

REVIEW

Thyroid hormone and the central control of homeostasis

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Abstract

It has long been known that thyroid hormone has profound direct effects on metabolism and cardiovascular function. More recently, it was shown that the hormone also modulates these systems by actions on the central autonomic control. Recent studies that either manipulated thyroid hormone signalling in anatomical areas of the brain or analysed seasonal models with an endogenous fluctuation in hypothalamic thyroid hormone levels revealed that the hormone controls energy turnover. However, most of these studies did not progress beyond the level of anatomical nuclei; thus, the neuronal substrates as well as the molecular mechanisms remain largely enigmatic. This review summarises the evidence for a role of thyroid hormone in the central autonomic control of peripheral homeostasis and advocates novel strategies to address thyroid hormone action in the brain on a cellular level.

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Introduction

Thyroid hormone has long been known for its profound effects on the metabolic rate and cardiovascular function (Magnus-Levy 1895, Klein & Ojamaa 2001). This becomes most evident in hyperthyroidism, which is accompanied by an increased metabolic rate and weight loss despite increased food intake as well as tachycardia (Klein & Ojamaa 2001, Kim 2008, Sainsbury & Zhang 2011). Conversely, weight gain and bradycardia are observed in hypothyroid patients (Kim 2008). Most of these effects have been attributed to the direct actions of thyroid hormones in the corresponding peripheral tissues such as the heart (Kahaly & Dillmann 2005) or metabolically active tissues such as skeletal muscle or fat (Short *et al.* 2001, Silva 2006). Several cellular mechanisms have been identified in these tissues (Short *et al.* 2001), which can explain the observed effects on the molecular level. However, recently, the concept has emerged that thyroid hormone also modulates these processes via one of its main target tissues – the brain (Fliers *et al.* 2010). This review summarises the currently available information on the actions of thyroid hormone in the brain with a focus on its interactions with the autonomic nervous system regulating metabolic and cardiovascular functions (see overview in Table 1).

Regulation of cellular thyroid hormone signalling

The main forms of thyroid hormone secreted by the thyroid gland are tetraiodothyronine (T_4) and 3,3', 5-triiodothyronine (T_3). T_4 has little biological activity by itself and is considered a prohormone, as activation occurs through outer ring deiodination to T_3 , the active form of thyroid hormone. The deiodination process is carried out by deiodinase type II (Dio2) or Dio1 (Bianco & Kim 2006). T_3 and T_4 can also be inactivated by inner ring deiodination carried out by Dio3 or Dio1, which leaves T_2 and reverse T_3 respectively. Whether these forms of thyroid hormone have inherent biological activity is still a matter of debate.

The level of deiodinase expression modulates the cellular availability of thyroid hormone. For instance, in activated brown fat, high levels of thyroid hormone are required for the upkeep of facultative thermogenesis – a condition that is achieved by the high expression of Dio2. Conversely, tissues that need protection from thyroid hormone express high levels of Dio3, e.g. the placenta, which shields the early developing embryo from overexposure to the hormone (Huang 2005).

Another level of regulation is the uptake of thyroid hormone into target organs or cells. While a few years ago it was still assumed that thyroid hormone can enter

Table 1 Summary of the central effects of thyroid hormone discussed in this review focussing on energy expenditure and uptake, seasonal adaptations and cardiovascular function

Affected system	Type of action	Consequence of central action
Energy expenditure	Acute	Thyroid hormone stimulates sympathetic output to brown fat (thermogenesis↑) and liver (gluconeogenesis↑)
	Developmental	Developmental hypothyroidism causes defective metabolic set point
Energy uptake	Acute	Thyroid hormone increases food intake via the hypothalamus
Body weight and reproduction	Seasonal	Modulation of hypothalamic thyroid hormone levels is needed for seasonal adaptations, e.g. body weight
Cardiovascular	Acute/developmental	Thyroid hormone interferes with the autonomic nervous system causing maladaptation upon stress, changes in temperature, activity, etc.

cells by passive diffusion through the cell membrane due to its lipophilic properties, this view has changed with the discovery of very specific hormone transporters such as the monocarboxylate transporter 8 (MCT8 (SLC16A2)) or organic-anion-transporting-polypeptide 1c1 (OATP1c1, OATP14) (Friesema *et al.* 2005, Visser *et al.* 2011). These molecules are essential for the uptake of thyroid hormones, which is impressively underlined by the observation that in the absence of MCT8, no significant amounts of T₃ can enter the brain (Dumitrescu *et al.* 2006, Trajkovic *et al.* 2007).

The final level of thyroid hormone signalling control is given by the expression of nuclear thyroid hormone receptors encoded by the genes *THRA* and *THRB* (Yen *et al.* 2006). These two genes give rise to several isoforms. The isoforms TR α 1 and TR β are regular thyroid hormone receptors, which bind DNA and T₃ and regulate transcription of target genes. By contrast, the isoform TR α 2 does not bind T₃ and probably constitutes another level of thyroid hormone signalling regulation as an antagonist (Yen 2001, Mittag *et al.* 2005, Yen *et al.* 2006). The functional TRs mediate the vast majority of thyroid hormone actions on the level of gene transcription; however, so-called non-genomic effects using other target molecules have been reported as well (Davis & Davis 1996).

Taken together, the activating and inactivating deiodinases, the specific transporters and the different receptor isoforms represent a fine regulatory system of cellular thyroid hormone signalling, somewhat independent of the levels of circulating hormone. More importantly, these elements can constitute specific genetic tools to manipulate thyroid hormone signalling on the cellular level using gain- or loss-of-function approaches.

Thyroid hormone acts developmentally and acutely in the brain

Thyroid hormone is of utmost importance for both the development and the maintenance of brain function (Bernal 2007). Disturbances in thyroid hormone

signalling during embryonal and early postnatal development can cause permanent defects in brain architecture (de Escobar *et al.* 2007), which persist into adulthood. In addition, transient alterations in thyroid hormone signalling in the adult also interfere with brain function; in contrast to developmental defects, however, these changes are usually reversible by appropriate treatment (Bernal 2007). Thus, when analysing the effects of thyroid hormone on peripheral homeostasis via the brain, it needs to be clearly established whether the observed phenotype is the consequence of a permanent developmental defect or an acute action of thyroid hormone. Often this information can be derived from the experimental or clinical paradigm, but in cases of congenital genetic problems – such as defects in thyroid hormone transport, activation or signalling – both aspects can overlap. This consequently results in a complex phenotype at different levels of homeostatic regulation mixing developmental and acute hormone actions.

Thyroid hormone modulates metabolism via the brain

The most investigated effects of thyroid hormone on the central control of homeostasis in rodents are those on metabolism and brown fat thermogenesis. Here, both developmental and acute actions of the hormone have been observed:

- Mice with a mutant thyroid hormone receptor α 1 show a profound hypermetabolism as a consequence of central brown fat overactivation (Sjogren *et al.* 2007). This hypermetabolic phenotype originates in embryonic brain development (Vujovic *et al.* 2009), where defective thyroid hormone receptor signalling seems to interfere with the proper establishment of the hypothalamic thermostat. As a consequence, the sympathetic drive to the brown fat is increased, which stimulates thermogenesis and energy expenditure in this tissue by a yet unknown mechanism independent of *UCPI*, as this gene was

found to be unaltered (Sjogren *et al.* 2007). A similar hypermetabolic phenotype has later also been observed in offspring from maternally hypothyroid sheep (Forhead *et al.* 2009); however, a recently found patient with a mutation in *TRα1* showed a borderline high body mass index (Bochukova *et al.* 2012). As this was also observed in a different *TRα1* animal model (Liu *et al.* 2003), it seems that different mutations in *TRα1* might give rise to different metabolic phenotypes – probably by altering the receptor's ability to interact with other nuclear coregulators.

- Acute hyperthyroidism is also associated with increased energy expenditure as well as hyperphagia in rodents (Lopez *et al.* 2010). Complex studies have been conducted to disassociate the central T_3 actions from its well-known peripheral effects (for a review see Mittag (2009)): injections of thyroid hormone into the arcuate nucleus increase food intake by up-regulating mammalian target of rapamycin (mTOR) and consequently increased mRNA levels of the orexigenic agouti-related protein (AGRP) and neuropeptide Y (NPY) as well as decreased expression of the anorexigenic

pro-opiomelanocortin (POMC; Varela *et al.* 2012). When injected into the ventromedial hypothalamus, they decrease the activity of the hypothalamic AMP-activated protein kinase (AMPK), thus increasing energy expenditure via stimulating brown fat thermogenesis through the sympathetic nervous system (Lopez *et al.* 2010). In the paraventricular nucleus, thyroid hormone elevates hepatic endogenous glucose production via the sympathetic nervous system (Klieverik *et al.* 2009). Although some of the underlying molecular targets have been identified (Fig. 1), many questions on the cellular and molecular level remain to be elucidated.

Thyroid hormone modulates seasonality via the brain

A different animal model that has and will no doubt continue to provide new insight into the central metabolic actions of thyroid hormone is the Siberian hamster (Warner *et al.* 2010). In contrast to the advanced but very interventive mouse/rat models, this rodent endogenously modulates hypothalamic thyroid hormone levels in adjustment to changing seasons.

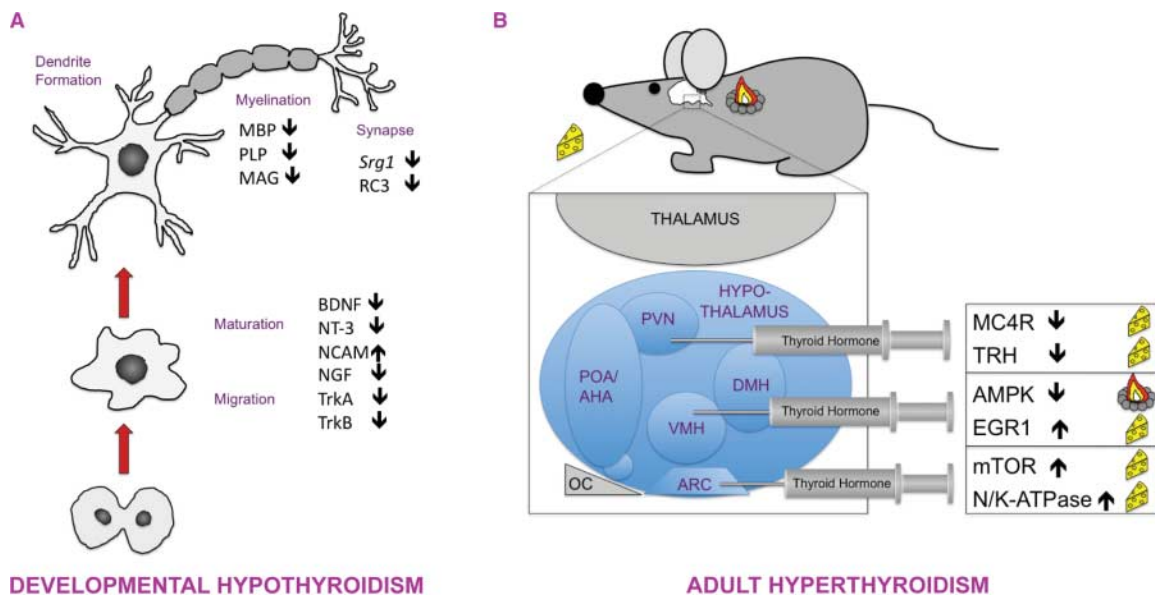


Figure 1 Developmental and acute targets of thyroid hormone in the brain. Identified targets of thyroid hormone during neuronal development (A) or in the adult hypothalamus (B), which may explain the effects of the hormone on central homeostasis. (A) Genes affected by developmental hypothyroidism (arrows indicate the directional effect of developmental hypothyroidism on gene expression; Alvarez-Dolado *et al.* 1994, Thompson and Potter 2000). (B) Genes found to be regulated by hypothalamic hyperthyroidism (arrows indicate directional effect of T_3 ; Lechan and Fekete 2006, Decherf *et al.* 2010, Lopez *et al.* 2010, Varela *et al.* 2012). Trk, neurotrophic tyrosine kinase receptor; NGF, nerve growth factor; NCAM, neural cell adhesion molecule; NT-3, neurotrophin 3; BDNF, brain-derived neurotrophic factor; MBP, myelin basic protein; PLP (PLP1), proteolipid protein 1; MAG, myelin-associated glycoprotein; *Srg1*, synaptotagmin-related gene 1; RC3, neurogranin; MC4R, melanocortin 4 receptor; TRH, thyrotropin releasing hormone; AMPK, AMP kinase; EGR1, early growth response protein 1; mTOR, mammalian target of rapamycin; N/K-ATPase, sodium–potassium ATPase; POA/AHA, preoptic area/anterior hypothalamic area; OC, optic chiasm; PVN, paraventricular nucleus of the hypothalamus; VMH, ventromedial hypothalamus; ARC, arcuate nucleus of the hypothalamus; DMH, dorsomedial hypothalamus.

Seasonality is an essential process for some species living in temperate or polar conditions, allowing the animal to anticipate the changing demands of the environment and to alter their physiology and behaviour accordingly. Studies on several photo-responsive species have shown an association between seasonality and local availability of T_3 in the hypothalamus, and more specifically, a correlation in expression of genes encoding for *Dio2* and *Dio3*, generally leading to a reduction in hypothalamic T_3 in a short day length (SD) across species, regardless of the species-specific enzyme levels (reviewed in Ebling (2010)). In the Siberian hamster, the use of hypothalamic implants providing a constant release of T_3 can prevent or recover the effects of SD on body weight loss (Barrett *et al.* 2007, Murphy *et al.* 2012). Additionally, torpor (a daily survival state of reduced metabolic activity during SD) is also prevented in these centrally T_3 -supplemented hamsters. Intact sympathetic signalling is required for torpor in mice and hamsters (Swoap & Weinshenker 2008, Braulke & Heldmaier 2010) and of particular importance is recovery from torpor via sympathetic activation of brown fat. Therefore, it is postulated that hypothalamic T_3 maintains a level of 'sympathetic tone' to prevent torpor, despite receiving seasonally driven signalling (Murphy *et al.* 2012).

Several studies have started to unravel the underlying central mechanism (Bechtold & Loudon 2007), which begins with the detection of a changing day length by the retino-hypothalamic pathway, triggering the output of melatonin from the pineal gland to target tissues. It has been hypothesised that this hormone then facilitates the release of TSH β from the pars tuberalis (Hanon *et al.* 2008), which in turn acts on the tanycytes, specialised ependymal cells lining the third ventricle of the hypothalamus (reviewed in Morgan & Hazlerigg (2008), Ebling (2010) and Dupre (2011)). The tanycytes are well known to play a crucial role in the regulation of hypothalamic thyroid hormone levels; in the Siberian hamster, an up-regulation of *Dio3* in tanycytes is observed, with the highest *Dio3* expression coinciding with the nadir in seasonal body weight (Barrett *et al.* 2007).

Despite the conclusive demonstration that changes in the availability of T_3 in the hypothalamus are crucial to facilitating seasonal changes in body weight, the downstream cellular and molecular targets of T_3 action in the seasonal regulation of energy metabolism still remain enigmatic.

Thyroid hormone modulates cardiovascular function via the brain

In addition to seasonal or acute metabolic adaptations, the brain also rapidly adjusts heart rate and blood pressure by the autonomic nervous system, for instance

upon alterations in environmental temperature (Swoap *et al.* 2008). As the symptoms of hyperthyroidism and catecholamine excess are clinically very similar, it was assumed for a long time that thyroid hormone might interact with the autonomic innervation of the heart. However, due to the very profound direct effects of the hormone on the cardiovascular system (Klein & Ojamaa 2001, Kahaly & Dillmann 2005), the subtle effects on the autonomic nervous system were often masked in experimental paradigms. More recent technologies, such as spectral analysis of heart rate variability, finally demonstrated a correlation between thyroid hormone levels and cardiac autonomic activity (Cacciatori *et al.* 2000, Burggraaf *et al.* 2001, Chen *et al.* 2006). Further studies on animal models showed that indeed thyroid hormone receptor $\alpha 1$ signalling is required for the autonomic adaptations of heart rate to stress, activity and temperature (Mittag *et al.* 2010). Despite the technological progress in the investigation of autonomic nervous system function, the underlying molecular mechanisms as well as the cellular targets remain poorly defined.

What are the cellular and molecular targets of thyroid hormone action in the brain?

The neuroanatomical substrates of thyroid hormone in the central control of the autonomic nervous system are largely enigmatic, often because the experimental techniques used are not precise enough to allow a resolution beyond the level of anatomical nuclei. For instance, a simple stereotaxic injection of thyroid hormone into the brain is likely to target all cells in that area and might even diffuse across the borders of neuroanatomical nuclei with additional side effects. Similarly, transfections or elimination of thyroid hormone receptors without cellular restrictions are expected to give rise to the same problem. Therefore, such an approach can only provide initial clues to the rough anatomical areas that might respond to thyroid hormone; it is suboptimal, however, in identifying specific cell populations and subsequently the underlying molecular mechanisms.

Consequently, to date, only a handful of thyroid hormone target genes have been identified at the cellular level in the brain (Thompson & Potter 2000, Santisteban & Bernal 2005). Some of them might indeed be implicated in the developmental defects caused by maternal or congenital hypothyroidism – such as problems with migration, incomplete axonal myelination or reduced dendrite and synapse formation (Fig. 1A) – while others could partially explain the acute effects of thyroid hormone on central homeostasis (Fig. 1B).

Nevertheless, novel model systems are sorely needed to investigate thyroid hormone signalling at the cellular

rather than the anatomical level and on the whole genome rather than the individual gene level. A big obstacle in the design of such studies is the poor quality of the commercially available TR antibodies; they often also give strong cytosolic staining, which is unlikely to result from specific binding to nuclear hormone receptors and rather indicates unspecific cross-reactivity. This lack of specificity in turn is likely to result in false positives in assays that depend on antibody quality such as chromatin immunoprecipitation or cell labelling by immunohistochemistry.

To overcome this obstacle, a novel animal model has been established recently, which expresses a TR α 1–GFP fusion protein. Subsequent analyses of these mice revealed that TR α 1 is expressed in almost all post-mitotic neurons (Wallis *et al.* 2010) with no detectable signal outside the nucleus. As the chimeric receptor has only minimal effects on the regulation of thyroid hormone target genes, this animal model will also be of value for chromatin immunoprecipitation experiments given the high quality of the available GFP antibodies.

Regarding the postmitotic expression of TR α 1 in almost all neurons, it is not surprising that thyroid hormone exerts a plethora of effects via the CNS and that it can act on migration and maturation during brain development as well as on neuronal function in the adult brain. More importantly, however, this finding underlines the necessity of cell-specific approaches to

unravel thyroid hormone signalling in the brain, as virtually all neurons in an anatomical nucleus, whether inhibitory or excitatory, can be expected to respond to alterations in thyroid hormone levels, maybe even with opposing effects.

Conclusion

Recent findings clearly demonstrate that thyroid hormone regulates peripheral homeostasis via central actions. This includes the cardiovascular system and metabolism, where the hormone seems to act in synergy with its peripheral actions, but also species-specific phenomena such as seasonality. However, all experimental paradigms that aim to address thyroid hormone actions on homeostasis need to carefully distinguish the central from the peripheral actions and the developmental from the acute actions of the hormone.

As thyroid hormone receptor is expressed in almost every postmitotic neuron, the step from the neuro-anatomical to the cellular level will be of particular relevance to understand the precise nature of thyroid hormone signalling in the brain. As genetic and neuroanatomical techniques have greatly advanced during the recent years, we are now equipped with the right tools to address these questions – in particular, the availability of several Cre mouse strains with

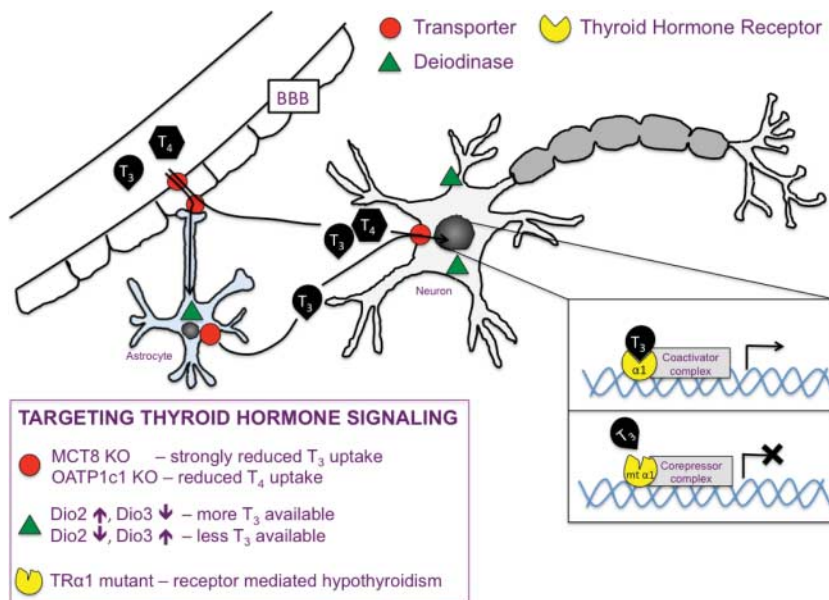


Figure 2 Targeting thyroid hormone signalling in the brain. Several different molecules such as transporters (circle), deiodinases (triangle) and receptors (pacman) are involved in controlling thyroid hormone actions in the brain (Heuer *et al.* 2005, Dumitrescu *et al.* 2006, Trajkovic *et al.* 2007, Wallis *et al.* 2010, Mayerl *et al.* 2012). BBB, blood brain barrier; Dio2/3, deiodinase type II or III; MCT8, monocarboxylate transporter 8; Oatp1c1, organic anion transporting polypeptide 1c1; TR, thyroid hormone receptor.

appropriate neuronal subtype specificity (Picou *et al.* 2012). Even more importantly, our knowledge on thyroid hormone signalling allows the design of genetic strategies to modulate hormonal action in a cell-specific manner (Fig. 2). In contrast to many other endocrine systems, we know about hormone activation, inactivation, selective transport and receptor function, which could be used in experimental paradigms such as

- the manipulation of thyroid hormone availability on the cellular level using specific neuronal promoters to reduce thyroid hormone import, e.g. by a conditional *Mct8* knockout,
- the combination of a specific Cre strain with the stereotaxic injection of a virus carrying a Cre-activatable mutant *TRα1* gene, or
- the isolation of defined neuronal populations from hypo- or hyperthyroid mice using fluorescence-activated cell sorting (Guez-Barber *et al.* 2012).

These types of experiments will allow identification of the effects of thyroid hormone on specific cell populations involved in the control of homeostasis and moreover will contribute to the unravelling of the underlying molecular mechanisms. Despite the fact that the toy itself is more than a century old, the playground for thyroid hormone has never been more promising.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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