Biochimica et Biophysica Acta xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

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

Review

Systemic regulation of adipose metabolism ☆

Christopher M. Carmean [a], Ronald N. Cohen [a,b], Matthew J. Brady [a,b,*]

[a] The Committee on Molecular Metabolism and Nutrition, University of Chicago, Chicago, IL 60637, USA
[b] Department of Medicine, Section of Endocrinology, Diabetes and Metabolism, University of Chicago, Chicago, IL 60637, USA

ARTICLE INFO

Article history:
Received 14 February 2013
Received in revised form 15 May 2013
Accepted 1 June 2013
Available online xxxx

Keywords:
Adipocyte
Pituitary
Lipolysis

ABSTRACT

White adipose tissue serves as a critical energy storage depot and endocrine organ. Adipocytes are subject to numerous levels of regulation, including neuronal, endocrine and metabolic. While insulin is the classical endocrine regulator of lipid metabolism in adipose tissue, other important endocrine hormones also control adipose tissue physiology. In this review, we will focus on the contribution of the pituitary in the modulation of adipocyte function, through the direct release of growth hormone as well as *via* the regulation of the thyroid gland and release of thyroid hormone. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

1. Introduction

White adipose tissue (WAT) is the largest energy reserve in the human body, and also plays a critical role as an endocrine organ in healthy and diseased states. Not surprisingly, there exists a complex network of communication between WAT and the brain, including sympathetic innervation of fat pads as well as adipocyte-derived signals such as leptin that directly signals in the neuronal cells. In this review, we will focus on the control of WAT physiology by signals emanating from the pituitary gland, specifically in the regulation of the hypothalamic/pituitary/thyroid axis as well as through the release of growth hormone into the systemic circulation.

The pituitary gland is considered the master endocrine gland due to its regulation of numerous physiological processes. The posterior pituitary is comprised of neuronal projections from the supraoptic and paraventricular nuclei in the hypothalamus, which release oxytocin and vasopressin into the general circulation. Oxytocin plays a critical role during child birth, while vasopressin acts on the kidney to regulate water retention and thus blood volume/pressure and electrolyte levels. In contrast, the anterior pituitary is a collection of endocrine cell types which are regulated by hypothalamic factors traveling through the hypophyseal portal vessel. The five principal cell types of the anterior pituitary are the corticotrophs, gonadotrophs, thyrotrophs, lactotrophs and somatotrophs. The first three cell types form the classical hypothalamic–pituitary–adrenal, –gonadal and –thyroid axes, respectively. Lactotrophs release prolactin while the somatotrophs produce growth hormone. Other reviews in this issue are covering the effects of glucocorticoids and sex hormones on WAT function, so this review will focus on the roles of the thyrotrophs and somatotrophs in the control of thyroid hormone or growth hormone, and the effects of these two endocrine hormones on gene expression and metabolism in WAT.

2. Thyroid hormone

Thyroid hormone exerts dramatic effects on all major metabolic tissues, including adipose tissue, liver, and muscle. The thyroid gland is located in the neck on either side of the esophagus with the two lobes connected by the isthmus. Thyroid hormone production and release are controlled by a classical hypothalamic–pituitary axis (Fig. 1). The hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the thyrotroph cells in the anterior pituitary to synthesize and release thyroid stimulating hormone (TSH; also called thyrotropin) into the general circulation. Binding of TSH to its G-protein coupled receptor on thyroid follicular cells exerts pleiotropic effects resulting in the enhanced synthesis and secretion of thyroid hormone. As with other hypothalamic/pituitary endocrine axes, the end product thyroid hormone feeds back to decrease TRH and TSH production.

Although the predominant form of thyroid hormone secreted by the thyroid gland is levothyroxine (T4), the active form that binds the thyroid hormone receptor (TR) is triiodothyronine (T3). The conversion of T4 to T3 occurs *via* deiodinases, enzymes that are expressed in liver, kidney, and other cells such as adipocytes [1]. Two of the deiodinase enzymes, Type 1 (or D1) and Type 2 (or D2) deiodinases, remove an iodine from T4 to generate the active form of thyroid hormone, T3. In contrast, Type 3 deiodinase (or D3) removes a different iodine from T4 to generate an inactive form of thyroid hormone, reverse T3 (rT3).

☆ This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

* Corresponding author at: Department of Medicine, 900 E. 57th St., Chicago, IL 60637, USA. Tel.: +1 773 702 2346; fax: +1 773 834 0581.
E-mail address: mbrady1@uchicago.edu (M.J. Brady).

0925-4439/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.bbadis.2013.06.004

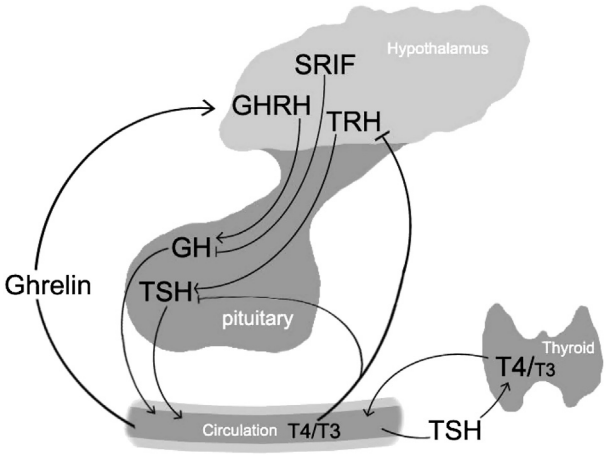

Fig. 1. Map of endocrine signaling mechanisms employed by the hypothalamic–pituitary axis in the control of thyroid hormone (TH) and growth hormone (GH) secretion. TH: Thyrotropin-releasing hormone (TRH) is secreted by cells in the arcuate nucleus of the hypothalamus into the hypophyseal portal system where it stimulates thyrotrophs in the anterior pituitary to release thyroid stimulating hormone (TSH) into the broader circulation. Once in circulation, TSH binds to TSH receptors in the thyroid to activate production of T4 and, to a lesser extent, T3 and their subsequent secretions into circulation. T4 is converted to T3 *via* deiodinases peripherally. Centrally, deiodinases in the hypothalamus and pituitary also convert T4 to T3, providing local feedback inhibition of the TRH and TSH release. GH: Growth hormone releasing hormone (GHRH) is secreted by the arcuate nucleus into the hypophyseal portal system where it stimulates somatotrophs in the anterior pituitary to release GH into the circulation. GHRH secretion can be increased by ghrelin, originating from endocrine cells of the gut. Hypothalamic release of somatostatin (SRIF) *via* the hypophyseal portal system inhibits GH secretion at the pituitary.

The TR is a nuclear transcription factor that binds DNA sequences termed thyroid hormone response elements and recruits other nuclear factors to mediate activation or repression of gene transcription depending on the underlying hormonal milieu and target DNA sequence [2]. In particular, on genes stimulated by thyroid hormone, the TR recruits corepressors such as NCoR and SMRT in the absence of T3. NCoR and SMRT in turn recruit a repression complex, including in particular HDAC3, with histone deacetylase activity. Deacetylation of lysine residues on histones renders chromatin in a transcriptionally inactive state. The binding of T3 to the ligand-binding domain of the TR results in a conformational change in the receptor, the release of the corepressor complex, and the recruitment instead of numerous coactivators. Coactivators have many functions; for example, some coactivators acetylate lysine residues of histone, whereas others link the TR complex with the basal transcriptional machinery. The net result of these various processes is to increase transcription of target genes. There are actually multiple TR isoforms encoded by two separate genes (TRα and TRβ). These TR isoforms exhibit tissue-specific distribution patterns, and TRα1 may be particularly important for adrenergic signaling in adipose tissue [2], but TRβ1 may play an important role in UCP 1 expression in BAT [3].

Thyroid hormone plays a crucial role in brain development in the developing fetus, growth in children and regulates numerous processes in the adult body, including basal metabolic rate, energy expenditure, and thermogenesis. Thyroid hormone also regulates organ physiology such as heart rate and contractile function. Clinically, patients with hypothyroidism (*i.e.*, an underactive thyroid gland) often note weight gain and increased fat mass, though the effect actually remains somewhat controversial [4]. It is clear, though, that thyroid hormone is one of the major endocrine mediators of the basal metabolic rate [5]. In brown adipose tissue (BAT), thyroid hormone is a regulator of UCP1 expression, and *via* this mechanism thyroid hormone regulates adaptive thermogenesis [6]. Here we will focus primarily on the effects of thyroid hormone on white adipose tissue (WAT) differentiation and function.

2.1. Thyroid hormone and adipogenesis

Adipocyte differentiation, or adipogenesis, proceeds by an orderly series of events and depends on the expression of key transcription factors such as C/EBP isoforms and PPARγ [7]. Initially, proliferation of adipocyte precursors occurs, whereas differentiation into lipid-laden adipocytes occurs after this round of proliferation takes place. Thyroid hormone leads to distinct effects depending on the particular stage of this process [8]. Initially, thyroid hormone suppresses proliferation of the adipocyte precursors [9]. Interestingly, there is also evidence that Type 3 deiodinase activity increases during this phase as well [10], suggesting that local down-regulation of T3 levels may be important to allow the proliferative stage of adipogenesis to proceed.

In contrast, thyroid hormone has different effects during the later stages of adipogenesis. Carmona et al. showed that C/EBPα, a major transcriptional regulator of adipogenesis, influences thyroid hormone action in BAT in multiple ways. For example, deiodinase activity was decreased in BAT of C/EBPα knock-out mice, which resulted in significantly lower T3 content [11]. To more directly study the effects of TRs on adipogenesis, Mishra et al. generated 3 T3-L1 cell line variants expressing mutant thyroid hormone receptors that exhibit impaired thyroid hormone signaling [12]. Interestingly 3 T3-L1 adipogenesis was decreased in these cell lines. In addition, this group was able to clarify TR isoform requirements by generating TR isoform-specific mutations. Through this process, they showed that the TRα1 isoform was particularly important for adipogenesis. Interestingly, PPARγ and C/EBPα expression was decreased in the mutant cell lines, and TR was recruited to the C/EBPα promoter [12]. Other studies suggest that the mutant TRα1 could interfere with PPARγ transcriptional activity [13] and in general there may be additional pathways of cross-talk between TRs and PPARs [14]. To assess the role of TRs on adipogenesis *in vivo*, Ying et al. created a mouse expressing a mutant TRα1 [13]. As might be expected from the *in vitro* data above, these mice had a lean phenotype due to decreased WAT mass [13]. In contrast, mice expressing a mutant TRβ receptor had normal WAT mass, though there was excess lipid in the liver of these mice [3]. Thus, thyroid hormone is an important regulator of adipogenesis, and its actions are specifically dependent on the TRα1 isoform, though TRβ1 plays important roles in other metabolic tissues.

2.2. Thyroid hormone modulation of lipogenesis and lipolysis

The adipocyte stores energy in times of caloric excess through the process of lipogenesis, whereas adipocyte triglyceride is broken down to glycerol and free fatty acids (lipolysis) during periods of fasting. Counter-intuitively, thyroid hormone enhances both of these processes. Although the exact mechanism by which thyroid hormone stimulates lipolysis is not fully understood, it has been known for many years that thyroid hormone enhances catecholamine-mediated lipolysis in both isolated adipocytes [15] and patients with clinical hyperthyroidism [16]. Hyperthyroidism increases β-2 adrenergic receptor number and appears to increase signaling at the post-receptor level as well [16]. The specific mechanisms by which thyroid hormone regulates adrenergic receptor function at a post-receptor level, though, have been controversial. Most likely, thyroid hormone acts at many levels of the adrenergic signaling pathway [17], including cAMP formation, alteration in G-protein subunit expression, and through decreasing phosphodiesterase activity [18]. Thyroid hormone also regulates the sympathetic nervous system centrally, but in this case excess thyroid hormone decreases central sympathetic outflow [17]. Thus, most of the clinical effects of hyperthyroidism mediated by the sympathetic nervous system do not depend on central regulation of sympathetic outflow, but instead appear as result from altered responses to catecholamine peripherally.

Please cite this article as: C.M. Carmean, et al., Systemic regulation of adipose metabolism, Biochim. Biophys. Acta (2013), http://dx.doi.org/10.1016/j.bbadis.2013.06.004