reticulum; TGN: trans-Golgi network; ISGs: immature secretory granules; C-s-sC: disulfide bond. The reader should note that proTRH-derived peptides are named by "p" for peptide followed by the single letter amino acid designation for the first and last amino acid of the peptide, along with the peptide length in subscript. Where these peptides are first mentioned, they are followed by the longer prepro-TRH name that describes their amino acid residue positions within the precursor.