Best Practice & Research Clinical Endocrinology & Metabolism xxx (2017) 1–17

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

10

Regulatory aspects of the human hypothalamus-pituitary-thyroid axis

Ferdinand Roelfsema, MD, PhD, Professor [a, *],
Anita Boelen, PhD, Associate Professor and Head [b],
Andries Kalsbeek, PhD, Professor [b, c],
Eric Fliers, MD, PhD, Professor and Head [b]

[a] Department of Internal Medicine, Section Endocrinology and Metabolic Diseases, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands
[b] Department of Endocrinology and Metabolism, Academic Medical Centre, University of Amsterdam, 1100 DD Amsterdam, The Netherlands
[c] Netherlands Institute for Neuroscience, Hypothalamic Integration Mechanisms, 1105 BA Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Available online xxx

Keywords:
thyrotropin
TSH
circadian rhythms
review
human

Thyroid hormones are essential for growth, differentiation and metabolism during prenatal and postnatal life. The hypothalamus-pituitary-thyroid (HPT)-axis is optimized for these actions. Knowledge of this hormonal axis is derived from decades of experiments in animals and man, and more recently from spontaneous mutations in man and constructed mutations in mice. This review examines the HPT-axis in relation to 24 h TSH profiles in men in various physiological and pathophysiological conditions, including obesity, age, longevity, and primary as well as central hypothyroidism. Hormone rhythms can be analyzed by quantitative methods, e.g. operator-independent deconvolution, approximate entropy and fitting the 24-h component by Cosinor analysis or related procedures. These approaches have identified some of the regulatory components in (patho)physiological conditions.

* Corresponding author. Leiden University Medical Center, Department of Internal Medicine, Section Endocrinology and Metabolic Diseases, PO Box 9600, 2300 RC Leiden, The Netherlands. Fax: +31 71 524 8136.
E-mail addresses: f.roelfsema@lumc.nl (F. Roelfsema), a.boelen@amc.uva.nl (A. Boelen), a.kalsbeek@amc.uva.nl (A. Kalsbeek), e.fliers@amc.uva.nl (E. Fliers).

https://doi.org/10.1016/j.beem.2017.09.004
1521-690X/

Introduction

The pituitary gland plays a central role in regulating the hypothalamus-pituitary-thyroid (HPT) axis by secreting thyroid stimulating hormone (TSH) acting on the thyroid gland. In addition to hormonal signals peripheral organs, including endocrine glands, are innervated by the autonomic nervous system which is important for fine tuning of metabolic and secretory processes. In the early sixties, it became evident that hormones such as cortisol, LH, GH, TSH and ACTH are secreted episodically and with a diurnal variation, each with their specific secretion pattern under physiological conditions. Further understanding of regulatory aspects became possible by the isolation of hypothalamic hormones (stimulatory or inhibitory) acting via the pituitary portal blood system on specific pituitary cell systems. The first isolated hypothalamic hormone was thyrotropin-releasing hormone (TRH) acting on the thyrotrope and causing release of TSH. The TSH antagonist, somatostatin, was discovered shortly thereafter [1,2].

Insights of human pituitary hormone regulation has been obtained during decades of investigations analyzing 24-h hormone rhythms under various conditions, including fasting, changes in the wake–sleep cycle, puberty, the menstrual cycle, aging, obesity and pituitary diseases including acromegaly and Cushing's disease. The purpose of this review is to summarize current knowledge on 24-h TSH secretion profiles in 1) healthy individuals and describe the influence of sex, age, body composition, wake–sleep cycle and the effects of certain drugs; 2) major endocrine disorders, including hyperthyroidism, primary hypothyroidism, central hypothyroidism, low triiodothyronine (T3) syndrome; and 3) to highlight current lack of knowledge of TSH profiles in patients with thyroid hormone resistance syndromes, T4-transporter defects, or deiodinase polymorphisms. Before discussing these aspects, a brief summary is provided of the central and peripheral regulation of the HPT-axis.

Hypothalamus-pituitary-thyroid (HPT) axis regulation

Precise regulation of circulating and intracellular concentrations of thyroid hormones (thyroxine (T4)) and the biologically active thyroid hormone triiodothyronine (T3) is essential for the control of metabolic processes, heat production, physical development, weight maintenance, cell differentiation and growth [3]. The prime stimulatory hormone for the thyroid gland is thyrotropin (TSH), with numerous secondary modulators, including insulin-like growth factor type I (IGF-I), inflammatory cytokines (Il-1, IL-6, and TNF-α), and iodide availability [4]. TSH release in turn is under the stimulatory control of the hypophysiotropic paraventricular TRH neurons, and under the inhibitory control of the neurotransmitters, dopamine and somatostatin, and negative feedback control by T4 and T3 [5]. The discovery that TRH was upregulated or downregulated by hypothyroidism and hyperthyroidism, respectively, established the central role of TRH in the HPT-axis [6]. The bioactive hypothalamic tripeptide TRH is processed from prepro-TRH in a subset of neurons in the paired paraventricular nuclei (PVN). TRH neurons project on the external median eminence, where nerve terminals secrete TRH into the portal blood-vessel system [7,8]. TRH is essential for proper functioning of the TSH-thyroid complex. Thus, human TRH-receptor mutations and murine mutations of the TRH gene both lead to (central) hypothyroidism [9,10]. Hypophysiotropic TRH neurons in the PVN receive monosynaptic input from leptin-responsive neurons in the arcuate nucleus, where the blood–brain barrier is less prominent. These neurons synthesize either proopiomelanocortin and cocaine-and-amphetamine-related transcript (POMC/CART) or agouti-related peptide and neuropeptide Y (AGRP/NPY). These metabotropic neurons, which express leptin receptors are crucial for energy homeostasis and food intake [11]. Several studies in human and rodents have shown downregulation of the HPT-axis at the central and peripheral levels during fasting, and this effect is mediated by a downregulation of the hypophysiotropic TRH neurons due to diminished serum leptin concentration, which induces increased NPY expression in the arcuate nucleus and increased local T3 concentration in the arcuate nucleus [12].

Feedback signaling by thyroid hormones on TRH gene transcription and peptide synthesis is important. Studies in the rat have shown that thyroid hormone feedback on TRH is regulated via local intracellular conversion of T4 into T3 by type 2 deiodinase (D2) in the tanycyte, a specialized glial cell, lining the third ventricle [11,13]. Thus, D2 knockout mice have inappropriately elevated TSH concentrations in the face of increased T4 concentrations [14].

Please cite this article in press as: Roelfsema F, et al.Regulatory aspects of the human hypothalamus-pituitary-thyroid axis, Best Practice & Research Clinical Endocrinology & Metabolism (2017), https://doi.org/10.1016/j.beem.2017.09.004