REVIEW

Effects of thyroid hormones on thermogenesis and energy partitioning

K Alexander Iwen^{1,2,*}, Rebecca Oelkrug^{2,*} and Georg Brabant^{1,3}

¹Medizinische Klinik I, Experimentelle und Klinische Endokrinologie, Universität zu Lübeck, Lübeck, Germany

²Department of Molecular Endocrinology, Center of Brain, Behavior and Metabolism, Universität zu Lübeck, Lübeck, Germany

³Department of Endocrinology, The Christie Manchester Academic Health Science Centre, Manchester, UK

Correspondence should be addressed to G Brabant: Georg.Brabant@uksh.de

*(K Alexander Iwen and R Oelkrug contributed equally to this work)

Abstract

Thyroid hormones (TH) are of central importance for thermogenesis, energy homeostasis and metabolism. Here, we will discuss these aspects by focussing on the physiological aspects of TH-dependent regulation in response to cold exposure and fasting, which will be compared to alterations in primary hyperthyroidism and hypothyroidism. In particular, we will summarise current knowledge on regional thyroid hormone status in the central nervous system (CNS) and in peripheral cells. In contrast to hyperthyroidism and hypothyroidism, where parallel changes are observed, local alterations in the CNS differ to peripheral compartments when induced by cold exposure or fasting. Cold exposure is associated with low hypothalamic TH concentrations but increased TH levels in the periphery. Fasting results in a reversed TH pattern. Primary hypothyroidism and hyperthyroidism disrupt these fine-tuned adaptive mechanisms and both, the hypothalamus and the periphery, will have the same TH status. These important mechanisms need to be considered when discussing thyroid hormone replacement and other therapeutical interventions to modulate TH status.

Key Words

- ▶ thyroid hormone
- ▶ energy homeostasis
- ▶ thermogenesis
- ▶ cold
- ▶ heat
- ▶ lipid metabolism
- ▶ glucose metabolism

*Journal of Molecular
Endocrinology*
(2018) **60**, R157–R170

Introduction

Thyroid hormones (THs) are key in regulating energy homeostasis in both humans and rodents. Maintaining core body temperature is critical for homeothermic species and thermoregulation requires fine-tuned energy partitioning. Here, we will summarise major components of thermoregulation as well as TH-mediated effects on these. We will discuss the contribution of the central nervous system (CNS) as well as peripheral organs and tissues to these processes. Further, we will summarise the effects of (i) cold or heat exposure and (ii) fasting or fed states on metabolic processes. Finally, the disruption of

these fine-tuned mechanisms by hyperthyroidism and hypothyroidism will be addressed.

Components of thermoregulation

In homeothermic species, thermal regulation is composed of a number of mechanisms designated to tightly control core body temperature to ensure optimal regulation of metabolic processes. In cooler environments endogenous, activity-dependent heat production of energy demanding metabolic cycles needs to be balanced with heat loss from

the body surface. Insulation of the body by fur represents an important mechanism to control heat loss (Cannon & Nedergaard 2011, Kasza *et al.* 2014, 2016, Alexander *et al.* 2015, Fischer *et al.* 2016), while the insulating effects of intradermal fat has been questioned at least in rodents (Fischer *et al.* 2016). Vasoconstriction or vasodilatation serves as additional major mechanisms to regulate body temperature via heat loss or conservation by peripheral body parts (Tansey & Johnson 2015). Further, behavioural changes may help to defend core body temperature in heat or cold exposure (Terrien *et al.* 2011), which is in humans reinforced by the option to change clothing and control the immediate environment by applying heaters or air-conditioning.

Heat production of the body is based on obligatory and facultative thermogenesis. Within the thermoneutral zone (TNZ), obligatory thermogenesis of basal metabolism is sufficient to maintain body temperature. A decrease of ambient temperature below the TNZ activates cold-sensitive thermoreceptors of the skin, reinforces cutaneous vasoconstriction and piloerection to optimise insulation and induces facultative thermogenesis, which consists of shivering and non-shivering thermogenesis.

Shivering thermogenesis is characterised by an activation of involuntary muscle activity to produce heat (Silva 2006), whereas non-shivering (or adaptive) thermogenesis depends predominantly on the activation of brown adipose tissue (BAT) (Cannon & Nedergaard 2004). Non-shivering thermogenesis is mainly initiated by a cutaneous cold-sensation, which via cold-sensitive thermoreceptors activates the sympathetic nervous system (SNS) (Nakamura & Morrison 2008). Subsequently, the SNS stimulates the release of noradrenaline from postganglionic sympathetic fibres and induces β 3-adrenergic receptor (ARB3)-mediated pathways that activate lipolysis and the release of free fatty acids (FFA, reviewed in Oelkrug *et al.* 2015). FFA stimulate mitochondrial energy dissipation by activation of the uncoupling protein 1 (UCP1) in the inner mitochondrial membrane. In the inactivated state, UCP1 is constitutively inhibited by purine nucleoside di- and triphosphates, but the release of FFA overcomes this inhibition (Heaton *et al.* 1978). Activated UCP1 acts as a proton channel, allowing protons to bypass the proton pathway commonly used by ATP synthase and thereby dissipates the proton motive force as heat instead of ATP; the exact mechanism, however, has not been resolved so far (Crichton *et al.* 2017). Additionally, UCP1 provokes the activation of the respiratory chain and cellular fatty acid oxidation to compensate for the loss in produced ATP (Ricquier 2017). UCP1 activity is

essential for BAT-mediated facultative thermogenesis, which is clearly shown by the thermogenic phenotype of UCP1-ablated mice (Enerback *et al.* 1997, Golozoubova *et al.* 2001). Furthermore, UCP1 activity has been shown to be important for maintaining a well-balanced energy homeostasis, as UCP1-knockout mice gain more body weight compared to controls when kept on a high-fat diet at thermoneutral conditions (Feldmann *et al.* 2009). The effect of non-shivering, facultative thermogenesis is particularly obvious in small rodents which have an unfavourable relation of body surface area to body volume and are thereby extremely sensitive to changes in ambient temperature. In these animals, cold exposure to 4°C increases oxygen consumption by 2- to 4-fold, mainly via an increase in efferent sympathetic activity to BAT and muscle (Lowell & Spiegelman 2000). While it was long believed that BAT was restricted to rodents and new-born humans, the rather recent description of BAT in adult humans has sparked a growing interest in human BAT-thermogenesis and its effects on the human metabolism (Cannon & Nedergaard 2012).

On the other hand, an increase in ambient temperature above the TNZ triggers processes that are also energy consuming. In response to a heat challenge, heat-dependent thermoreceptors of the skin are activated to induce vasodilatation and sweating (Cannon & Nedergaard 2004). These mechanisms increase heat loss via the body surface and thereby allow to decrease body temperature and to maintain it at an optimal level. In addition, the metabolic needs of the body are reduced by inactivity (Tansey & Johnson 2015).

Conclusively both, heat production as well as heat conservation, clearly increase energy expenditure above the needs in thermoneutrality (Cannon & Nedergaard 2004, Silva 2005, Westerterp 2017).

Thyroid hormones and the regulation of thermogenesis

The role of THs to directly stimulate energy expenditure has been well described and studied in great detail, whereas its role in the regulation of body temperature has not been completely elucidated as yet. It is widely accepted that THs modulate thermogenesis directly by changing the functionality and transcription rate of UCP1 and obligatory thermogenesis by increasing metabolic cycling or by direct actions on the sodium/potassium and the calcium pump in skeletal muscle (Silva 2006). In addition to these peripheral effects, THs affect sympathetic nervous system activity and interact with the central control of

SNS outflow and also with the energy partitioning of substrate fluxes in the periphery. The effects of THs on central and peripheral components of thermoregulation will be systematically discussed in the following parts of this article.

Central regulation of core body temperature by thyroid hormones

As confirmed in multiple experimental models of hypothyroidism and hyperthyroidism, both in animal models and humans, THs may act directly on key metabolically active organs and thus alter obligatory thermogenesis. This aspect of thermogenesis may also be regulated via the central nervous system, but the main impact of these central regulators is to integrate different external stimuli and to adapt facultative thermogenesis accordingly (Coppola *et al.* 2007, Herwig *et al.* 2008, Klieverik *et al.* 2009b, Lopez *et al.* 2010). This regulatory circuit respond to changes in external temperature clues sensed e.g. by skin temperature sensors but also directly to alterations in core body temperature via a complex, multilocular central nervous system of temperature sensitive centres interacting with different aspects of thermal regulation.

Within the past years, novel complex interactions within the hypothalamus regarding THs, thermogenesis and energy partitioning, have been revealed mainly in rodents. Here, we will restrict the discussion to centres in the dorsomedial (DMH), the ventromedial (VMH), the preoptic area (POA), and the paraventricular nucleus (PVH) of the hypothalamus because all regions have been shown to interact with THs. Most importantly, the PVH contains hypophysiotropic TSH-releasing hormone (TRH) neurons, which regulate the HPT and sensitively respond to changes in TH status by reducing TRH release into the hypothalamo-hypophyseal portal system. Anatomically, hypophysiotropic TRH neurons are located in a species-specific manner: In rats, they are only located in the medial and periventricular subdivisions at the mid and caudal levels of the PVN, in mice, these neurons can be found only at the mid-level of the PVN (Fekete & Lechan 2014). The TRH-thyroid-stimulating hormone (TSH)-TH feedback loop is mediated by a direct activation of thyroid hormone receptor (TR) isoform β -dependent signalling to decrease TRH and TSH secretion. Recent observations suggest an important modulating role of tanycytes at the blood-brain barrier to control hypothalamic TH concentrations (Muller-Fielitz *et al.* 2017). Following cold exposure, TRH neurons are activated and induce an

increase in preproTRH processing, release of TRH from the median eminence and a subsequent stimulation of the thyroid with higher circulating TH levels (Nillni 2010). Thus, both TRH/TSH and TH concentrations are increased indicating an alteration of the set-point of the hypothalamic-pituitary-thyroid (HPT) axis following cold stimulation, an observation confirmed in humans (Celi *et al.* 2010, Joseph-Bravo *et al.* 2016).

The PVH neurons receive input from other central regions such as the POA (Larsen *et al.* 1994). The latter respond to peripheral vascular temperature sensors, which detect changes in ambient temperature and/or core body temperature. In addition, these sensors transmit afferent autonomic signals to the brain stem and the POA of the hypothalamus. Direct heating or cooling of the POA results in a modulation of thermogenesis by changing efferent SNS-signalling through activation of γ -aminobutyric acid (GABA)ergic neurons, which project to the dorsomedial DMH and the VMH (Morrison 2016). Activation as well as inhibition of these neurons powerfully decreased or increased core body temperature by app. 2°C by modulating sympathetic tone to BAT, liver and muscle (Tan *et al.* 2016, Zhao *et al.* 2017).

Cooling of the POA has direct effects on the regulation of the HPT. In rats, it induces a shift of the set-point of the TRH-TSH-TH axis and an increased release of THs (Martelli *et al.* 2014). In contrast, i.c.v. injections of triiodothyronine (T3) with an increased T3 concentration in the POA results in a dose-dependent decrease in TRH and TSH, interestingly accompanied by a drop in core temperature (Moffett *et al.* 2013). Both observations obtained in a difficult methodological setting and so far, unconfirmed indicate a direct regulatory role of the POA to link core body temperature and thyroid function.

Apart from these TRH-mediated adaptations of the hypothalamic-pituitary-thyroid axis and subsequent changes in TH-regulated thermogenesis, TRH affect thermogenesis of the BAT by activating BAT-innervating neurons in the spinal cord. Cold exposure activates cold-sensitive hypothalamic neurons that express TRH. These neurons subsequently activate neurons in the spinal cord, thereby increasing the sympathetic outflow to BAT (Cabral *et al.* 2012). Through both mechanisms TRH may thus mediate thermogenesis, and this explains why TRH-knockout mice are intolerant to cold (Yamada *et al.* 2003).

Thyroid hormones and energy partitioning

The arcuate nucleus (ARC) is located close to the median eminence and is key in integrating peripheral information

on energy stores, nutritional and metabolic signals due to its anatomical site with a relatively permeable blood–brain barrier (Smith & Ferguson 2014). As discussed in multiple excellent reviews, the ARC is central to the control of food intake and energy expenditure either directly or via close neuronal interaction with other hypothalamic centres such as the PVH, DMH or VMH (Cone 2005, Krashes *et al.* 2016). NPY/AGRP-positive neurons of the ARC dominate the regulation of energy intake whereas proopiomelanocortin- (POMC) and melanocortin receptor subtype 4- (MC4R) ARC neurons control energy expenditure.

Both are targets of the TH feedback loop. By that they act as a relay centre integrating TH-dependent signalling on energy partitioning and the distribution of metabolic cycling in response to temperature challenges. Changing the nutritional supply expressed by an increase of glucose concentrations within the physiological range induces an increase in TRH expression (Breit *et al.* 2016). These *ex vivo* and *in vitro* experiments indicating a direct nutritional link on the HPT axis fit well with the inhibition of preproTRH (and CRH) in the PVH during fasting, a process again controlled by the ARC. In knockout mice lacking either MC4R or NPY or both, the drop of TRH, TSH and peripheral TH could convincingly be attributed to NPY/AGRP indicating a nutritionally driven link to the central control of the thyroid axis. This is paralleled by a hepatic, MC4R and NPY governed effect on the metabolism of thyroxine (T₄) and T₃ (Vella *et al.* 2011). T₃ repress MC4R within the PVH and ARC in a dose-dependent manner by specifically binding to TRA and TRB (Decherf *et al.* 2010). T₃ availability in these nuclei is regulated by uptake of T₄ (and T₃) from the blood into the surrounding microglia where the deiodinase type 2 (DIO2) converts T₄ to T₃. Both hormones are delivered via a monocarboxylate transporter 8-dependent mechanism to their targets in the ARC, i.e. AGRP-positive neurons. Microglial DIO2 appears to be acutely upregulated during starving, whereas an increased mitochondrial biogenesis is regarded to play an important memory function to regulate food intake following starvation and to compensate for the accompanying weight loss (Coppola *et al.* 2007).

The described physiological pattern of inhibition or activation of TRH under starvation or abundant energy supply alters the setpoint of the HPT axis and by that modulates the peripheral metabolism. Leptin has a pivotal role in mediating this adaption. Leptin levels drop in response to food deprivation, causing a shift in the HPT axis setpoint via the ARC (previously summarised in detail (Fekete & Lechan 2014)). In the fasted state, local T₃ levels

also rise in the ARC and the excitability of AGRP neurons increases. Via projections to the PVH, AGRP release suppresses TRH processing and secretion by inhibiting MC4R (Decherf *et al.* 2010). This mechanism alters the setpoint of the HPT axis with lower TRH and subsequently TSH concentrations for a given circulating TH level. The pattern is in line with observations in hypothyroid rats. When local hypothalamic levels of T₃ decreased, AGRP expression decreased in parallel; this could be reversed by acute T₃ application (Herwig *et al.* 2008). It thus fits closely to the above discussed modulation of the setpoint by a cold or hot environment where similar changes in the activity of TRH processing was observed (Fig. 1). Lopez and coworkers further delineated the biochemical cascade of T₃ feedback on hypothalamic centres and stressed the importance of the VMH for the feedback of TH. Following acute T₃ administration, they identified adenosine monophosphate-activated protein kinase (AMPK) as the major signalling target. T₃ decreased AMPK, which increased malonyl-CoA, decreased carnitine-palmitoyl-transferase (CPT) alongside with an increased AGRP/NPY expression, which activated the SNS outflow and acutely induced hyperthermia at thermoneutrality (Lopez *et al.* 2010, Lage *et al.* 2016).

Recent data indicate that co-receptors of the TH receptors, like retinoid X, farnesoid X and liver X receptor (LXR), play an important role in the regulation of the negative feedback of TH on the hypothalamus, dominantly mediated via TRB (Ribeiro *et al.* 2001, Mullur *et al.* 2014). LXR, activated by cholesterol metabolites and oxysterols, represses TRH synthesis and release. They alter the setpoint of the HPT axis, but at the same time, MC4R pathways are repressed and AGRP is activated, a process which could be counteracted by T₃ (Ghaddab-Zroud *et al.* 2014). These data illustrate that the HPT axis may be activated or inhibited by a central modulation of local hypothalamic TH levels, caused by temperature-dependent or nutritionally derived cues that, in conjunction with a modulation of other factors like the SNS activity, will alter the peripheral regulation of TH-dependent metabolic pathways in target organs like BAT, WAT, liver and muscle.

Interestingly, the VMH also modulates a peripheral feedback via leptin and insulin signalling. Insulin sensitivity is markedly increased by selective deletion of activating transcription factor 4 (ATF4) in AGRP neurons. This deletion was paralleled with decreased WAT and increased BAT activity as well as core body temperature of the animals, a pattern also observed in response to cold exposure (Deng *et al.* 2017). It appears to be mediated by stimulation of phosphatidylinositol-4,5-bisphosphate

Figure 1

Neurohumoral and metabolic adaptations to (A) cold exposure and (B) fasting. Selected interactions between relevant hypothalamic nuclei, consecutive neurohumoral signalling and resulting effects on metabolically important organs and tissues are depicted. Details are discussed in the summary section of the main text. Well-established effects are represented by solid lines while more recently described interactions are illustrated by dotted lines. ARC, arcuate nucleus; BAT, brown adipose tissue; DMH, dorsomedial hypothalamus; HPT, hypothalamic-pituitary-thyroid; NA, noradrenaline; POA, preoptic area; PVH, paraventricular nucleus of the hypothalamus; SNS, sympathetic nervous system; TRH, TSH-releasing hormone; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; VMH, ventromedial hypothalamus; WAT, white adipose tissue.

3-kinase and subsequent forkhead box O1 (FOXO1) inhibition in the ARC. FOXO1-knockout animals are characterised by increased energy expenditure. Conversely, FOXO1 upregulation increases AGRP expression in ARC, increases food intake and decreases body core temperature as well as BAT activity as measured by UCP1 expression (Hasegawa *et al.* 2012, Deng *et al.* 2017). Sirtuin 1 which co-regulates TRs appears to be an important modulator of FOXO-1 (Suh *et al.* 2013, Cyr *et al.* 2015). In addition, necdin, which negatively regulates the activity of FOXO1 in the ARC, is regulated by T3. Necdin is downregulated in hyper- and upregulated in hypothyroidism, it may contribute to TH-mediated energy partitioning and to the modulation of the HPT axis, the later by its effects on PVH expression of TRH (Hasegawa *et al.* 2012).

ATD4 as well as necdin again appear to modulate the setpoint of the HPT and in part of the thermostat. Novel data suggest that other factors important for the feedback regulation may also interact with the setpoint of the thyroid axis.

Thyroid hormone-mediated effects on adipose tissue

The major function of WAT is to store energy, which may be mobilised in situations of increased demand such as cold stress, fasting or disease. With the discovery of leptin, the role of WAT as an active player in the control of energy homeostasis has been established (Zhang *et al.* 1994, Luo & Liu 2016). Mobilisation of substrates is regulated by SNS activity and at the cellular level is mainly mediated through ARB3-induced lipolysis in WAT (Mund & Frishman 2013). Interestingly, in humans, WAT of different anatomical locations is characterised by a different sensitivity to lipolysis, which is greater in visceral than in subcutaneous WAT (Wajchenberg 2000). Depot-specific differences in lipolysis rates can also be seen in mice (Wuest *et al.* 2012).

As mentioned earlier, BAT contributes significantly to thermogenesis, in a SNS-mediated fashion, for which it uses mainly triglycerides and glucose. These substrates can be provided (i) directly from dietary sources but, especially in the fasted state, are (ii) mobilised from stored energy in WAT and BAT. To facilitate a rapid breakdown of triglycerides for beta oxidation, BAT persists of multilocular cellular lipid droplets and thus provides a high lipid surface (Keipert & Jastroch 2014). Furthermore, it displays a high mitochondrial content of up to 8% to facilitate high-energy turnover rates (Rousset *et al.* 2004).

Whereas mice and rats possess BAT throughout their entire life span, BAT expression is limited to certain ages in other species, e.g. in lambs and rabbits, it disappears several days to months after birth (reviewed in [Oelkrug *et al.* 2015](#)). In humans, BAT was regarded to be restricted to a short period after birth, but recently has been detected in adults using [18F]-fluorodeoxyglucose positron emission tomography-computed tomography techniques ([Nedergaard *et al.* 2007](#), [Cypess *et al.* 2009](#), [van Marken Lichtenbelt *et al.* 2009](#), [Virtanen *et al.* 2009](#), [Iwen *et al.* 2017](#)). Remarkably, brown adipocytes are not restricted to the classical BAT depots but can also develop within WAT upon adrenergic stimulation or pharmacological intervention ([Keipert & Jastroch 2014](#), [Warner & Mittag 2016](#)). This so-called 'browning' of WAT and the subsequent development of beige or brite ('brown in white') adipose tissue, has recently been proposed as a major target for the treatment of metabolic disorders in humans ([Petrovic *et al.* 2010](#), [Harms & Seale 2013](#)), as this depots may add to heat production and energy partitioning under certain (patho-) physiological conditions ([Cohen & Spiegelman 2015](#)). However, it is still a matter of debate if adult human 'BAT' predominantly consists of brown or brown-like (beige) adipocytes and if beige adipocytes can contribute to higher energy turnover rates ([Warner & Mittag 2016](#)).

THs also induce 'browning' of WAT by direct and indirect effects. In the central nervous system, administration of T3 to the VMH, but not to the ARC, induces 'browning' of WAT as shown by increased expression of markers like UCP1, cidea and peroxisome proliferator-activated receptor gamma coactivator 1 alpha ([Martinez-Sanchez *et al.* 2017](#)). Further, the 'browning' of WAT by a conjugate of T3 and glucagon which allows to selectively target only glucagon receptor positive tissues including WAT and liver, suggests T3-specific effects on WAT ([Finan *et al.* 2016](#)). TRB agonists ([Lin *et al.* 2015](#)) and hyper- and hypothyroidism in a rodent model also mediated thermogenesis ([Weiner *et al.* 2016](#), [Martinez-Sanchez *et al.* 2017](#)). In line with these findings, association studies suggest similar direct effects in humans ([Martinez-Sanchez *et al.* 2017](#)).

Interestingly, TSH has been implicated in mediating similar direct effects on WAT. In elegant but currently not independently reproduced experiments, Endo and Kobayashi dissected an isolated lipolytic effect of TSH on WAT in mice bearing a mutation of the TSH receptor (hyt mice). By induction of lipolysis, TSH regulated fuel availability for BAT. It exerted further direct TSH receptor-driven effects on UCP1 expression and thermogenesis in

BAT ([Endo & Kobayashi 2008, 2012](#)). This suggested role of TSH may provide an additional mechanism to increase FA levels during both, cold exposure and fasting.

In both, WAT and BAT, the cellular concentration of T3 can be modified, as deiodinase 1 (DIO1) and DIO2 are expressed in WAT and DIO2 in BAT ([Calvo & Obregon 2011](#)). Studies in general or fat specific DIO2-knockout animals ([Christoffolete *et al.* 2004](#), [Castillo *et al.* 2011](#), [Fonseca *et al.* 2014](#)) support an important role of intracellular T3 in BAT for fatty acid oxidation and lipogenesis. The latter may impair thermogenesis, a defect that could be overcome by an increased lipolysis through compensatory stimulating SNS input. T3 activates UCP1 in concert with the systemic nervous system and fatty acids ([Reitman *et al.* 1999](#), [Lanni *et al.* 2003](#), [Sell *et al.* 2004](#)), and these effects are mediated by stimulation of adiponutrin, a triacylglycerol lipase, which hydrolyses triacylglycerol to fatty acids in WAT and BAT ([Obregon 2014](#)). In contrast, lipoprotein lipase (LPL) is downregulated by T3.

The different isoforms of thyroid hormone receptors TRA1, TRA2 and TRB1 are detectable in WAT and BAT. TRB expression in BAT is closely linked to UCP1 expression, while adrenergic responsiveness of thermogenesis is TRA dependent ([Ribeiro *et al.* 2001](#)). A loss of TRA1 function, at least with a TRA P398H mutation, induces a predominantly increase in visceral body fat. This is associated with a reduction in adaptive thermogenesis ([Liu *et al.* 2003, 2007](#)) along with an impaired lipolysis, insulin resistance and hyperleptinemia ([Bianco & Silva 1988](#), [Hernandez & Obregon 1996](#)).

Thyroid hormone-mediated effects on the liver

TH act on hepatic lipid partitioning via low-density lipoprotein (LDL)-receptor (LDLR)-dependent and -independent pathways. Studies in mice suggest that a wide variety of known TH transporters are expressed in the liver. Hyperthyroidism significantly increased monocarboxylate transporter 10 (MCT10) and large amino acid transporter-1 (LAT1) expression ([Engels *et al.* 2015](#)) as well as DIO1. Interestingly, DIO1 has recently been shown to be greatly downregulated in insulin receptor-knockout animals, and this is paralleled by reduced apolipoprotein A1 (*Apoa1*) gene expression as well lowered high-density lipoprotein (HDL) cholesterol levels ([Liu *et al.* 2016](#)). This regulation of DIO1 and its impact on HDL cholesterol thus reflects pathophysiological changes observed in the metabolic syndrome. It appears to be mediated via a specific thyroid hormone response element and does not

reflect general hepatic hypothyroidism as total hepatic T3 levels remained constant. Further, DIO2-knockout animals are insulin resistant with clearly increased hepatic triglycerides under high-fat diet (Marsili *et al.* 2011) fitting to observations in humans with a polymorphism of DIO2 (Mentuccia *et al.* 2002, Dora *et al.* 2010).

The partitioning of energy from WAT to the liver is achieved by a TH-dependent action on specific transporters such as fatty acid transporter proteins, liver fatty acid (FA)-binding proteins and FA translocase in hepatocytes. Hyperthyroidism increases and hypothyroidism decreases this triglyceride-derived FA uptake into the liver (Klieverik *et al.* 2009a). TH stimulate the known key lipogenic transcription factors sterol regulatory element-binding protein-1c (Hashimoto *et al.* 2006), LXR (Hashimoto *et al.* 2007) and carbohydrate-responsive element-binding protein (Hashimoto *et al.* 2009) and stimulate transcription of central lipogenic enzymes such as acetyl-CoA carboxylase, malic enzyme, fatty acid synthase, and Spot14 (Liu & Brent 2010). Resistance to TH induced by TRB mutations have been studied in the model of PV/PV mice (Cheng *et al.* 2010, Zhu & Cheng 2010). They demonstrated markedly increased hepatic lipid accumulation, whereas silencing of TRA resulted in decreased expression of lipogenic genes. This suggests a fine-tuning of lipid partitioning via TR-specific pathways (Fozzatti *et al.* 2011). Another important mechanism for hepatic lipid regulation is oxidation of FA controlled by TH derived from WAT but as well be released from triglyceride stores within the liver via hepatic lipases. Prolonged exposure to TH increases FA oxidation (Oppenheimer *et al.* 1991) through hepatic lipase (Nozaki *et al.* 1992). An even more important mechanism than this stimulation of hepatic beta-oxidation of FFA by TH is an increase of lipophagy under TH (Sinha *et al.* 2012, Liu & Czaja 2013). Inhibition of this autophagic process *in vitro* significantly influences ketogenesis indicating impairment of beta-oxidation via a TRB-associated process (Sinha *et al.* 2012, 2014). THs further affect CPT1 and AMPK in the liver just as described for hypothalamic centres. In addition, recent data suggest a role of TSH via TSH receptor-mediated pathways on AMPK activity (Zhang *et al.* 2015b). There are additional CPT1-dependent effects on glycolysis, which is positively controlled by TH. As shown for the hypothalamic regulation, CPT1 and pyruvate dehydrogenase lipoamide kinase isozyme 4 important for energy sensing are modulated via a direct interaction of T3 with sirtuin1 (Thakran *et al.* 2013).

Apart from direct action of TH on LDLR-dependent pathways, there are additional T3 effects on lipid

partitioning independent of LDLR as both, T3 and the TRB agonist GC1, effectively lower serum cholesterol in LDLR knockout mice by stimulation of Cyp7A1 (Lin *et al.* 2012). Expression of Cyp7A1 induces metabolism of cholesterol to bile acids (BA) and stimulates their excretion (Bonde *et al.* 2014). BA acts through a specific receptor, TGR5, expressed in the small intestine but also in BAT, skeletal and cardiac muscle, liver, pancreas and the thyroid (Duboc *et al.* 2014). BA-activated TGR5 stimulates intracellular cAMP formation in BAT, activates DIO2 most likely through an interaction with tauroursodeoxycholic acid (Watanabe *et al.* 2006, da-Silva *et al.* 2011), and this induces thermogenesis in BAT. On the basis of association studies, it seems likely that this applies as well to humans (Ockenga *et al.* 2012), but this was only confirmed in normal-weight but not in obese subjects (Brufau *et al.* 2010). BA and TSH levels are negatively associated (Patti *et al.* 2009, Ockenga *et al.* 2012, Song *et al.* 2016). There is a putative negative feedback of BA on the pituitary via pituitary TGR5 (Doignon *et al.* 2011, Ockenga *et al.* 2012), but TSH may directly suppress BA formation and secretion via SREBP-2/hepatocyte nuclear factor 4 alpha/CYP7A1 signalling (Song *et al.* 2015). Hyperthyroidism, most likely via TRB dependent activation, reduces proprotein convertase subtilisin/kexin type 9 (PCSK9) in circulation, lipoprotein cholesterol, apolipoprotein B and APOA1 as well as lipoprotein (a) but has no effect on cholesterol synthesis (Bonde *et al.* 2014).

By interaction of the transcription factors TRB, retinoid X receptor and peroxisome proliferator-activated receptor (PPAR) alpha, T3 apparently stimulates fibroblast growth factor 21 (FGF21). These findings are exciting as in animal models, FGF21 has recently been shown to modulate hedonic eating behaviour and suppress the intake of sweet food (Talukdar *et al.* 2016, von Holstein-Rathlou *et al.* 2016). However, investigations in FGF21 knockout animals suggest that TH and FGF21 are independently regulated and may replace each other in certain critical metabolic situations (Domouzoglou *et al.* 2014, Zhang *et al.* 2015a). This fits to data in humans in whom no change in FGF21 was observed in hyperthyroidism or TRB agonist treatment (Bonde *et al.* 2014).

Thyroid hormone-mediated effects on glucose metabolism via pancreatic beta-cells and myocytes

The effects of TH on glucose metabolism have been recently reviewed in several extensive reviews including some of our group (Duntas *et al.* 2011, Iwen *et al.* 2013).

The hypothalamic changes associated with fasting and thus low glucose availability or high energy intake have been discussed above in the chapter related to the action of TH in energy partitioning.

Therefore, we will only shortly summarise some of the key data of TH action in primary hyperthyroidism or hypothyroidism and discuss the most recent studies published in more detail. Oral glucose tolerance testing in hyperthyroidism and hypothyroidism both show an increased cumulative glucose and insulin response indicating significant TH dose-dependent insulin resistance (Mitrou *et al.* 2010). This was surprising as other data on the expression of glucose transporters suggest parallel tissue-specific upregulation of glucose transporter (GLUT) 1, 3, 4 and 5 by TH with decreased levels in hypo- and increased in hyperthyroidism. While in hypothyroidism insulin resistance rests directly on decreased transport of glucose to the respective tissue along with a decreased clearance of insulin, the development of insulin resistance in thyrotoxicosis is unclear. It has been discussed that it depends on a downregulation of hepatic glycogen synthesis and increased glycogenolysis under thyrotoxic conditions. In contrast, in a recently published rat model, glucose tolerance improved by 15% with an improvement in insulin resistance index by 34% when the animals were rendered hyperthyroid for a prolonged period of time (Vazquez-Anaya *et al.* 2017). These discrepant results were explained by increased transport of TH to the muscle and by an upregulation of the TH transporter MCT10 and the intramuscular DIO2. Thus, the availability of T3 and of glucose in the muscle seems to be fine-tuned by TH. Upregulation of sirtuin1 and UCP2 suggest a stimulation of glucose turn-over (Vazquez-Anaya *et al.* 2017). In addition, AMPK activity in skeletal muscle is upregulated in hyperthyroid states (Park *et al.* 2002, Winder *et al.* 2003, Branvold *et al.* 2008, Irrcher *et al.* 2008).

The data on direct effects of TH on the beta-cell mass and on insulin secretion and secretion are even more controversial. In the rat beta-cell line RIN5F, beta-cell proliferation appears to be stimulated via TRA-dependent signalling and the release of insulin is increased *in vitro* and *in vivo* (Furuya *et al.* 2010, Harris *et al.* 2017). In contrast, *ex vivo* studies following treatment with high doses of T3 suggest an increased apoptosis of beta-cells fitting to studies on the effects of experimental hypothyroidism during the last weeks of ovine gestation where a stimulated beta-cell mass and hyperinsulinemia was found (Jorns *et al.* 2010, Harris *et al.* 2017). With the known effects of hypothyroidism on insulin resistance, the latter findings could be explained by an indirect

effect of insulin resistance on the beta-cell. This might as well explain a stunning effect of TH replacement in a single patient with an insulin receptor mutation and severe insulin resistance. Increasing the dose of thyroxine resulted in a dramatic improvement in insulin sensitivity along with the reappearance of active BAT (Skarulis *et al.* 2010). It may also explain the increase in GLUT4 expression and improvement of insulin resistance in type 2 diabetic patients when exposed to cold (Hanssen *et al.* 2015).

Thyroid hormone-mediated effects on peripheral blood flow

It is beyond the scope of this review to discuss in detail the role of TH on cardiovascular regulation and the heart. Their important role through TRA on the heart rate, on positive inotropy and on heart hypertrophy has recently been reviewed in great detail (Klein & Danzi 2016).

TH-mediated effects on vasoconstriction and vasodilatation have recently been addressed in rodents. In animals with an impaired function of TRA both, vasoconstriction following phenylephrine and vasodilatation following acetylcholine application, is impaired. Thus, thermoregulation via the tail of the animal is no longer operative with profound consequences for cardiovascular function and thermogenesis (Warner *et al.* 2013). Overall, this aspect of thermoregulation has not been studied in great detail. Additional effects of TH-mediated vasoconstriction or vasodilatation for thermoregulation in mice and humans need to be addressed in future studies.

Summary of physiological responses

Considering the mechanisms discussed earlier, a clear role of TH emerged to optimise metabolic adaptation to changes in environment such as exposure to cold or to low energy availability. As schematically shown in Fig. 1A and B, these conditions are characterised by central hypothyroidism as in response to cold exposure and central hyperthyroidism as in fasting.

Under exposure to low temperatures, heat-sensitive neurons in the POA are inactivated, which in turn causes an increase in GABAergic neuronal inputs to the DMH and subsequently to an activation of an efferent sympathetic drive to temperature-sensitive vessels, WAT, BAT, liver and muscle. Whether cold-sensitive neurons are also involved is currently unclear. In parallel, this cold-induced activation via afferent sympathetic neurons

induces an increase in TRH and TSH and a shift of the HPT axis towards higher TH levels. They activate sympathetic efferences to temperature-sensitive vessels resulting in vasoconstriction. Elevated TSH levels allow to optimise the flux of substrates to metabolic organs. High TSH levels may directly induce lipolysis. This effect fuels brown adipocytes with adequate substrates to produce heat under efferent SNS stimulation. There might be an additional effect on T3-dependent browning of WAT. The stimulation of the HPT axis, causing increases in TSH and subsequently TH levels, together with a rise in the SNS activity increases glucose production. It may be supported by positive effects of TH on insulin synthesis and release, but this effect is controversial and not well studied under the fine-tuning conditions of cold exposure. Similarly, the slight increase in TH associated with the change in the setpoint of the HPT axis stimulates the expression of glucose transporters in target tissue like the liver and muscle and thus provides the substrate to endure long-standing or more extensive cold environment by shivering.

The opposite is true for low energy availability as in fasting (Fig. 1B). Here, the negative feedback of leptin on DIO2 is reduced to produce a central state of hyperthyroidism, which leads via inhibition of PVH-derived TRH to a decrease in TSH and a shift in the HPT axis towards a lower set point. This process is greatly supported by an increase in hunger-stimulating peptides like AGRP. AGRP further blocks MC4R and decreases TRH. It is paralleled by a decreased action on melanocortin-derived stimulation of efferent SNS pathways to the periphery via hypothalamic nuclei as the DMH. Whether the slight increase of central TH is uniform and sufficient to counteract this silencing of SNS activity via an activation of the T3-dependent VMH-SNS pathway is not well investigated but appears unlikely. Similarly, the T3 effect on the anterior hypothalamic area (AHA) on blood pressure is likely to be small but not studied under these conditions. WAT, BAT, liver and muscle will under these conditions not be activated to produce FA and glucose. Both pathways will greatly save energy and reduce resting energy expenditure. The lack of TH drive in parallel with low sympathetic activation of peripheral vessels will dissipate heat and in turn stimulate the feeling of cold due to a drop in in core body temperature. Afferent cold-sensitive sympathetic pathways will then be activated when core body temperature drops below a critical threshold and by activation of the POA-DMH-efferent SNS pathway maintain core temperature at a metabolically optimal level.

Summary of pathophysiological changes

Primary hyperthyroidism and hypothyroidism clearly contrast to these conditions as the fine-tuning of central and peripheral TH action is lost under these conditions (Fig. 2A and B).

In primary hypothyroidism, the lack of TH will override the central adaptation and induce by disinhibition TRH release and pituitary TSH secretion. High TSH levels will stimulate lipolysis from WAT and BAT, but the silenced efferent sympathetic drive to the BAT will not allow to adequately consume the fuel. Glucose uptake in the liver and muscle is reduced due to the lack of TH-dependent stimulation of glucose transporter expression, which may cause increased circulating glucose levels. With a reduction of pancreatic insulin synthesis and secretion this will result in insulin resistance. The silencing of metabolic pathways under these conditions may in turn cause a decrease in core body temperature which can no longer be counteracted via TH release from the thyroid gland but only via an afferent sympathetic signalling via POA and DMH to induce efferent sympathetic stimulation. This feedback may kick in early as low TH levels along with a missing sympathetic drive to vascular regulation appear not to allow an adequate early vascular counter-regulation.

Finally, in primary hyperthyroidism (Fig. 2B) high central TH levels downregulate TRH synthesis and release. The subsequent pronounced decrease in TSH secretion no longer contributes to lipolysis, but there appears to be a direct peripheral lipolytic drive through the AMPK-malonyl-CPT1 pathway to provide triglycerides. In contrast, local increase of TH levels in the VMH oppose these AMPK-malonyl-CPT1 driven effects via activation of sympathetic efferences to the liver and BAT. In BAT, they ignite heat production, which is augmented by T3-dependent conversion of WAT to beige fat. In addition, it stimulates hepatic glucose production. The positive action on metabolism also includes cardiovascular system. Via direct central stimulation of parvalbuminergic neurons of the AHA blood pressure is increased. TH directly induces positive chronotropic and inotropic effects on the heart via activation of TRA and blood pressure is also increased by vasoconstriction through increased TH action and sympathetic drive. All these mechanisms will rapidly facilitate an increase in core body temperature. By means of negative feedback heat sensitive neurons in the POA will be activated and decrease via GABAergic projections to the DMH and VMH sympathetic outflow. As TH directly stimulates insulin synthesis and secretion a

Figure 2

Neurohumoral and metabolic disruptions in (A) hypothyroidism and (B) hyperthyroidism. Selected interactions between relevant hypothalamic nuclei, neurohumoral signalling and resulting effects on key metabolic functions of important organs are depicted. Details on the disruption of physiological adaptations by these pathophysiological conditions are discussed in the summary section of the main text. Well-established effects are represented by solid lines while more recently described interactions are illustrated by dotted lines. ARC, arcuate nucleus; BAT, brown adipose tissue; DMH, dorsomedial hypothalamus; HPT, hypothalamic-pituitary-thyroid; NA, noradrenaline; POA, preoptic area; PVH, paraventricular nucleus of the hypothalamus; SNS, sympathetic nervous system; TRH, TSH-releasing hormone; TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; VMH, ventromedial hypothalamus; WAT, white adipose tissue.

variable degree of insulin resistance may result depending on the degree of action on beta cell, glucose production and local regulation. Fine-tuning of peripheral regulation is further governed by many factors including leptin modulating GLUT expression and deiodinases.

Both figures provide a highly simplified scheme to explain some of the energy flux associated with an alteration in TH status and its impact on thermogenesis. They illustrate the complexity of the regulation and the large number of further components influencing it. Most importantly, it has been shown that modulation of the activity of temperature sensitive neurons in the POA dramatically alters thermoneutrality and by that the setpoint of the feedback. Energy stores such as subcutaneous fat depots and particularly intradermal fat storage may have profound influence on the insulation process. The schematic model further did not specifically address alterations in food intake via feedback on hedonic and obligatory signal pathways in appetite regulation. Most important, almost all of these data are obtained from animal models which may not reflect the situation in humans. Despite these drawbacks the model may help to better evaluate the current knowledge on TH dependent alterations induced in humans on thermogenesis.

Declaration of interest

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

Funding

This work was supported by a grant of the Deutsche Forschungsgemeinschaft, BR 915/12-1.

References

- Alexander CM, Kasza I, Yen CL, Reeder SB, Hernando D, Gallo RL, Jahoda CA, Horsley V & MacDougald OA 2015 Dermal white adipose tissue: a new component of the thermogenic response. *Journal of Lipid Research* **56** 2061–2069. (<https://doi.org/10.1194/jlr.R062893>)
- Bianco AC & Silva JE 1988 Cold exposure rapidly induces virtual saturation of brown adipose tissue nuclear T3 receptors. *American Journal of Physiology* **255** E496–E503. (<https://doi.org/10.1152/ajpendo.1988.255.4.E496>)
- Bonde Y, Breuer O, Lutjohann D, Sjöberg S, Angelin B & Rudling M 2014 Thyroid hormone reduces PCSK9 and stimulates bile acid synthesis in humans. *Journal of Lipid Research* **55** 2408–2415. (<https://doi.org/10.1194/jlr.M051664>)
- Branvold DJ, Allred DR, Beckstead DJ, Kim HJ, Fillmore N, Condon BM, Brown JD, Sudweeks SN, Thomson DM & Winder WW 2008 Thyroid hormone effects on LKB1, MO25, phospho-AMPK, phospho-CREB, and PGC-1alpha in rat muscle. *Journal of Applied Physiology* **105** 1218–1227. (<https://doi.org/10.1152/jappphysiol.00997.2007>)
- Breit A, Wicht K, Boekhoff I, Glas E, Lauffer L, Muckter H & Gudermann T 2016 Glucose enhances basal or melanocortin-induced

- cAMP-response element activity in hypothalamic cells. *Molecular Endocrinology* **30** 748–762. (<https://doi.org/10.1210/me.2016-1001>)
- Brufau G, Bahr MJ, Staels B, Claudel T, Ockenga J, Boker KH, Murphy EJ, Prado K, Stellaard F, Manns MP, *et al.* 2010 Plasma bile acids are not associated with energy metabolism in humans. *Nutrition and Metabolism* **7** 73. (<https://doi.org/10.1186/1743-7075-7-73>)
- Cabral A, Valdivia S, Reynaldo M, Cyr NE, Nillni EA & Perello M 2012 Short-term cold exposure activates TRH neurons exclusively in the hypothalamic paraventricular nucleus and raphe pallidus. *Neuroscience Letters* **518** 86–91. (<https://doi.org/10.1016/j.neulet.2012.04.059>)
- Calvo RM & Obregon MJ 2011 Presence and regulation of D1 and D2 deiodinases in rat white adipose tissue. *Metabolism* **60** 1207–1210. (<https://doi.org/10.1016/j.metabol.2011.01.014>)
- Cannon B & Nedergaard J 2004 Brown adipose tissue: function and physiological significance. *Physiological Reviews* **84** 277–359. (<https://doi.org/10.1152/physrev.00015.2003>)
- Cannon B & Nedergaard J 2011 Nonshivering thermogenesis and its adequate measurement in metabolic studies. *Journal of Experimental Biology* **214** 242–253. (<https://doi.org/10.1242/jeb.050989>)
- Cannon B & Nedergaard J 2012 Yes, even human brown fat is on fire! *Journal of Clinical Investigation* **122** 486–489.
- Castillo M, Hall JA, Correa-Medina M, Ueta C, Kang HW, Cohen DE & Bianco AC 2011 Disruption of thyroid hormone activation in type 2 deiodinase knockout mice causes obesity with glucose intolerance and liver steatosis only at thermoneutrality. *Diabetes* **60** 1082–1089. (<https://doi.org/10.2337/db10-0758>)
- Celi FS, Brychta RJ, Linderman JD, Butler PW, Alberobello AT, Smith S, Courville AB, Lai EW, Costello R, Skarulis MC, *et al.* 2010 Minimal changes in environmental temperature result in a significant increase in energy expenditure and changes in the hormonal homeostasis in healthy adults. *European Journal of Endocrinology* **163** 863–872. (<https://doi.org/10.1530/EJE-10-0627>)
- Cheng SY, Leonard JL & Davis PJ 2010 Molecular aspects of thyroid hormone actions. *Endocrine Reviews* **31** 139–170. (<https://doi.org/10.1210/er.2009-0007>)
- Christoffolete MA, Linardi CC, de Jesus L, Ebina KN, Carvalho SD, Ribeiro MO, Rabelo R, Curcio C, Martins L, Kimura ET, *et al.* 2004 Mice with targeted disruption of the Dio2 gene have cold-induced overexpression of the uncoupling protein 1 gene but fail to increase brown adipose tissue lipogenesis and adaptive thermogenesis. *Diabetes* **53** 577–584. (<https://doi.org/10.2337/diabetes.53.3.577>)
- Cohen P & Spiegelman BM 2015 Brown and beige fat: molecular parts of a thermogenic machine. *Diabetes* **64** 2346–2351. (<https://doi.org/10.2337/db15-0318>)
- Cone RD 2005 Anatomy and regulation of the central melanocortin system. *Nature Neuroscience* **8** 571–578. (<https://doi.org/10.1038/nn1455>)
- Coppola A, Liu ZW, Andrews ZB, Paradis E, Roy MC, Friedman JM, Ricquier D, Richard D, Horvath TL, Gao XB, *et al.* 2007 A central thermogenic-like mechanism in feeding regulation: an interplay between arcuate nucleus T3 and UCP2. *Cell Metabolism* **5** 21–33. (<https://doi.org/10.1016/j.cmet.2006.12.002>)
- Crichton PG, Lee Y & Kunji ER 2017 The molecular features of uncoupling protein 1 support a conventional mitochondrial carrier-like mechanism. *Biochimie* **134** 35–50. (<https://doi.org/10.1016/j.biochi.2016.12.016>)
- Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, *et al.* 2009 Identification and importance of brown adipose tissue in adult humans. *New England Journal of Medicine* **360** 1509–1517. (<https://doi.org/10.1056/NEJMoa0810780>)
- Cyr NE, Steger JS, Toorie AM, Yang JZ, Stuart R & Nillni EA 2015 Central Sirt1 regulates body weight and energy expenditure along with the POMC-derived peptide alpha-MSH and the processing enzyme CPE production in diet-induced obese male rats. *Endocrinology* **156** 961–974. (<https://doi.org/10.1210/en.2014-1970>)
- da-Silva WS, Ribich S, Arrojo e Drigo R, Castillo M, Patti ME & Bianco AC 2011 The chemical chaperones tauroursodeoxycholic and 4-phenylbutyric acid accelerate thyroid hormone activation and energy expenditure. *FEBS Letters* **585** 539–544. (<https://doi.org/10.1016/j.febslet.2010.12.044>)
- Decherf S, Seugnet I, Koudhi S, Lopez-Juarez A, Clerget-Froidevaux MS & Demeneix BA 2010 Thyroid hormone exerts negative feedback on hypothalamic type 4 melanocortin receptor expression. *PNAS* **107** 4471–4476.
- Deng J, Yuan F, Guo Y, Xiao Y, Niu Y, Deng Y, Han X, Guan Y, Chen S & Guo F 2017 Deletion of ATF4 in AgRP neurons promotes fat loss mainly via increasing energy expenditure. *Diabetes* **66** 640–650. (<https://doi.org/10.2337/db16-0954>)
- Doignon I, Julien B, Serriere-Lanneau V, Garcin I, Alonso G, Nicou A, Monnet F, Gigou M, Humbert L, Rainteau D, *et al.* 2011 Immediate neuroendocrine signaling after partial hepatectomy through acute portal hyperpressure and cholestasis. *Journal of Hepatology* **54** 481–488. (<https://doi.org/10.1016/j.jhep.2010.07.012>)
- Domouzoglou EM, Fisher FM, Astapova I, Fox EC, Kharitononkov A, Flier JS, Hollenberg AN & Maratos-Flier E 2014 Fibroblast growth factor 21 and thyroid hormone show mutual regulatory dependency but have independent actions in vivo. *Endocrinology* **155** 2031–2040. (<https://doi.org/10.1210/en.2013-1902>)
- Dora JM, Machado WE, Rheinheimer J, Crispim D & Maia AL 2010 Association of the type 2 deiodinase Thr92Ala polymorphism with type 2 diabetes: case-control study and meta-analysis. *European Journal of Endocrinology* **163** 427–434. (<https://doi.org/10.1530/EJE-10-0419>)
- Duboc H, Tache Y & Hofmann AF 2014 The bile acid TGR5 membrane receptor: from basic research to clinical application. *Digestive and Liver Disease* **46** 302–312. (<https://doi.org/10.1016/j.dld.2013.10.021>)
- Duntas LH, Orgiazzi J & Brabant G 2011 The interface between thyroid and diabetes mellitus. *Clinical Endocrinology* **75** 1–9. (<https://doi.org/10.1111/j.1365-2265.2011.04029.x>)
- Endo T & Kobayashi T 2008 Thyroid-stimulating hormone receptor in brown adipose tissue is involved in the regulation of thermogenesis. *American Journal of Physiology: Endocrinology and Metabolism* **295** E514–E518. (<https://doi.org/10.1152/ajpendo.90433.2008>)
- Endo T & Kobayashi T 2012 Expression of functional TSH receptor in white adipose tissues of hyt/hyt mice induces lipolysis in vivo. *American Journal of Physiology: Endocrinology and Metabolism* **302** E1569–E1575. (<https://doi.org/10.1152/ajpendo.00572.2011>)
- Enerback S, Jacobsson A, Simpson EM, Guerra C, Yamashita H, Harper ME & Kozak LP 1997 Mice lacking mitochondrial uncoupling protein are cold-sensitive but not obese. *Nature* **387** 90–94. (<https://doi.org/10.1038/387090a0>)
- Engels K, Rakov H, Zwanziger D, Moeller LC, Homuth G, Kohrle J, Brix K & Fuhrer D 2015 Differences in mouse hepatic thyroid hormone transporter expression with age and hyperthyroidism. *European Thyroid Journal* **4** 81–86. (<https://doi.org/10.1159/000381020>)
- Fekete C & Lechan RM 2014 Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. *Endocrine Reviews* **35** 159–194. (<https://doi.org/10.1210/er.2013-1087>)
- Feldmann HM, Golozoubova V, Cannon B & Nedergaard J 2009 UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. *Cell Metabolism* **9** 203–209. (<https://doi.org/10.1016/j.cmet.2008.12.014>)
- Finan B, Clemmensen C, Zhu Z, Stemmer K, Gauthier K, Muller L, De Angelis M, Moreth K, Neff F, Perez-Tilve D, *et al.* 2016 Chemical hybridization of glucagon and thyroid hormone optimizes therapeutic impact for metabolic disease. *Cell* **167** 843.e814–857.e814. (<https://doi.org/10.1016/j.cell.2016.09.014>)
- Fischer AW, Csikasz RI, von Essen G, Cannon B & Nedergaard J 2016 No insulating effect of obesity. *American Journal of Physiology: Endocrinology and Metabolism* **311** E202–E213. (<https://doi.org/10.1152/ajpendo.00093.2016>)
- Fonseca TL, Werneck-De-Castro JP, Castillo M, Bocco BM, Fernandes GW, McAninch EA, Ignacio DL, Moises CC, Ferreira AR,

- Gereben B, *et al.* 2014 Tissue-specific inactivation of type 2 deiodinase reveals multilevel control of fatty acid oxidation by thyroid hormone in the mouse. *Diabetes* **63** 1594–1604. (<https://doi.org/10.2337/db13-1768>)
- Fozzatti L, Lu C, Kim DW & Cheng SY 2011 Differential recruitment of nuclear coregulators directs the isoform-dependent action of mutant thyroid hormone receptors. *Molecular Endocrinology* **25** 908–921. (<https://doi.org/10.1210/me.2010-0474>)
- Furuya F, Shimura H, Yamashita S, Endo T & Kobayashi T 2010 Liganded thyroid hormone receptor- α enhances proliferation of pancreatic beta-cells. *Journal of Biological Chemistry* **285** 24477–24486. (<https://doi.org/10.1074/jbc.M109.100222>)
- Ghaddab-Zroud R, Seugnet I, Steffensen KR, Demeneix BA & Clerget-Froidevaux MS 2014 Liver X receptor regulation of thyrotropin-releasing hormone transcription in mouse hypothalamus is dependent on thyroid status. *PLoS ONE* **9** e106983. (<https://doi.org/10.1371/journal.pone.0106983>)
- Golozoubova V, Hohtola E, Matthias A, Jacobsson A, Cannon B & Nedergaard J 2001 Only UCP1 can mediate adaptive nonshivering thermogenesis in the cold. *FASEB Journal* **15** 2048–2050. (<https://doi.org/10.1096/fj.00-0536fje>)
- Hanssen MJ, Hoeks J, Brans B, van der Lans AA, Schaart G, van den Driessche JJ, Jorgensen JA, Boeschoten MV, Hesselink MK, Havekes B, *et al.* 2015 Short-term cold acclimation improves insulin sensitivity in patients with type 2 diabetes mellitus. *Nature Medicine* **21** 863–865. (<https://doi.org/10.1038/nm.3891>)
- Harms M & Seale P 2013 Brown and beige fat: development, function and therapeutic potential. *Nature Medicine* **19** 1252–1263. (<https://doi.org/10.1038/nm.3361>)
- Harris SE, De Blasio MJ, Davis MA, Kelly AC, Davenport HM, Wooding FBP, Blache D, Meredith D, Anderson M, Fowden AL, *et al.* 2017 Hypothyroidism in utero stimulates pancreatic beta cell proliferation and hyperinsulinaemia in the ovine fetus during late gestation. *Journal of Physiology* **595** 3331–3343. (<https://doi.org/10.1113/jp273555>)
- Hasegawa K, Kawahara T, Fujiwara K, Shimpuku M, Sasaki T, Kitamura T & Yoshikawa K 2012 Necdin controls Foxo1 acetylation in hypothalamic arcuate neurons to modulate the thyroid axis. *Journal of Neuroscience* **32** 5562–5572. (<https://doi.org/10.1523/JNEUROSCI.0142-12.2012>)
- Hashimoto K, Yamada M, Matsumoto S, Monden T, Satoh T & Mori M 2006 Mouse sterol response element binding protein-1c gene expression is negatively regulated by thyroid hormone. *Endocrinology* **147** 4292–4302.
- Hashimoto K, Matsumoto S, Yamada M, Satoh T & Mori M 2007 Liver X receptor- α gene expression is positively regulated by thyroid hormone. *Endocrinology* **148** 4667–4675.
- Hashimoto K, Ishida E, Matsumoto S, Okada S, Yamada M, Satoh T, Monden T & Mori M 2009 Carbohydrate response element binding protein gene expression is positively regulated by thyroid hormone. *Endocrinology* **150** 3417–3424.
- Heaton GM, Wagenvoort RJ, Kemp A Jr & Nicholls DG 1978 Brown-adipose-tissue mitochondria: photoaffinity labelling of the regulatory site of energy dissipation. *European Journal of Biochemistry* **82** 515–521. (<https://doi.org/10.1111/j.1432-1033.1978.tb12045.x>)
- Hernandez A & Obregon MJ 1996 T3 potentiates the adrenergic stimulation of type II 5'-deiodinase activity in cultured rat brown adipocytes. *American Journal of Physiology* **271** E15–E23.
- Herwig A, Ross AW, Nilaweera KN, Morgan PJ & Barrett P 2008 Hypothalamic thyroid hormone in energy balance regulation. *Obesity Facts* **1** 71–79. (<https://doi.org/10.1159/000123428>)
- Irrcher I, Walkinshaw DR, Sheehan TE & Hood DA 2008 Thyroid hormone (T3) rapidly activates p38 and AMPK in skeletal muscle in vivo. *Journal of Applied Physiology* **104** 178–185. (<https://doi.org/10.1152/jappphysiol.00643.2007>)
- Iwen KA, Schroder E & Brabant G 2013 Thyroid hormones and the metabolic syndrome. *European Thyroid Journal* **2** 83–92. (<https://doi.org/10.1159/000351249>)
- Iwen KA, Backhaus J, Cassens M, Walzl M, Hedesan OC, Merkel M, Heeren J, Sina C, Rademacher L, Windjager A, *et al.* 2017 Cold-induced brown adipose tissue activity alters plasma fatty acids and improves glucose metabolism in men. *Journal of Clinical Endocrinology and Metabolism* **102** 4226–4234.
- Jorns A, Sennholz C, Naujok O & Lenzen S 2010 Beta cell mass regulation in the rat pancreas through glucocorticoids and thyroid hormones. *Pancreas* **39** 1167–1172. (<https://doi.org/10.1097/MPA.0b013e3181dfce4f>)
- Joseph-Bravo P, Jaimes-Hoy L & Charli JL 2016 Advances in TRH signaling. *Reviews in Endocrine and Metabolic Disorders* **17** 545–558. (<https://doi.org/10.1007/s11154-016-9375-y>)
- Kasza I, Suh Y, Wollny D, Clark RJ, Roopra A, Colman RJ, MacDougald OA, Shedd TA, Nelson DW, Yen MI, *et al.* 2014 Syndecan-1 is required to maintain intradermal fat and prevent cold stress. *PLoS Genetics* **10** e1004514. (<https://doi.org/10.1371/journal.pgen.1004514>)
- Kasza I, Hernando D, Roldan-Alzate A, Alexander CM & Reeder SB 2016 Thermogenic profiling using magnetic resonance imaging of dermal and other adipose tissues. *JCI Insight* **1** e87146.
- Keipert S & Jastroch M 2014 Brite/beige fat and UCP1 – is it thermogenesis? *Biochimica et Biophysica Acta* **1837** 1075–1082. (<https://doi.org/10.1016/j.bbabi.2014.02.008>)
- Klein I & Danzi S 2016 Thyroid disease and the heart. *Current Problems in Cardiology* **41** 65–92. (<https://doi.org/10.1016/j.cpcardiol.2015.04.002>)
- Klieverik LP, Coomans CP, Endert E, Sauerwein HP, Havekes LM, Voshol PJ, Rensen PC, Romijn JA, Kalsbeek A & Fliers E 2009a Thyroid hormone effects on whole-body energy homeostasis and tissue-specific fatty acid uptake in vivo. *Endocrinology* **150** 5639–5648. (<https://doi.org/10.1210/en.2009-0297>)
- Klieverik LP, Janssen SE, van Riel A, Foppen E, Bisschop PH, Serlie MJ, Boelen A, Ackermans MT, Sauerwein HP, Fliers E, *et al.* 2009b Thyroid hormone modulates glucose production via a sympathetic pathway from the hypothalamic paraventricular nucleus to the liver. *PNAS* **106** 5966–5971. (<https://doi.org/10.1073/pnas.0805355106>)
- Krashes MJ, Lowell BB & Garfield AS 2016 Melanocortin-4 receptor-regulated energy homeostasis. *Nature Neuroscience* **19** 206–219. (<https://doi.org/10.1038/nn.4202>)
- Lage R, Ferno J, Nogueiras R, Dieguez C & Lopez M 2016 Contribution of adaptive thermogenesis to the hypothalamic regulation of energy balance. *Biochemical Journal* **473** 4063–4082. (<https://doi.org/10.1042/BCJ20160012>)
- Lanni A, Moreno M, Lombardi A & Goglia F 2003 Thyroid hormone and uncoupling proteins. *FEBS Letters* **543** 5–10. ([https://doi.org/10.1016/S0014-5793\(03\)00320-X](https://doi.org/10.1016/S0014-5793(03)00320-X))
- Larsen PJ, Hay-Schmidt A & Mikkelsen JD 1994 Efferent connections from the lateral hypothalamic region and the lateral preoptic area to the hypothalamic paraventricular nucleus of the rat. *Journal of Comparative Neurology* **342** 299–319. (<https://doi.org/10.1002/cne.903420211>)
- Lin JZ, Martagon AJ, Hsueh WA, Baxter JD, Gustafsson JA, Webb P & Phillips KJ 2012 Thyroid hormone receptor agonists reduce serum cholesterol independent of the LDL receptor. *Endocrinology* **153** 6136–6144. (<https://doi.org/10.1210/en.2011-2081>)
- Lin JZ, Martagon AJ, Cimini SL, Gonzalez DD, Tinkey DW, Biter A, Baxter JD, Webb P, Gustafsson JA, Hartig SM, *et al.* 2015 Pharmacological activation of thyroid hormone receptors elicits a functional conversion of white to brown fat. *Cell Reports* **13** 1528–1537. (<https://doi.org/10.1016/j.celrep.2015.10.022>)
- Liu YY & Brent GA 2010 Thyroid hormone crosstalk with nuclear receptor signaling in metabolic regulation. *Trends in Endocrinology and Metabolism* **21** 166–173. (<https://doi.org/10.1016/j.tem.2009.11.004>)
- Liu K & Czaja MJ 2013 Regulation of lipid stores and metabolism by lipophagy. *Cell Death and Differentiation* **20** 3–11. (<https://doi.org/10.1038/cdd.2012.63>)
- Liu YY, Schultz JJ & Brent GA 2003 A thyroid hormone receptor alpha gene mutation (P398H) is associated with visceral adiposity and impaired catecholamine-stimulated lipolysis in mice. *Journal of Biological Chemistry* **278** 38913–38920. (<https://doi.org/10.1074/jbc.M306120200>)

- Liu YY, Heymann RS, Moatamed F, Schultz JJ, Sobel D & Brent GA 2007 A mutant thyroid hormone receptor alpha antagonizes peroxisome proliferator-activated receptor alpha signaling in vivo and impairs fatty acid oxidation. *Endocrinology* **148** 1206–1217. (<https://doi.org/10.1210/en.2006-0836>)
- Liu J, Hernandez-Ono A, Graham MJ, Galton VA & Ginsberg HN 2016 Type 1 deiodinase regulates ApoA-I gene expression and ApoA-I synthesis independent of thyroid hormone signaling. *Arteriosclerosis, Thrombosis, and Vascular Biology* **36** 1356–1366.
- Lopez M, Varela L, Vazquez MJ, Rodriguez-Cuenca S, Gonzalez CR, Velagapudi VR, Morgan DA, Schoenmakers E, Agassandian K, Lage R, *et al.* 2010 Hypothalamic AMPK and fatty acid metabolism mediate thyroid regulation of energy balance. *Nature Medicine* **16** 1001–1008. (<https://doi.org/10.1038/nm.2207>)
- Lowell BB & Spiegelman BM 2000 Towards a molecular understanding of adaptive thermogenesis. *Nature* **404** 652–660. (<https://doi.org/10.1038/35007527>)
- Luo L & Liu M 2016 Adipose tissue in control of metabolism. *Journal of Endocrinology* **231** R77–R99. (<https://doi.org/10.1530/JOE-16-0211>)
- Marsili A, Aguayo-Mazzucato C, Chen T, Kumar A, Chung M, Lunsford EP, Harney JW, Van-Tran T, Gianetti E, Ramadan W, *et al.* 2011 Mice with a targeted deletion of the type 2 deiodinase are insulin resistant and susceptible to diet induced obesity. *PLoS ONE* **6** e20832. (<https://doi.org/10.1371/journal.pone.0020832>)
- Martelli D, Luppi M, Cerri M, Tupone D, Mastrotto M, Perez E, Zamboni G & Amici R 2014 The direct cooling of the preoptic-hypothalamic area elicits the release of thyroid stimulating hormone during wakefulness but not during REM sleep. *PLoS ONE* **9** e87793. (<https://doi.org/10.1371/journal.pone.0087793>)
- Martinez-Sanchez N, Moreno-Navarrete JM, Contreras C, Rial-Pensado E, Ferno J, Nogueiras R, Dieguez C, Fernandez-Real JM & Lopez M 2017 Thyroid hormones induce browning of white fat. *Journal of Endocrinology* **232** 351–362. (<https://doi.org/10.1530/JOE-16-0425>)
- Mentuccia D, Proietti-Pannunzi L, Tanner K, Bacci V, Pollin TI, Poehlman ET, Shuldiner AR & Celi FS 2002 Association between a novel variant of the human type 2 deiodinase gene Thr92Ala and insulin resistance: evidence of interaction with the Trp64Arg variant of the beta-3-adrenergic receptor. *Diabetes* **51** 880–883. (<https://doi.org/10.2337/diabetes.51.3.880>)
- Mitrou P, Raptis SA & Dimitriadis G 2010 Insulin action in hyperthyroidism: a focus on muscle and adipose tissue. *Endocrine Reviews* **31** 663–679. (<https://doi.org/10.1210/er.2009-0046>)
- Moffett SX, Giannopoulos PF, James TD & Martin JV 2013 Effects of acute microinjections of thyroid hormone to the preoptic region of hypothyroid adult male rats on sleep, motor activity and body temperature. *Brain Research* **1516** 55–65. (<https://doi.org/10.1016/j.brainres.2013.04.017>)
- Morrison SF 2016 Central control of body temperature. *F1000Research* **5** 880. (<https://doi.org/10.12688/f1000research.7958.1>)
- Muller-Fielitz H, Stahr M, Bernau M, Richter M, Abele S, Krajka V, Benzin A, Wenzel J, Kalies K, Mittag J, *et al.* 2017 Tanycytes control the hormonal output of the hypothalamic-pituitary-thyroid axis. *Nature Communications* **8** 484. (<https://doi.org/10.1038/s41467-017-00604-6>)
- Mullur R, Liu YY & Brent GA 2014 Thyroid hormone regulation of metabolism. *Physiological Reviews* **94** 355–382. (<https://doi.org/10.1152/physrev.00030.2013>)
- Mund RA & Frishman WH 2013 Brown adipose tissue thermogenesis: beta3-adrenoreceptors as a potential target for the treatment of obesity in humans. *Cardiology in Review* **21** 265–269. (<https://doi.org/10.1097/CRD.0b013e31829cabff>)
- Nakamura K & Morrison SF 2008 A thermosensory pathway that controls body temperature. *Nature Neuroscience* **11** 62–71. (<https://doi.org/10.1038/nn2027>)
- Nedergaard J, Bengtsson T & Cannon B 2007 Unexpected evidence for active brown adipose tissue in adult humans. *American Journal of Physiology: Endocrinology and Metabolism* **293** E444–E452. (<https://doi.org/10.1152/ajpendo.00691.2006>)
- Nilni EA 2010 Regulation of the hypothalamic thyrotropin releasing hormone (TRH) neuron by neuronal and peripheral inputs. *Frontiers in Neuroendocrinology* **31** 134–156. (<https://doi.org/10.1016/j.yfrne.2010.01.001>)
- Nozaki S, Shimomura I, Funahashi T, Menju M, Kubo M & Matsuzawa Y 1992 Stimulation of the activity and mRNA level of hepatic triacylglycerol lipase by triiodothyronine in HepG2 cells. *Biochimica et Biophysica Acta* **1127** 298–302. ([https://doi.org/10.1016/0005-2760\(92\)90235-N](https://doi.org/10.1016/0005-2760(92)90235-N))
- Obregon MJ 2014 Adipose tissues and thyroid hormones. *Frontiers in Physiology* **5** 479.
- Ockenga J, Valentini L, Schuetz T, Wohlgemuth F, Glaeser S, Omar A, Kasim E, duPlessis D, Featherstone K, Davis JR, *et al.* 2012 Plasma bile acids are associated with energy expenditure and thyroid function in humans. *Journal of Clinical Endocrinology and Metabolism* **97** 535–542. (<https://doi.org/10.1210/jc.2011-2329>)
- Oelkrug R, Polymeropoulos ET & Jastroch M 2015 Brown adipose tissue: physiological function and evolutionary significance. *Journal of Comparative Physiology B* **185** 587–606. (<https://doi.org/10.1007/s00360-015-0907-7>)
- Oppenheimer JH, Schwartz HL, Lane JT & Thompson MP 1991 Functional relationship of thyroid hormone-induced lipogenesis, lipolysis, and thermogenesis in the rat. *Journal of Clinical Investigation* **87** 125–132. (<https://doi.org/10.1172/JCI114961>)
- Park SH, Paulsen SR, Gammon SR, Mustard KJ, Hardie DG & Winder WW 2002 Effects of thyroid state on AMP-activated protein kinase and acetyl-CoA carboxylase expression in muscle. *Journal of Applied Physiology* **93** 2081–2088.
- Patti ME, Houten SM, Bianco AC, Bernier R, Larsen PR, Holst JJ, Badman MK, Maratos-Flier E, Mun EC, Pihlajamaki J, *et al.* 2009 Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obesity* **17** 1671–1677. (<https://doi.org/10.1038/oby.2009.102>)
- Petrovic N, Walden TB, Shabalina IG, Timmons JA, Cannon B & Nedergaard J 2010 Chronic peroxisome proliferator-activated receptor gamma (PPARgamma) activation of epididymally derived white adipocyte cultures reveals a population of thermogenically competent, UCP1-containing adipocytes molecularly distinct from classic brown adipocytes. *Journal of Biological Chemistry* **285** 7153–7164. (<https://doi.org/10.1074/jbc.M109.053942>)
- Reitman ML, He Y & Gong DW 1999 Thyroid hormone and other regulators of uncoupling proteins. *International Journal of Obesity and Related Metabolic Disorders* **23** (Supplement 6) S56–S59. (<https://doi.org/10.1038/sj.ijo.0800948>)
- Ribeiro MO, Carvalho SD, Schultz JJ, Chiellini G, Scanlan TS, Bianco AC & Brent GA 2001 Thyroid hormone–sympathetic interaction and adaptive thermogenesis are thyroid hormone receptor isoform–specific. *Journal of Clinical Investigation* **108** 97–105. (<https://doi.org/10.1172/JCI200112584>)
- Ricquier D 2017 UCP1, the mitochondrial uncoupling protein of brown adipocyte: a personal contribution and a historical perspective. *Biochimie* **134** 3–8. (<https://doi.org/10.1016/j.biochi.2016.10.018>)
- Rousset S, Alves-Guerra MC, Mozo J, Miroux B, Cassard-Doulcier AM, Bouillaud F & Ricquier D 2004 The biology of mitochondrial uncoupling proteins. *Diabetes* **53** (Supplement 1) S130–S135. (<https://doi.org/10.2337/diabetes.53.2007.S130>)
- Sell H, Deshaies Y & Richard D 2004 The brown adipocyte: update on its metabolic role. *International Journal of Biochemistry and Cell Biology* **36** 2098–2104. (<https://doi.org/10.1016/j.biocel.2004.04.003>)
- Silva JE 2005 Thyroid hormone and the energetic cost of keeping body temperature. *Bioscience Reports* **25** 129–148. (<https://doi.org/10.1007/s10540-005-2882-9>)
- Silva JE 2006 Thermogenic mechanisms and their hormonal regulation. *Physiological Reviews* **86** 435–464. (<https://doi.org/10.1152/physrev.00009.2005>)
- Sinha RA, You SH, Zhou J, Siddique MM, Bay BH, Zhu X, Privalsky ML, Cheng SY, Stevens RD, Summers SA, *et al.* 2012 Thyroid hormone

- stimulates hepatic lipid catabolism via activation of autophagy. *Journal of Clinical Investigation* **122** 2428–2438. (<https://doi.org/10.1172/JCI60580>)
- Sinha RA, Singh BK & Yen PM 2014 Thyroid hormone regulation of hepatic lipid and carbohydrate metabolism. *Trends in Endocrinology and Metabolism* **25** 538–545. (<https://doi.org/10.1016/j.tem.2014.07.001>)
- Skarulis MC, Celi FS, Mueller E, Zemskova M, Malek R, Hugendubler L, Cochran C, Solomon J, Chen C & Gorden P 2010 Thyroid hormone induced brown adipose tissue and amelioration of diabetes in a patient with extreme insulin resistance. *Journal of Clinical Endocrinology and Metabolism* **95** 256–262. (<https://doi.org/10.1210/jc.2009-0543>)
- Smith PM & Ferguson AV 2014 Metabolic signaling to the central nervous system: routes across the blood brain barrier. *Current Pharmaceutical Design* **20** 1392–1399. (<https://doi.org/10.2174/13816128113199990560>)
- Song Y, Xu C, Shao S, Liu J, Xing W, Xu J, Qin C, Li C, Hu B, Yi S, *et al.* 2015 Thyroid-stimulating hormone regulates hepatic bile acid homeostasis via SREBP-2/HNF-4 α /CYP7A1 axis. *Journal of Hepatology* **62** 1171–1179. (<https://doi.org/10.1016/j.jhep.2014.12.006>)
- Song Y, Zhao M, Zhang H, Zhang X, Zhao J, Xu J & Gao L 2016 Thyroid-stimulating hormone levels are inversely associated with serum total bile acid levels: a cross-sectional study. *Endocrine Practice* **22** 420–426. (<https://doi.org/10.4158/EP15844.OR>)
- Suh JH, Sieglaff DH, Zhang A, Xia X, Cvorovic A, Winnier GE & Webb P 2013 SIRT1 is a direct coactivator of thyroid hormone receptor β 1 with gene-specific actions. *PLoS ONE* **8** e70097. (<https://doi.org/10.1371/journal.pone.0070097>)
- Talukdar S, Owen BM, Song P, Hernandez G, Zhang Y, Zhou Y, Scott WT, Paratala B, Turner T, Smith A, *et al.* 2016 FGF21 regulates sweet and alcohol preference. *Cell Metabolism* **23** 344–349. (<https://doi.org/10.1016/j.cmet.2015.12.008>)
- Tan CL, Cooke EK, Leib DE, Lin YC, Daly GE, Zimmerman CA & Knight ZA 2016 Warm-sensitive neurons that control body temperature. *Cell* **167** 47.e15–59.e15. (<https://doi.org/10.1016/j.cell.2016.08.028>)
- Tansey EA & Johnson CD 2015 Recent advances in thermoregulation. *Advances in Physiology Education* **39** 139–148. (<https://doi.org/10.1152/advan.00126.2014>)
- Terrien J, Perret M & Aujard F 2011 Behavioral thermoregulation in mammals: a review. *Frontiers in Bioscience* **16** 1428–1444. (<https://doi.org/10.2741/3797>)
- Thakran S, Sharma P, Attia RR, Hori RT, Deng X, Elam MB & Park EA 2013 Role of sirtuin 1 in the regulation of hepatic gene expression by thyroid hormone. *Journal of Biological Chemistry* **288** 807–818. (<https://doi.org/10.1074/jbc.M112.437970>)
- van Marken Lichtenbelt WD, Vanhomerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P & Teule GJ 2009 Cold-activated brown adipose tissue in healthy men. *New England Journal of Medicine* **360** 1500–1508.
- Vazquez-Anaya G, Martinez B, Sonanez-Organis JG, Nakano D, Nishiyama A & Ortiz RM 2017 Exogenous thyroxine improves glucose intolerance in insulin-resistant rats. *Journal of Endocrinology* **232** 501–511. (<https://doi.org/10.1530/JOE-16-0428>)
- Vella KR, Ramadoss P, Lam FS, Harris JC, Ye FD, Same PD, O'Neill NF, Maratos-Flier E & Hollenberg AN 2011 NPY and MC4R signaling regulate thyroid hormone levels during fasting through both central and peripheral pathways. *Cell Metabolism* **14** 780–790. (<https://doi.org/10.1016/j.cmet.2011.10.009>)
- Virtanen KA, Lidell ME, Orava J, Heglin M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, *et al.* 2009 Functional brown adipose tissue in healthy adults. *New England Journal of Medicine* **360** 1518–1525.
- von Holstein-Rathlou S, BonDurant LD, Peltekian L, Naber MC, Yin TC, Claflin KE, Urizar AI, Madsen AN, Ratner C, Holst B, *et al.* 2016 FGF21 Mediates Endocrine Control of Simple Sugar Intake and Sweet Taste Preference by the Liver. *Cell Metabolism* **23** 335–343. (<https://doi.org/10.1016/j.cmet.2015.12.003>)
- Wajchenberg BL 2000 Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocrine Reviews* **21** 697–738. (<https://doi.org/10.1210/edrv.21.6.0415>)
- Warner A & Mittag J 2016 Breaking BAT: can browning create a better white? *Journal of Endocrinology* **228** R19–R29.
- Warner A, Rahman A, Solsjo P, Gottschling K, Davis B, Vennstrom B, Arner A & Mittag J 2013 Inappropriate heat dissipation ignites brown fat thermogenesis in mice with a mutant thyroid hormone receptor α 1. *PNAS* **110** 16241–16246. (<https://doi.org/10.1073/pnas.1310300110>)
- Watanabe M, Houten SM, Matak C, Christoffolete MA, Kim BW, Sato H, Messaddeq N, Harney JW, Ezaki O, Kodama T, *et al.* 2006 Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* **439** 484–489. (<https://doi.org/10.1038/nature04330>)
- Weiner J, Kranz M, Kloting N, Kunath A, Steinhoff K, Rijntjes E, Kohrle J, Zeisig V, Hankir M, Gebhardt C, *et al.* 2016 Thyroid hormone status defines brown adipose tissue activity and browning of white adipose tissues in mice. *Scientific Reports* **6** 38124. (<https://doi.org/10.1038/srep38124>)
- Westerterp KR 2017 Control of energy expenditure in humans. *European Journal of Clinical Nutrition* **71** 340–344. (<https://doi.org/10.1038/ejcn.2016.237>)
- Winder WW, Hardie DG, Mustard KJ, Greenwood LJ, Paxton BE, Park SH, Rubink DS & Taylor EB 2003 Long-term regulation of AMP-activated protein kinase and acetyl-CoA carboxylase in skeletal muscle. *Biochemical Society Transactions* **31** 182–185. (<https://doi.org/10.1042/bst0310182>)
- Wuest S, Yang X, Liu J, Schoenle EJ & Konrad D 2012 Inverse regulation of basal lipolysis in perigonadal and mesenteric fat depots in mice. *American Journal of Physiology: Endocrinology and Metabolism* **302** E153–E160. (<https://doi.org/10.1152/ajpendo.00338.2011>)
- Yamada M, Satoh T & Mori M 2003 Mice lacking the thyrotropin-releasing hormone gene: what do they tell us? *Thyroid* **13** 1111–1121. (<https://doi.org/10.1089/10507250360731505>)
- Zhang Y, Proenca R, Maffei M, Barone M, Leopold L & Friedman JM 1994 Positional cloning of the mouse obese gene and its human homologue. *Nature* **372** 425–432. (<https://doi.org/10.1038/372425a0>)
- Zhang A, Sieglaff DH, York JP, Suh JH, Ayers SD, Winnier GE, Kharitonov A, Pin C, Zhang P, Webb P, *et al.* 2015a Thyroid hormone receptor regulates most genes independently of fibroblast growth factor 21 in liver. *Journal of Endocrinology* **224** 289–301. (<https://doi.org/10.1530/JOE-14-0440>)
- Zhang X, Song Y, Feng M, Zhou X, Lu Y, Gao L, Yu C, Jiang X & Zhao J 2015b Thyroid-stimulating hormone decreases HMG-CoA reductase phosphorylation via AMP-activated protein kinase in the liver. *Journal of Lipid Research* **56** 963–971. (<https://doi.org/10.1194/jlr.M047654>)
- Zhao ZD, Yang WZ, Gao C, Fu X, Zhang W, Zhou Q, Chen W, Ni X, Lin JK, Yang J, *et al.* 2017 A hypothalamic circuit that controls body temperature. *PNAS* **114** 2042–2047. (<https://doi.org/10.1073/pnas.1616255114>)
- Zhu X & Cheng SY 2010 New insights into regulation of lipid metabolism by thyroid hormone. *Current Opinion in Endocrinology, Diabetes and Obesity* **17** 408–413. (<https://doi.org/10.1097/MED.0b013e32833d6d46>)

Received in final form 27 January 2018

Accepted 6 February 2018

Accepted Preprint published online 6 February 2018