Hypothalamic regulation of metabolism
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Citation for published version (APA):
Zhang, Z. (2017). Hypothalamic regulation of metabolism: Role of thyroid hormone and estrogen
1 General introduction
Endocrine and neural regulation of homeostasis

All living beings on earth are subjected to various changes in the external environment. In order to maintain internal homeostasis, sophisticated mechanisms were developed. Homeostasis is finely regulated both via the endocrine and nervous system. The endocrine system produces chemical substances called hormones to transfer information to regulate body functions. Generally, hormones produced from endocrine glands are secreted into the systemic circulation to reach their target tissues, where they bind to their relevant receptors inducing genomic or non-genomic reactions. These hormonal reactions may also occur in the same cells where they are produced, so called autocrine actions, or in target cells in the direct vicinity which are then called paracrine actions. The nervous system produces chemical substances that are called neurotransmitters, transferring information between neurons in the brain or between neurons and peripheral target tissues. The neurotransmitters produced by neurons are either released at synapses, triggering action potentials at the post-synaptic site, or released from nerve terminals or neurons into the circulation having distant effects as (neuro-) hormones.

The endocrine and nervous systems closely interact. The secretion of many hormones is regulated by the central nervous system (CNS), e.g., via the hypothalamic-pituitary-target gland systems. Reciprocally, many hormones originating in peripheral tissues act on the CNS to modulate neuronal function. Traditionally, hormones are released into the circulation to act on distant target sites in the body. However, emerging evidence shows that many of the peripheral hormones may also exert peripheral functions by acting on the brain. For example, leptin, although produced in peripheral white adipose tissue (WAT), is a critical neuromodulator controlling energy homeostasis via the brain [1].

In the CNS, the hypothalamus is the key brain area that integrates neuronal and hormonal signals. It receives neuro-humoral information and sends neural, neurosecretory or autonomic motor outputs to regulate energy homeostasis. The hypothalamus comprises many different nuclei, each controlling distinct aspects of energy metabolism. The hypothalamic paraventricular nucleus (PVN), for example, is important for neuroendocrine regulation by its projections to the median eminence and posterior pituitary gland. Hypophysiotropic hormones, including thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH) and corticotropin-releasing hormone (CRH) are released into the median eminence to control the release of trophic hormones from the anterior pituitary. However, the PVN also projects to many other brain areas including...
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the brainstem and the spinal cord, to regulate autonomic function [2, 3]. Another important hypothalamic nucleus, adjacent to the third ventricle and the median eminence, is the arcuate nucleus (ARC). It contains two antagonistic groups of neurons, i.e., the agouti-related peptide (AgRP) and proopiomelanocortin (POMC) containing neurons, both pivotal in the regulation of food intake [4], but with opposite effects. A third hypothalamic nucleus with a key role in metabolic regulation is the ventromedial hypothalamus (VMH), as it is involved in the control of energy intake and expenditure [5]. The three hypothalamic nuclei mentioned here are also important targets for the endocrine actions of thyroid hormone and estrogen.

1.2 Thyroid hormone

Thyroid hormone (TH) is essential for ontogenesis, development, differentiation and metabolism in a vast range of species. The major thyroid hormone thyroxine (T4) compromises up to 80% of secreted THs from the thyroid gland in humans [6]. The bioactive thyroid hormone triiodothyronine (T3) is produced within the thyroid gland to a minor extent, the majority of T3 is converted from T4 by deiodinating enzymes expressed locally in various tissues. This extra level of regulation allows the body to locally control the availability of T3 independently of circulating TH, which is critical during specific (patho) physiological conditions, including cold exposure and illness [7]. There are three major enzymes regulating TH metabolism, named iodothyronine deiodinase type 1 (D1), type 2 (D2) and type 3 (D3). D2, with its ability of outer ring deiodination, is important for the activation of TH from T4 to T3; whereas D3 is able to inactivate TH by inner ring deiodination. By contrast, D1 is able to do both outer and inner ring deiodination [8, 9] (Figure 1.1). Recent findings indicate that the differential expression of various types of deiodinases is critical for local TH homeostasis and TH mediated physiology [7, 10]. The TH plasma concentration is finely regulated in the context of the hypothalamus-pituitary-thyroid gland (HPT) axis, which is characterized by negative feedback regulation at the level of the pituitary and hypothalamus. At the central level, hypophysiotropic neurons in the PVN of the hypothalamus produce TRH, which reaches the anterior pituitary gland through the median eminence and the portal system. Upon TRH stimulation, thyroid-stimulating hormone (thyrotropin or TSH) is released into the general circulation and stimulates TH synthesis and secretion by the thyroid gland. T3 and T4 serve as a negative feedback signal at the level of the pituitary and PVN, inhibiting TSH release (Figure 1.1). In this way it is possible to keep stable TH levels. Importantly, the set point of the HPT axis is flexible and may respond to a number of (patho) physiological situations including fasting and inflammation [11].
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TH is involved in many metabolic processes in the body [12]. Its physiological functions are clearly illustrated by the syndromes of their excess and shortage, respectively, hyperthyroidism and hypothyroidism. Hyperthyroidism results in increased metabolic rate and weight loss [13, 14]. Animal studies demonstrated an increased sympathetic tone and energy expenditure leading to a decrease in body weight in spite of hyperphagia [15]. By contrast, hypothyroidism, resulting from a shortage of TH, induces a lower metabolic rate and increased weight gain. Moreover, animals with hypothyroidism show decreased locomotor activity [16]. The primary effects of T3 are mediated through thyroid hormone receptors (TRα and TRβ). Thyroid hormone receptors homodimerize or heterodimerize with the retinoic X receptor (RXR), which then binds to thyroid hormone responsive elements (TREs) thereby stimulating or inhibiting TH responsive gene transcription [17, 18]. In addition to this genomic action, TH is able to interact with membrane receptors or cellular signal transduction pathways, which have been shown to play an important role in regulating growth, development, and metabolism[19, 20].

![Figure 1.1 HPT axis and thyroid hormone metabolism.](image)

### 1.3 TRH and its non-hypophysiotropic function

TRH plays a key role in determining the set point of TSH secretion and TH homeostasis [11, 21]. In humans, TRH-positive neurons are found mostly in the dorsocaudal
subdivision of the PVN [22]. In the rat, the hypophysiotropic TRH neurons reside exclusively in the medial and periventricular subdivisions of the parvocellular PVN and send axons to the median eminence (ME) to finally control the release of TSH from the anterior pituitary gland [23, 24]. TRH neurons receive dense innervations from other neurons within and outside of the PVN [25, 26], allowing for a neuronal interaction between the thyroid system and other neuroendocrine and neural systems (Figure 1.2). For example, alpha-melanocyte stimulating hormone (α-MSH)/cocaine- and amphetamine-regulated transcript (CART) and AgRP/neuropeptide Y (NPY) neurons from ARC innervate TRH neurons in the PVN [27, 28], providing an anatomical basis for down-regulation of the HPT axis during food deprivation [11, 29]. The biological clock suprachiasmatic nucleus (SCN) also sends its efferent fibres to the PVN TRH neurons, which is important for the diurnal TSH rhythm [30].

In addition to its well-known function in determining the set point of the HPT axis, TRH has a number of non-hypophysiotropic effects involved in the regulation of brain function and energy homeostasis [23, 31]. For example, TRH controls locomotor activity including stimulation of motor and behavioural activities [32, 33], potentiating d-amphetamine- or cocaine-induced locomotor activity [34] [35] and antagonizing alcohol or β-endorphin induced locomotor depression [36, 37]. In addition to the endocrine regulation on food intake via thyroid hormone, TRH also controls appetite directly via neuronal circuits. Both systemic and central TRH administrations reduce food intake [38-40]. Notably, fasting inhibits hypophysiotropic TRH neurons through the orexigenic and anorexic neuronal projections from ARC. However, also the non-hypophysiotropic TRH neurons in the PVN are densely innervated by axons containing CART, NPY and AgRP from ARC [28, 41], suggesting an additional role of the PVN TRH neurons in food regulation. TRH also plays an important role in glucose metabolism. Animals with disrupted TRH signalling show impaired glucose metabolism [42] while central administration of TRH or its analogue was shown to induce hyperglycaemia [43, 44]. Another important function of non-hypophysiotropic TRH neurons is their prominent role in thermoregulation. Systemic TRH administration antagonized pentobarbital-induced hypothermia [45]. Intracerebroventricular (ICV) administration of TRH increased brown adipose tissue (BAT) and core temperature, which was attenuated by sympathetic denervation of BAT [46], suggesting a central effect mediated via the autonomic nervous system. Many studies have shown that TRH injections into the preoptic area of the anterior hypothalamus (POA), a well-recognized primary site for thermoregulation, induce hyperthermia [47-49]. In addition, TRH administration into the POA inhibited heat-sensitive neurons and activated cold-sensitive neurons [47, 49], a mechanism
increasing body heat production and conservation [50]. However, ablation of the POA did not block TRH antagonism of pentobarbital-induced hypothermia, suggesting that sites other than the POA may also mediate the thermogenic effect of TRH [51]. Indeed, TRH injection directly into other distinct hypothalamic areas including DMH and VMH have also been shown to induce hyperthermia [46, 48, 52].

All homoeothermic animals endeavour to maintain a steady body temperature regardless the variation in their external environment. An efficient cold defence mechanism requires an accurate coordination of energy sources (e.g. glucose and fatty acids) and heat production (e.g. shivering and adaptive thermogenesis). Intriguingly, cold exposure greatly increases TRH mRNA and peptide expression in the PVN [54-56], suggesting a pivotal role of PVN TRH during cold defence response. In fact, TRH and the PVN have been shown separately to be involved both in thermoregulation and glucose metabolism, two important adaptive systems during cold exposure, through both endocrine [11, 23, 56] and neuronal pathways [47, 55]. However, direct evidence linking TRH release in the PVN and cold response remains lacking.

Figure 1.2 Inputs to thyrotropin-releasing hormone (TRH) neurons in the PVN involved in energy metabolism. NE, norepinephrine; NTS, nucleus tractus solitarii; ME, median eminence; ANS, autonomic nervous system. Image adapted from Joseph-Bravo, 2004 [25] and Fekete, 2006 [53].
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1.4 Central regulation of thyroid hormone on energy metabolism

In addition to direct effects of TH on target tissues, a number of metabolic effects of TH have recently been shown to be mediated indirectly via the CNS, especially via the hypothalamus [57-59] (Figure 1.3). Previous studies from our group demonstrated that T3 administration directly in the PVN by microdialysis for 2h increased blood glucose concentrations and glucose production by the liver [60]. The hyperglycaemic effect of intrahypothalamic T3 was further proven to be mediated through activation of the sympathetic input to the liver [61]. Studies by Lopez et al showed yet another hypothalamic nucleus, the VMH, to be involved in T3 mediated thermogenesis in BAT [59]. Acute T3 injection in the VMH induced a rapid increase in the activity of sympathetic input to BAT [62]. Furthermore, Kong et al showed increased food intake in rats after a single injection of T3 in the VMH [63]. Later research identified T3-mediated UCP2 activation in the ARC, which was assumed to cause the increased food intake [64]. Another study also pointed towards the ARC as the key site for central T3 regulation of food intake, as stereotactic T3 injection in the ARC increased food intake in rats [65]. The stimulating effect by T3 was probably mediated through the mammalian target of rapamycin (mTOR) pathway as pharmaceutical inhibition of mTOR in the ARC blocked the hyperphagia observed in hyperthyroid rats [65]. Another example of T3-mediated metabolic effects via hypothalamic nuclei was the observation that a population of parvalbuminergic neurons in the anterior hypothalamus (AH) is associated with TH mediated autonomic control of cardiovascular function [66]. Finally, studies in Siberian hamsters provided evidence for a seasonal metabolic effect of T3 in the hypothalamus. Placement of T3-containing pellets in the PVN mimicked a long-day metabolic condition affecting body weight and reproduction [67, 68]. Together, these studies point to a range of TH effects that are mediated at least in part via hypothalamic nuclei [61]. Of note, the duration of the experiments reported so far was mainly short term with a time range from minutes to hours (Figure 1.3). Therefore, it is unknown at present what the role of these novel pathways is in the more chronic setting.
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1.5 Estrogen

Estrogen is one of the primary sex hormones critical in the regulation of reproduction, development and metabolism. There are three major naturally occurring forms of estrogen, i.e., estrone (E1), estradiol (E2), and estriol (E3), with E2 as the most potent and prevalent endogenous estrogen [69]. Circulating estrogens are converted from androgens by the cytochrome P450 enzyme aromatase [70]. Normally, the ovaries are the main source for estrogen production in females, although the conversion of androgen precursors in other tissues is often of clinical importance, e.g. during menopause. E2 acts primarily through the estrogen receptors (ERs) ERα and ERβ [71]. These nuclear receptors are located mainly in the cytoplasm and upon E2 activation translocate to the nucleus where they regulate gene expression by binding to the classic ER response element (ERE) [72, 73]. However, ERs can also transduce signals via non-classic pathways by interacting with: 1) existing transcription factors, such as the AP-1 complex, without direct DNA binding [74]; 2) membrane initiated ERs (mERs) which act through kinases to phosphorylate other transcription factors or G protein-coupled receptors (GPCRs), including GPR30 and Gq-mER [75, 76]; 3) ligand-independent activation through phosphorylation by growth factor receptors [77, 78].

Production of E2 is under control of the hypothalamus-pituitary-gonadal (HPG) axis. GnRH neurons in the hypothalamus release GnRH into the median eminence reaching...
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the anterior pituitary where it stimulates the synthesis and secretion of the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH enter the circulation acting at the ovaries to stimulate gametogenesis and E2 production. E2 has both negative and positive feedback effects on GnRH secretion. It was generally believed that GnRH neurons lack ERs and that the feedback regulation is primarily mediated via kisspeptin (kiss1) neurons [79-82], which have direct projections to GnRH cell bodies in the POA and their terminals in the median eminence. E2 inhibits Kiss1 neurons in the ARC while stimulates Kiss1 neurons in the anteroventral periventricular nucleus (AVPV) therefore exerting both negative and positive feedback control of E2 production [82]. Interestingly, kisspeptin neurons are also involved in energy metabolism forming an essential link between energy status and reproductive function [83]. Of note, collecting studies recently demonstrated that ERs, especially mERs (e.g. GPR30 and STX-R) are expressed in GnRH neurons enabling a direct estrogenic regulation on GnRH neurons [84-86].

In addition to its primary role of regulating reproduction, E2 has numerous physiological effects on metabolism and brain functions including cognition, bone remodelling, adipose tissue metabolism, food intake and energy expenditure [87-89]. Men and women show differences in body fat distribution with men having more central, visceral fat deposition resulting in an “apple-shaped body” and women having more subcutaneous fat around the hips resulting in a “pear-shaped body”. E2 plays an important role in this sexual dimorphism [90]. Estrogen deficiency in postmenopausal women or ovariectomy in rodents induces increased visceral adiposity, and E2 replacement can reverse these changes [91-93]. The mechanism for the estrogenic regulation of fat distribution has remained unclear to some extent. Both androgen receptors (AR) and ERs are found in different white adipose tissue compartments (WATs) [94, 95]. It has been suggested that the differential expression patterns of ERs and AR as well as different amount of sympathetic innervations in different fat depots are important in determining adipose tissue distribution [96-98].

In addition to fat distribution per se, the role of E2 on adiposity has been extensively studied. ERα and aromatase (ArKO) knockout mice showed increased adiposity reflected by both increased adipocyte number and size [99-101], while ERβ knockout mice did not exhibit obesity [100, 102]. Ovariectomized ERα knockout mice showed decreased adiposity which was restored by E2 replacement, indicating an opposite role of ERβ in adipose tissue regulation [103, 104]. In adipocytes, E2 regulates the expression and activity of key enzymes that are involved in lipid metabolism. For example, E2 increases
the expression and activity of hormone sensitive lipase (HSL), the rate limiting enzyme for hydrolysis of stored triglycerides (TG) [105-107], while it decreases lipoprotein lipase activity (LPL), a key enzyme for lipogenesis from free fatty acids (FFAs) in adipose tissue [108, 109]. Additionally, E2 protects against adiposity and weight gain by suppressing food intake and promoting energy expenditure. E2 deficiency in ovariectomized animals resulted in hyperphagia and reduced energy expenditure which was reversed after E2 treatment [110-112]. In women, caloric intake varies according to the menstrual cycle with less feeding when E2 reaches its peak levels [113, 114], consistent with observations in rodents [115]. Different studies showed that E2 was able to interact within the CNS with orexigenic (e.g. NPY and MCH) and anorexigenic peptides (e.g. insulin and leptin) to decrease food intake [116-119]. Furthermore, E2 regulates energy expenditure [111]. This may explain why menopause is associated with reduced energy expenditure [91, 120].

Bones are essential structures in vertebrates to support body shape and protect soft organs. Even in adulthood, bones are constantly broken down (resorption) and rebuild again (formation), a process named bone remodelling [121] (Figure 1.4). In the bone remodelling compartment, the multinuclear foamy cells, osteoclasts (OCs), start with breaking down bone. This is followed by new bone synthesis by another group of cells called osteoblasts (OBs). The neuronal-like osteocytes are also important in the remodelling process, as they form networks which are important for sensing and transducing mechanical information (Figure 1.4) [122]. E2 is a key regulator for bone remodelling both in women and men [123]. This has clinical significance, as after menopause when circulating E2 drops significantly, bone mass decreases resulting in increased fracture risk [124]. E2 replacement may prevent postmenopausal bone loss and the increased fracture risk [125, 126]. Clinical observations and animal research indicated unmatched increases in both bone resorption and bone formation during estrogen deficiency, leading to a net bone loss [127, 128]. ERs are found in all types of bone cells, including OCs [129, 130], OBs [131] [132] and osteocytes [133, 134] suggesting a direct action of E2 regulation on bone [135, 136]. Consistently, OC specific ERα knockout mice showed decreased trabecular bone mass due to the lack of E2 suppression on OCs [137-139]. In vitro and in vivo studies have demonstrated that E2 inhibits bone resorption by inducing apoptosis and differentiation of OCs [140-142]. Indirect regulation of bone involves interactions with local oxidative stress [143], as well as with a number of cytokines including interleukin (IL)-1, tumour necrosis factor-alpha (TNF-α), nuclear factor-kappa B (NF-kB) [144], macrophage-colony stimulating factor (M-CSF), and prostaglandins [145, 146].
1.6 Central role of E2 in fat and bone metabolism

E2 critically regulates white adipose tissue metabolism and bone remodelling through peripheral actions. However, compelling evidence suggests that E2 can also regulate energy metabolism through the CNS [118, 147, 148]. Earlier studies have shown a direct central regulation of E2 on food intake and bodyweight by placement of E2 implants in the hypothalamus [149-151]. Later studies indicated that the anorectic effect of E2 was mediated by activation of POMC neurons in the ARC independently of leptin signalling [152]. WAT is innervated by sympathetic nerves, which has been shown essential for leptin induced lipolysis [153, 154]. An early study showed that decreased fat pad weight after E2 administration was attenuated by denervation in retroperitoneal WAT [155], indicating a sympathetic regulation of WAT by E2. Additionally, Clegg et al. showed that central E2 administration restored the changes in fat distribution after ovariectomy by altering leptin sensitivity, indicating a central control of E2 on WAT metabolism [156]. Although it was still unclear which brain areas may mediate this estrogenic effect on WAT, more recent cell specific ERα knockout studies indicated that the VMH played a critical role in WAT regulation [157, 158]. The VMH has also been shown to be involved in the regulation of energy expenditure by E2. Lopez et al. demonstrated that local E2 administration into the VMH stimulated BAT thermogenesis through the AMP-activated protein kinase (AMPK)-sympathetic nervous system (SNS) pathway [159]. In line, genetic...
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deletion of ERα in the VMH of mice resulted in reduced energy expenditure and locomotor activity [157, 158, 160].

Since 2000, the sympathetic regulation of bone by leptin revealed a direct link between the brain and bone metabolism [161]. Leptin administration by ICV injection in ob/ob (leptin-deficient) mice completely rescued their high bone mass phenotype. Later studies showed that this was mediated by a sympathetic or CART pathway originating in the VMH [162, 163]. Recent studies have shown additional brain-derived peptides, neurotransmitters and cytokines including NPY [164], serotonin [165], neuromedin U [166], brain-derived neurotrophic factor (BDNF) [167], and interleukin-1 (IL-1) [168] to be involved in the regulation of bone remodelling via the CNS [169, 170]. There is also a growing body of evidence to support central regulation of bone by E2. First, deletion of the beta 2 adrenergic receptor (Adrb2) prevented ovariectomy induced bone loss [169], suggesting an essential role of sympathetic signalling in the E2 regulation of bone. The crucial role of estrogen signalling in the brain for bone metabolism was confirmed by studies showing increased bone mass in mice with a brain specific ERα knockout [171,
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172]. The concept of central regulation of bone metabolism by E2 was further supported by the observation that peripheral estrogen receptor antagonist treatment could not completely block the effect of E2 replacement on trabecular bone mineral density in ovariectomized mice [173]. The main findings for effects of E2 on bone and WAT are summarized in Figure 1.5.

1.7 Research questions and thesis outline

In this thesis, we aimed to investigate the indirect effects of TH and E2 via the CNS on energy metabolism by the administration of T3, E2 and TRH into specific hypothalamic nuclei.

Following the observation of acute metabolic effects of T3 administration in the PVN and VMH, we were interested to see whether there would be also effects of longer lasting, chronic T3 administration in the PVN or VMH. In Chapter 2, we therefore aimed to establish an experimental model for chronic T3 administration in distinct hypothalamic nuclei. In Chapter 3, we investigated the chronic effects of central T3 administration in the PVN and VMH on energy metabolism.

Systemic E2 replacement rescues the metabolic disturbance resulting from ovariectomy. Triggered by the evidence for a central regulation of E2 on WAT and bone metabolism, in Chapter 4 we investigated whether these rescuing effects of E2 on WAT metabolism and bone remodelling are mediated through the CNS.

TRH is an important regulator for thermogenesis. Cold exposure increases TRH expression primarily in the PVN; meanwhile, energy sources (e.g. glucose and fatty acids) and heat production (e.g. shivering and adaptive thermogenesis) are activated for proper cold defence. In Chapter 5, we investigated the role of TRH administered in the PVN in the cold defence in rats. Finally, in Chapter 6 we investigated the effects of TRH administration on BAT activation in human subjects.

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