HHS Public Access

Author manuscript

Nat Rev Endocrinol. Author manuscript; available in PMC 2020 June 11.

Published in final edited form as:

Nat Rev Endocrinol. 2019 October ; 15(10): 590–600. doi:10.1038/s41574-019-0237-z.

Interconnection between circadian clocks and thyroid function

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Abstract

Circadian rhythmicity is an approximately 24h cell-autonomous period driven by transcription–translation feedback loops of specific genes, which are referred to as ‘circadian clock genes’. In mammals, the central circadian pacemaker, which is located in the hypothalamic suprachiasmatic nucleus, controls peripheral circadian clocks. The circadian system regulates virtually all physiological processes, which are further modulated by changes in external environment, such as light exposure and timing of food intake. Chronic circadian disruption caused by shift work, travel across time zones or irregular sleep-wake cycles has long-term consequences on our health and is an important lifestyle factor that contributes to the risk of obesity, type 2 diabetes mellitus and cancer. Although the hypothalamic–pituitary–thyroid axis is under the control of the circadian clock via the suprachiasmatic nucleus pacemaker, daily TSH secretion profiles are disrupted in some patients with hypothyroidism and hyperthyroidism. Disruption of circadian rhythms has been recognized as a perturbation of the endocrine system and of cell cycle progression. Expression profiles of circadian clock genes are abnormal in well-differentiated thyroid cancer but not in the benign nodules or a healthy thyroid. Therefore, the characterization of the thyroid clock machinery might improve the preoperative diagnosis of thyroid cancer.

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Author contributions

All author researched data for the article, contributed to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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Introduction

Thyroid hormones (precursor thyroxine T_4 and active T_3) are iodine containing compounds (iodothyronines) that are important for metabolism, heat production, proper development and differentiation of cells, and growth. Thyroid hormone synthesis and secretion are primarily regulated by TSH, which is derived from thyrotrophs located in the pars distalis in the anterior pituitary gland. TSH production and secretion are regulated by hypothalamic thyrotropin-releasing hormone (TRH). Circulating thyroid hormones control the synthesis and release of TRH and TSH from pars distalis as part of a classic negative-feedback loop called the 'hypothalamic–pituitary–thyroid (HPT) axis'[1,2](FIG. 1).

Organisms are exposed to various rhythmic events, such as daily and seasonal cycles. To better adapt to these cyclic environmental changes, organisms have evolved biological clocks. An approximately 24-h cell-autonomous circadian clock is present in virtually all cells of the body, and this circadian system tightly regulates physiological functions and endocrine rhythms[3].

Several lines of evidence indicate that chronic circadian disruption, which can be caused by shift work or travel across time zones, has long-term consequences on human health and increases the risk of weight gain, type 2 diabetes mellitus, cardiovascular disease and several types of cancer[4–7]. Circadian disruption of the endocrine system is one of the main mechanisms that mediates these circadian-related adverse consequences[6–8]. Many endocrine factors are known to show time-dependent variations; for example, TSH secretion exhibits a clear daily rhythmicity, and the HPT axis is under circadian control via the central circadian pacemaker in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus[9].

In this article, we review the interconnection between circadian clocks and thyroid function. We first describe the regulatory mechanisms controlling the HPT axis and provide an overview of the circadian system. We then summarize the current state of knowledge regarding the circadian regulation of the HPT axis. Furthermore, we discuss the connection between disruptions of central and peripheral circadian pacemakers and thyroid function. In addition, we highlight the possible link between thyroid cancer and disrupted circadian machinery.

HPT axis and thyroid hormone activation

In this section, we provide a brief overview of the regulatory mechanism of the HPT axis and highlight the importance of local activation of thyroid hormone. TSH, which is a pituitary-derived hormone that stimulates the thyroid gland to produce T_4 and T_3, is a non-covalently linked heterodimer glycoprotein that consists of α and β subunits. The release of TSH is controlled by the tripeptide hormone TRH (FIG. 1). Derived from a subset of neurons in the paraventricular nucleus of the hypothalamus, TRH is secreted from the hypothalamic median eminence to the anterior pituitary via the hypothalamic–hypophyseal portal system.[1,2,10].

TRH binds to its membrane receptor on thyrotrophs in the pars distalis of the anterior pituitary and stimulates the synthesis of TSH by inducing mRNA expression of *TSHA* and

TSHB, which encode the TSH α and β subunits, respectively[11]. The most sensitive marker of thyroid hormone action are blood levels of TSH, which are elevated in patients with hypothyroidism owing to reduced negative feedback suppression of TRH and TSH. The thyroid gland machinery is stimulated to produce thyroid hormones by TSH binding to the TSH receptor (a G protein-coupled receptor on the thyroid follicle cell membrane), which in turn stimulates the secondary messengers c AMP and inositol phosphate[12].

In vertebrates, thyroid hormone is the only hormone that contains iodine. Iodine is taken up from the bloodstream into thyroid follicles. Thyroglobulin, which is a protein that is produced by thyroid epithelial cells, is secreted and stored in the follicular lumen. Thyroglobulin acts as a backbone for tyrosine residues that are subsequently iodinated. After internalization from follicular lumen into follicular cells, iodinated thyroglobulin is degraded through the lysosomal pathway, to release mainly T_4 and some T_3 into the bloodstream. These two iodothyronines circulate, bound reversibly to thyroid hormone-binding proteins: thyroxine-binding globulin, transthyretin, and albumin[2]. Unbound, also known as 'free', thyroid hormone is transported into target tissues by membrane transporters. The most important membrane transporter for the brain is the monocarboxylate transporter 8 (MCT8)[13] and the most important transporters in other tissue are MCT8 and the organic anion transporter polypeptide OATP1C1[14].

As the mammalian thyroid gland predominantly produces the hormone precursor, T_4, local activation of thyroid hormone at target tissues is an important mechanism of thyroid hormone action[2,15]. Following entry into the cell, thyroid hormone is metabolized by deiodinase enzymes. Type 1 iodothyronine deiodinase (DIO1) and type 2 iodothyronine deiodinase (DIO2) function principally as thyroid hormone activators, generating T_3 from T_4 by removing one iodine from the 5' position of T_4[15]. They have variable levels of expression in tissues and cell types and in different species; DIO1 is commonly found in liver and kidney, and type 3 iodothyronine deiodinase (DIO3) is normally expressed in the central nervous system and placenta, while DIO2 is more widely expressed in humans. However, unlike humans, rodents express little or no DIO2 in their myocardium[16].

DIO3 inactivates thyroid hormone by removing iodine from the 5 position of T_4 and T_3, which generates the inactive iodothyronines reverse T_3 and T_2, respectively[16]. Locally generated T_3 is partially released from tissues to the circulation[16]. As thyroid hormones act on nuclear hormone receptors to regulate target gene expression, released T 3 and T_4 act as part of a feedback loop that inhibits the production of hypothalamic-derived TRH and pars distalis-derived TSH (FIG. 1).

The thyroid hormone receptor has isoforms, TRα and TRβ. When T_3-bound, these two receptors repress *TRH* and *TSHB* gene expression by binding to some thyroid hormone response elements (sequences containing [A/G]GGT[G/C/A]A) on DNA as either a thyroid hormone receptor monomer, thyroid hormone receptor homodimer, and/or thyroid hormone receptor –retinoid X receptor heterodimer in the *TRH* promoter[17] or the *TSHB* promoter[18,19]. In the presence or absence of thyroid hormone, the thyroid hormone receptor complexes regulate positively or negatively target gene expression by interacting with co-activators or co-repressors, respectively[2].

Circadian clocks and the master pacemaker

Circadian clocks are highly conserved, endogenous time-keeping mechanisms present in virtually all living organisms. These clocks generate self-sustained oscillations with an approximately 24-h period, referred to as 'circadian rhythms'[3]. Circadian rhythms modulate multiple physiological and behavioral processes, including sleep–wake cycles, hormone release and metabolism[3].

In mammals, these daily rhythms are primarily controlled by a population of neurons and astrocytes in the SCN, a paired structure located in the anterior hypothalamus above the optic chiasm[20,21]. The SCN, which is considered the master pacemaker, receives direct light information from the retina through the retinohypothalamic tract (FIG. 2). Within the retina, intrinsically photosensitive ganglion cells are primarily responsible for 'circadian photoreception' and the entrainment of the circadian pacemaker to environmental light–dark cycles[22,23], while classical rod and cone photoreceptors have only a supportive role (of note, more than 50% of people who are totally blind have normal entrainment of the circadian pacemaker because their intrinsically photosensitive retinal ganglion cells are intact). Most peripheral tissues and cells also contain self-sustained circadian oscillators that, under normal conditions, are synchronized with the SCN clock via neural and humoral pathways (that is, the autonomous nervous system and the 24-h rhythms of glucocorticoid and melatonin levels)[3,24,25].

Molecular mechanisms of the clockwork

The 2017 Nobel Prize for Physiology or Medicine was awarded for the discovery of the molecular mechanism driving circadian rhythms[26]. Briefly, circadian rhythms are generated by transcription–translation feedback loops consisting of circadian clock genes and proteins[27] (FIG. 3). The basic helix-loop-helix proteins circadian locomotor output cycles kaput (CLOCK) and brain and muscle Arnt-like protein 1 (BMAL1) heterodimerize to form a transcriptional activator complex and activate the period (*PER*) and cryptochrome (*CRY*) repressor genes through E-box (CACGTG) enhancers, whose protein products in turn repress their own transcription[28,29]. The CLOCK–BMAL1 heterodimer also induces reverse strand of ERBα (REV-ERBα) and REV-ERBβ, and retinoic acid receptor-related orphan receptor-α (RORα), RORβ and RORγ, which regulate *CLOCK* and *BMAL1* genes through ROR elements but exert opposite effects on gene transcription, thus constituting a second important interlocking feedback loop[30–32] (FIG. 3).

The transcription–translation feedback loops of circadian clock genes drive rhythmic expression of many clock-controlled genes. The latter represent between 3% and 16% of the transcriptome in a given tissue[33]. As clock-controlled genes include genes that modulate transcription, signal transduction, protein turnover and metabolism, the circadian clocks influence various cellular, organ and physiological functions in a manner that depends on the time of day.

Circadian regulation of the HPT axis

Evidence of TSH rhythms.

In this section we describe how the internal circadian clock regulates the mammalian HPT axis and thyroid function. As is the case for other pituitary hormones, TSH secretion is partly controlled by the central circadian pacemaker in the SCN[34,35] (FIG. 2). In humans, circulating TSH levels exhibit a clear daily rhythm. Plasma concentrations begin to rise in the late afternoon or early evening before sleep onset, and reach maximal levels during the early part of the night. Following the nighttime peak in TSH, plasma TSH concentration then declines during the rest of the sleep period until reaching low daytime levels.

Multiple studies that examined sleep deprivation and acute shifts of the sleep period have reported that TSH release into the blood is inhibited during sleep[36,37]. The interaction between the circadian-controlled nocturnal rise in TSH and the inhibitory effect of sleep is illustrated in the lower panel in FIG. 4, which shows the mean profile of plasma TSH levels in healthy young men who were sampled at 20-min intervals over a 53-h period, including an 8-h period of ‘normal’ average night sleep, a night of total sleep deprivation and an 8-h period of daytime recovery sleep[36]. TSH release, which is normally inhibited during sleep, continues to occur during nocturnal sleep deprivation. Therefore, morning plasma TSH levels are roughly twice as high in humans who have had a sleepless night than in humans who have had a night of normal sleep[36].

The upper panel in FIG. 4 illustrates a representative individual plasma TSH profile. It shows that a low amplitude **ultradian** rhythm of TSH is also present in humans, which reflects the pulsatile release of the hormone[34,38] (Table 1). This ultradian rhythm seems to be influenced by the sleep stage such as the slow-wave sleep[38] and food intake[39]. Thyroid hormone and glucocorticoid have also been to modulate the pulsatile secretion of TSH in healthy men[40].

Mechanisms.

The mechanisms generating ultradian TSH rhythms are still unclear[41,42]. Several studies have reported no intergender differences in circadian and ultradian TSH release patterns[43,44]; however, a paper from 2015 based on 324,750 outpatients with no known thyroid disease found that females have higher plasma TSH levels than males[45].

In addition to the well-characterized rhythm in plasma levels of TSH, daily variations in plasma thyroid hormone levels have also been reported in the humans and in wild-type rats[46,47]. Some studies, however, have not detected these variations[48,49]. This discrepancy is thought to result from differences in experimental conditions and analytical tools between research groups[50]. It should also be noted that nocturnal rodents might not be an ideal model to explore the mechanisms underlying the human temporal control of TSH and thyroid hormone release. The reason that laboratory rodents are not an ideal model is because they undergo multiphasic sleep during the light phase whereas humans have a consolidated nocturnal sleep period.

Neural projections from the SCN to TRH neurons in the paraventricular nucleus form the anatomical basis for the daily rhythms in TRH synthesis and secretion, and thus are responsible for rhythmic TSH secretion from the pars distalis[9,51–53] (FIG. 2). Indeed, in rats, an SCN lesion abolishes the rhythmicity of circulating TSH and thyroid hormones, which suggests that the SCN is involved in the regulation of the HPT axis[53,54] (Table 1); however, peripheral clocks can also regulate rhythmic transcription of genes that regulate hormone secretion, for example, human growth hormone (*GH*)[55]. Indeed, in the mouse TαT1.1 thyrotroph cell line, the circadian rhythmicity of *Tshb* expression is regulated by the local circadian clock (REV-ERBα) along with the Tr complex co-activator nuclear receptor corepressor 1 (NCOR1)[56] (Table 1). Of note, however, hypophysectomy extinguishes the rhythmicity of circulating thyroid hormone levels, but not the rhythmicity of circadian clock genes (*Per1* and *Bmal1*) in rat thyroid[57]. These data suggest that the daily rhythm of thyroid hormone release from the thyroid gland is regulated by the central circadian pacemaker in the SCN via rhythmic TSH secretion, rather than by the local circadian clock in the thyroid gland.

Some studies have demonstrated that genes encoding thyroid hormone receptors exhibit rhythmic expression in mouse white adipose tissue (*Thra* and *Thrb*), brown adipose tissue (*Thra*), kidney (*Thra*), and liver (*Thra*)[58–60]. Furthermore, real-time qPCR has shown rhythmic expression of thyroid hormone receptors in rat liver (*Thra* and *Thrb*)[54]. A lesion study in rats showed that the rhythmic expression of liver TRα is regulated by the SCN, whereas that of TRβ is affected by food intake[54]. Interestingly, in humans, mice and rats, the *Thra* overlaps with *Rev-erba*, which is on the opposite DNA strand[61]. This finding lead to the speculation that circadian *Thra* expression is mediated by an antisense mechanism[61]; however, strand-specific RNA-sequencing revealed that *Thra* does not show a clear oscillation in mouse liver[62]. Arrhythmic expression of both *Thr* genes has also been reported in mouse skeletal muscle[58]. These discrepancies could be due to tissue-specific expression patterns or the analytical methods used.

Circadian rhythms in thyroid diseases

In the previous section, we described the link between circadian clocks and thyroid function. Here we consider the relationship between circadian rhythms and thyroid diseases, specifically hypothyroidism and hyperthyroidism.

Hypothyroidism.

A reduced production of thyroid hormones is the central feature of hypothyroidism. Loss of the thyroid gland function through a destructive processes including autoimmunity (Hashimoto disease), irradiation, or surgical ablation, and congenital defects in hormone synthesis or gland development are termed ‘primary hypothyroidism’. Central hypothyroidism is caused by dysfunction of the pituitary (secondary hypothyroidism) or the hypothalamus (tertiary hypothyroidism). Defects or damage to brain regions results in insufficient stimulation of the normal thyroid gland. Approximately 99.9% of cases of hypothyroidism are caused by primary hypothyroidism, but it depends on age[63,64].

The term ‘subclinical hypothyroidism’ is applied to primary hypothyroidism when TSH is high but free T_4 is still in the normal range. In this form of mild hypothyroidism, total TSH secretion is increased above the upper limit of normal while in severe hypothyroidism the increase could be as high as ~200-fold[65]. The daily TSH secretion pattern is sustained in mild hypothyroidism, but markedly high serum TSH levels in severe cases obliterate the detection of rhythmicity[66,67]. A study from 2016 revealed higher serum TSH levels and an elevated risk of subclinical hypothyroidism in night shift workers than non-night shift workers[68] (FIG. 5a). However, because the authors of this study measured serum TSH levels at only one time point during the day, careful evaluation is necessary as this alteration could be caused by a phase shift of the TSH rhythm. Autoimmune thyroid disorders are also associated with shift work[69].

In central hypothyroidism caused by inactivating mutations in TRH and TRH receptor, serum TSH concentration is within subnormal or mildly increased levels[70]. In such cases, however, circulating T_4 levels are diminished. Cranial irradiation therapy for brain tumors and leukemia also cause abnormal TRH secretion patterns, leading to disrupted or absent TSH rhythm[71]. Glycosylation influences the bioactivity and half-life of glycoprotein hormones[72], and the pars distalis TSH glycans are mainly biantennary and sulfated complexes[73]. Diminished T_4 levels accompanied by elevated or normal TSH levels in central hypothyroidism are caused by a reduction in the bioactivity of TSH due to increased sialylation of glycan[74]. As TRH regulates sulfation and sialylation of TSH glycan[75], TRH deficiency also induces abnormal glycosylation of TSH, resulting in loss of the normal circadian pattern of TSH secretion[71,76].

Defects in thyroid hormone receptors cause reduced sensitivity to the hormone[77]. In patients with a mutation in *THRB*, elevated serum T_4 and T_3 and slightly elevated or normal TSH are observed due to a reduced negative feedback of the HPT axis[77]. Enlargement of the thyroid gland and increased synthesis of thyroid hormone result from an increase in TSH bioactivity[78]. In most patients, basal serum TSH concentration is normal and the circadian rhythm is preserved[79].

Decreased sensitivity to thyroid hormone caused by THRA mutations manifests in affected tissues expressing mainly the THRA gene[80]. The clinical features of such patients are dysmorphic features, skeletal dysplasia, growth retardation and intellectual deficit[80]. The associated biochemical abnormalities include low or low to normal T_4 concentrations and high or high to normal T_3 concentrations[80].

Hyperthyroidism.

In marked contrast to hypothyroidism, hyperthyroidism is characterized by excessive quantities of thyroid hormones in the presence of normal thyroid hormone receptor expression[50]. Common conditions causing hyperthyroidism include overstimulation of the thyroid gland by immunoglobulins that bind to the TSH receptor, activating mutations of the TSH receptor and (although rarely) TSH producing pituitary tumors[50]. Circadian rhythmicity of serum TSH levels in hyperthyroidism is not expected as TSH is suppressed and diurnal rhythm of thyroid hormone does not occur because hormone synthesis and secretion is under the control of immunoglobulins[81]. In rare instances of hyperthyroidism

that result from TSH producing pituitary adenomas, the TSH secretion pattern is more irregular, but the diurnal rhythm is preserved[82].

Thyroid hormone and gene expression

Next, we describe how thyroid hormone deficiency and excess affect the circadian clock. When wheel running activity rhythms were studied under constant condition, surgical removal of the thyroid and parathyroid glands shortens the period of circadian activity rhythms in rats[83,84], and thiourea and thyroxine administration lengthens the period of circadian activity rhythms in hamsters and rats[84,85](Table 2). However, as knocking out *Thrb* does not directly alter the circadian behaviour of mice[86], effects of thyroid hormones on circadian behaviour might be mediated by Trα. It is interesting to note that Trα is predominantly expressed in the heart[87].

In rats, the expression patterns of circadian clock genes (*Per2*, *Bmal1*, *Rev-erba*, and *Rora*) and clock-controlled genes (*Pdk4* and *Ucp3*) in the heart are affected by hyperthyroidism and hypothyroidism, which suggests that chronic alterations in thyroid status affect the circadian clock and metabolic function in this organ[88](Table 2). In the rat brain, thyroidectomy affects the expression of PER2 in the bed nucleus of the stria terminalis, as well as the amygdala, while it does not affect the SCN clock[89](Table 2). Moreover, co-culture with thyroid gland does not modulate the circadian rhythms of Rat-1 fibroblasts[90]. These data indicate that abnormal serum levels of thyroid hormone affects the circadian clocks in peripheral tissues, which might be dependent on tissue-specific thyroid hormone receptor regulation.

The circadian clock and tumorigenesis

In this section, we describe the molecular link between circadian clocks and cancer. Disruption of the circadian clocks due to shift work or travel across time zones leads to circadian desynchrony, or jet lag, which reflects a mismatch between the internal biological clock and external time cues[91] (BOX 1; FIG. 5a).

Chronic circadian disruption has long-term consequences on our health and increases the risk of cancers in the immune, skeletal, digestive and reproductive organs that require cell proliferation, metabolism, and DNA damage repair to maintain daily function[7]. In fact, variants of various clock genes (*PER1, PER2 and PER3*, and *CRY1 and CRY2*, in addition to *REV-ERB* genes and *ROR* genes) are associated with thyroid cancer in humans[7]. Circadian disruption also affects endocrine functions, including glucocorticoid, melatonin, and pituitary hormone)[8]. Specifically, in the HPT axis, disruption of plasma levels of TSH and T_3 have been observed in shift work, jet lag and chronic sleep debt in humans[37,68,92,93] (Table 1; FIG. 5b). The normal evening rise of plasma levels of TSH is decreased or absent in human in a sleep debt condition achieved by bedtime restriction for 4 h for six nights compared with a fully rested condition (allowed 12 h in bed per night for six nights)[37] (Table 1; FIG. 5b).

Because chronic circadian disruption has long-term consequences on our health[7], it is necessary to evaluate the effects of long-term circadian and sleep disruption on the HPT

axis. Some studies suggest that elevated concentrations of serum TSH is linked to the incidence of human thyroid cancer[94–96]; however, it is not clear if this is causative or the consequence of the cancer. Furthermore, two 2018 cohort studies that investigated circadian disruption in flight attendants and flight crews did not provide convincing evidence of an association with elevated risk of thyroid cancers[97,98]. Therefore, further studies are indeed required to clarify the relationship between circadian disruption and thyroid cancer further studies are indeed required to clarify the relationship between circadian disruption and thyroid cancer.

Loss of cell cycle regulation also leads to the development of cancer[99–101]. It remains unclear whether, and if so to what extent, circadian clocks are involved in this process; however, synchronization of circadian clock function in tumor cells impinges on the cell cycle and suppresses cellular growth[99]. Emerging evidence suggests molecular connections between the circadian clock and cell cycle regulators, such as Wee1 (which inhibits the G2/M transition by phosphorylation of CDK1), and Cyclin B1 (Ccnb1) in melanoma cells. For example, Clock/Bmal1 activates *Wee1* in mouse liver, and PER influences the transcription of *WEE1* and *CCNB1* in human cancer cell[100,101].

PER1 and PER2 are necessary for transcriptional activation of cell cycle checkpoint genes in several mouse tissues[102]. *Bmal1* positively regulates the p53 tumor suppressor pathway and has anti-tumor activity in human pancreatic cancer[103]. Genetic manipulations in mice have demonstrated the direct relationship between tumor and clock genes through activation of cell cycle in spontaneous and radiation-induced tumor development in liver, ovary, kidney[104], lymphoid tissue[105] and lung[106]. In the case of thyroid cancer, increased expression of the circadian clock component DEC1 (differentially expressed in chondrocytes 1), which targets the E-box, is reported to drive the expression of many cell cycle-related genes and promotes thyroid cancer in humans[107](Table 1).

Circadian clocks in thyroid nodules and thyroid cancer.

In this section, we explore the potential link between circadian clocks and the development of thyroid cancer. Although the aforementioned studies suggest that there could be a causal link from disruption of the circadian system to cancer, other studies have established a link in the opposite direction[108,109]. Multiple aspects of tumours, including the *RAS* and *MYC* oncogenes, can induce dysregulation of circadian clocks in human cancer cell lines[108,109]. While it remains unclear whether the circadian clock is actually disrupted within human tumors *in vivo*, it is important to characterize the profiles of clock disruption in human cancers in order to develop novel anti-tumor strategies.

Thyroid nodules, defined as any discrete mass in the thyroid gland, can often represent an abnormal growth of thyroid cells in discrete regions within the thyroid gland, are often detected in humans, but most are non-cancerous (benign)[110]. Well-differentiated thyroid cancer constitutes the vast majority (more than 90%) of all thyroid cancers[111,112]. Poorly differentiated thyroid carcinoma is less common than well-differentiated thyroid cancer but is more aggressive[111,112]. Robust circadian oscillation of clock genes has been observed in primary cultured thyrocytes established from healthy human thyroid tissue and benign nodules[113]; however, the up-regulation of *BMAL1* and down-regulation of *CRY2* have been

detected in tissue samples from well-differentiated thyroid cancer, and dramatic changes in circadian clock genes expression has been reported in poorly differentiated thyroid carcinoma[113]. Therefore, it is hypothesized that the circadian clock machinery in the thyroid could be altered during malignant transformation[113] (Table 2). Thyroid nodules are detected in up to 65% of the general populations and are usually benign[110]. Mutational analysis and gene expression analyses are two common molecular tests for malignancy. Mutational analysis involves sequencing specific proto-oncogenes, such as *BRAF* and *RAS*, for possible mutations. In contrast, gene expression analysis examines specific gene sets, called 'gene expression classifiers'. However, because of the low positive predictive value, refinement in molecular testing strategies with improved diagnostic performance is required[110]. As alterations in the clock machinery are observed in malignant transformation of thyroid nodules, it is hypothesized that characterization of circadian clock genes expression might help improve pre-operative diagnosis of thyroid nodules. This hypothesis should be addressed in future studies.

Seasonal rhythms and thyroid function

In addition to circadian rhythms, thyroid function is intimately linked to seasonal rhythms. In this section we discuss the link between seasonal rhythms and thyroid function. Most animals exhibit seasonal changes in physiology and behaviour, such as reproduction, migration and hibernation, in order to adapt to seasonal changes in environment[114]. In rats and hamsters, the circadian rhythms of levels of TSH and thyroid hormones in the blood exhibit seasonal changes[115,116].

Seasonality has also been reported in humans, including alterations in mood, immune function, duration and amplitude of melatonin secretion, endocrine function and gene expression[117,118]. Some studies in humans reported that levels of thyroid hormone in the circulation decrease during the summer[119,120]. Although several studies have demonstrated that humans exhibit seasonality in circulating levels of TSH[119,121], other cohort studies have argued that TSH has little seasonality[45,122]. In thyrotoxicosis, the peak incidence of diagnosis of hyperthyroidism probably occurs during the summer because the symptoms of heat intolerance in patients with hyperthyroidism are more noticeable during the summer period[123]. Thyroid cancers exhibit an annual rhythm, with markedly more patients presenting with the disease during the late autumn and winter[124]. The underlying mechanisms of seasonal regulation of these thyroid diseases remains to be elucidated.

Seasonal reproduction of animals ensures the survival of offspring. A 2008 functional genomic analysis of seasonal breeding animals revealed unexpected roles of TSH and thyroid hormone in the regulation of seasonality[125]. Long-day stimulus induces TSH production in the pars tuberalis of the pituitary gland in birds[125]. TSH derived from the pars tuberalis acts on the hypothalamus to induce *DIO2* and downregulate *DIO3*[125] (FIG. 6). The switch from DIO2 to DIO3 fine-tunes local bioactive thyroid hormone concentrations within the hypothalamus, which in turn regulates seasonal reproduction in birds and mammals[126–129]. Thyrotrophs in the pars tuberalis lack TRH receptors and thyroid hormone receptors, which makes pars tuberalis-derived TSH independent from the HPT axis in mammals[73,130].

The hormone melatonin, which is released by the pineal gland, provides an endocrine representation of seasonal information (such as changes in day length) via the SCN–pineal pathway in mammals[131]. Studies using knockout mice revealed that thyrotrophs in the pars tuberalis are the targets of nocturnal melatonin; specifically, pars tuberalis-derived TSH is negatively regulated by melatonin via the MT1 melatonin receptor[128,132] (FIG. 6). A 2014 murine study revealed that pars tuberalis TSH is secreted into the circulation at a level similar to pars distalis-derived TSH, but has minimal effects on the thyroid gland[73] (BOX 2; FIG. 6). Hibernation in mammals, including primates and rodents, is also an important adaptation strategy[133,134]. A 2018 in hamsters demonstrated that *Dio2* expression is decreased in the brown adipose tissue during hibernation[135], suggesting important roles for thyroid hormone in various seasonal adaptation mechanisms.

Future directions

The precise role of circadian clocks in thyroid function and diseases needs to be addressed in future studies. Thyroid-specific conditional knockout of circadian clock genes and/or circadian clock manipulation within the functional thyroid tissue derived from embryonic or pluripotent stem cells would provide an opportunity to test the link between circadian clock and thyroid function and disease[136].

The disruption of circadian clocks has been implicated in various diseases, and accordingly the identification of circadian clock modulators might provide new opportunities for treatment of clock-related disorders[137]. Studies from 2018 and 2019 have demonstrated that agonists of the REV-ERB proteins are specifically lethal to cancer cells and that a selective CK2 inhibitor inhibits cancer cell growth[138,139]. Therefore, pharmacological modulation of the circadian machinery may be an innovative and selective strategy for treating a wide spectrum of cancers, including thyroid cancer[139].

Conclusions

To better adapt to daily environmental changes, animals have evolved circadian clock for the regulation of various physiological and endocrine rhythms[3]. The HPT axis is controlled by the circadian system, with a predominant role for the central pacemaker in the SCN, as well as the sleep-wake cycle[34,35,53,54]. Thyroid status such as hypothyroidism, hyperthyroidism, and thyroid cancer affects peripheral circadian clocks[83–90]. Thus, thyroid function and circadian clocks are interconnected. Epidemiologic studies have suggested that chronic circadian disruption has long-term consequences on our health and is an important lifestyle factor that contributes to the risk of developing obesity, diabetes, cancer, and cardiovascular disease[4–7]. Indeed, chronic sleep dept disrupts rhythmic TSH secretion[37]. Generalized disruption of the endocrine system is one of the important mechanisms thought to mediate the adverse effects of circadian misalignment[6–8]. Although several studies suggested that elevated serum TSH level is linked to the incidence of human thyroid cancer[94–96], relationship between circadian disruption and thyroid cancer require further investigation. By contrast, perturbation of oncogene can induce dysregulation of circadian clock[108,109] and disrupted circadian clock gene expression is reported during thyroid nodule malignant transformation[113]. Since disruption of circadian clocks has been implicated in various

diseases[137], pharmacological modulation of the circadian clock machinery might provide a new strategy for the treatment of thyroid diseases[139].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the JSPS KAKENHI Grant-in-Aid for Specially Promoted Research (26000013), for Young Scientists (B) (17K15574), the Human Frontier Science Program (RGP0030/2015), and the National Institutes of Health (PO1 AG-11412 and R01 DK-15070). WPI-ITbM is supported by the World Premier International Research Center Initiative (WPI), MEXT, Japan.

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Box 1.

Central clock versus peripheral clocks

The mammalian circadian system is comprised of the central master pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) and a multitude of peripheral circadian clocks that use the same molecular machinery as the SCN clock and receive synchronizing inputs from the central clock. When disconnected from the central clock, the peripheral clocks are capable of generating self-sustained circadian oscillations under constant environmental conditions for at least a few cycles[25]. Circadian misalignment occurs when the central clock is not aligned with the peripheral clocks and/or when distinct peripheral clocks are not in synchrony with each other[91]. Circadian misalignment can happen when a stimulus that affects a peripheral tissue (such as the feeding schedule for the liver) does not affect another peripheral tissue (for example, those that are not sensitive or less sensitive to dietary cues)[3].

Box 2.

Pars tuberalis TSH and macro-TSH

TSH is a glycoprotein[72]. A 2014 study in mice revealed that TSH derived from pars tuberalis is secreted into the circulation but has little bioactivity in the thyroid gland[73]. TSH from the pars tuberalis has decreased bioactivity because it forms macro-TSH complexes with immunoglobulin (IgG) and albumin in the circulation[73]. These complexes form as the result of differences in *N*-glycosylation patterns between TSH derived from the pars tuberalis (with sialylated multibranched *N*-glycans) and TSH derived from the pars distalis (with sulfated bi-antennary *N*-glycans)[73] (FIG. 6). Therefore, tissue-specific glycosylation of TSH in the pars tuberalis and pars distalis compartmentalizes TSH function, thereby preventing functional crosstalk within the body. These tissue-specific features of glycosylation seem to be due to tissue-specific expression of glycosyltransferases[73].

In humans, primary or central hypothyroidism and hyperthyroidism are sometimes associated with high serum levels of macro-TSH complex (that is, high molecular weight TSH-IgG complex with reduced bioactivity)[140–142]. However, high serum levels of TSH that result from the presence of macro-TSH complex are found in the absence of thyroid dysfunction and in the presence of normal thyroid hormone levels, although the underlying mechanism for this remains unclear[143,144]. The dynamics of circulating TSH in individuals with high TSH but without thyroid dysfunction are similar to those of TSH that is derived from pars tuberalis. That is, the circulating TSH in these individuals has sialylated multibranched *N*-glycans with low bioactivity and a long half-life[74,75,141,142,145]. Although seasonality has been reported in many human functions, such as mood, immune function, metabolism and hormone secretion, their underlying mechanisms remain unknown[117,118]. Therefore, the functional significance of human TSH derived from the pars tuberalis is of interest[146].

Key points

- The hypothalamic–pituitary–thyroid axis is controlled by the central circadian pacemaker located in the suprachiasmatic nucleus.
- Daily TSH secretion profiles are often disrupted in patients with hypothyroidism or hyperthyroidism.
- Circadian dysfunction caused by shift work, travel across time zones or irregular sleep-wake cycles might be a novel lifestyle risk factor for disturbances in thyroid homeostasis in modern societies.
- Disruption of circadian clock genes *in vivo* and *in vitro* disturb cell cycle progression.
- The circadian clock is thought to be disrupted in well-differentiated thyroid cancer.

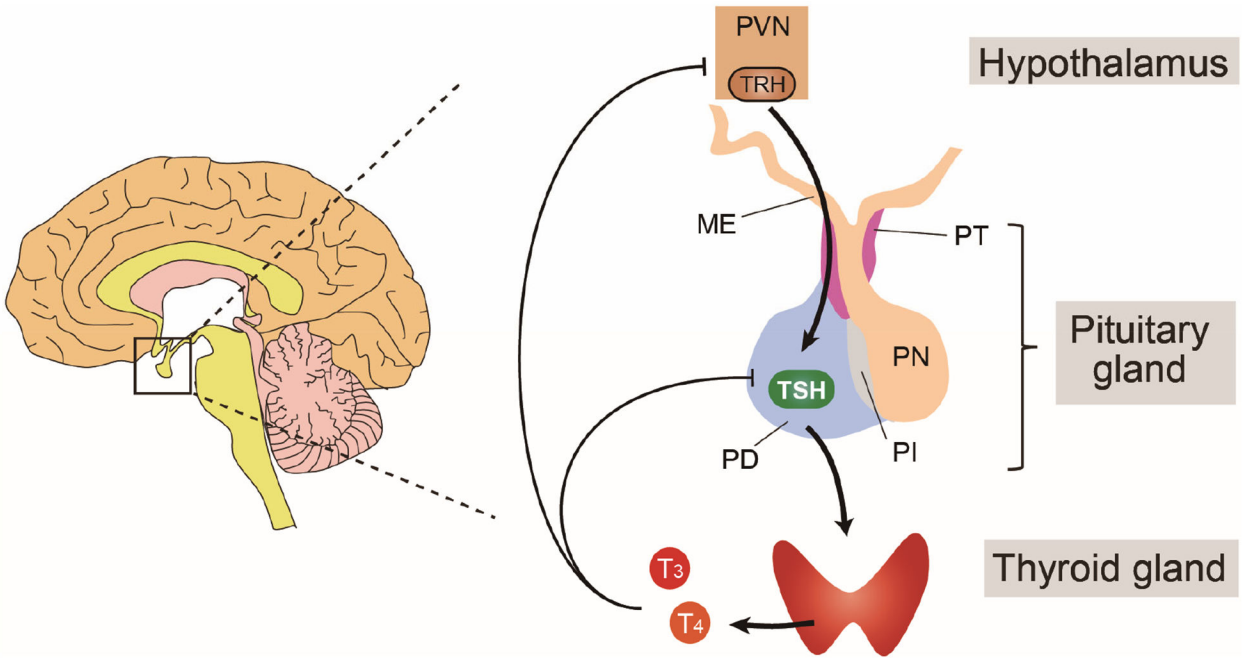

Figure 1. Hypothalamic–pituitary–thyroid axis.

Thyrotropin-releasing hormone (TRH) produced in the paraventricular nucleus (PVN) is secreted from the median eminence (ME) and transported to the pituitary via the hypothalamus–hypophyseal portal system. TRH stimulates thyrotrophs to synthesize TSH in the pars distalis (PD) of the pituitary gland by upregulating mRNA levels of *TSHA* and *TSHB*. TSH stimulates the thyroid gland to produce thyroid hormones (predominantly the prohormone T_4) via the TSH receptor on the thyroid follicle cell membrane. TSH induces most of the essential events in thyroid hormone production. T_3 derived from circulating T_4 regulates synthesis and release of TRH and pars distalis TSH as part of a negative feedback loop mediated by the thyroid hormone receptor. This regulatory pathway is called the 'hypothalamic–pituitary–thyroid axis'[1,2]. PT, pars tuberalis; PN, pars intermediate; PI, pars nervosa.

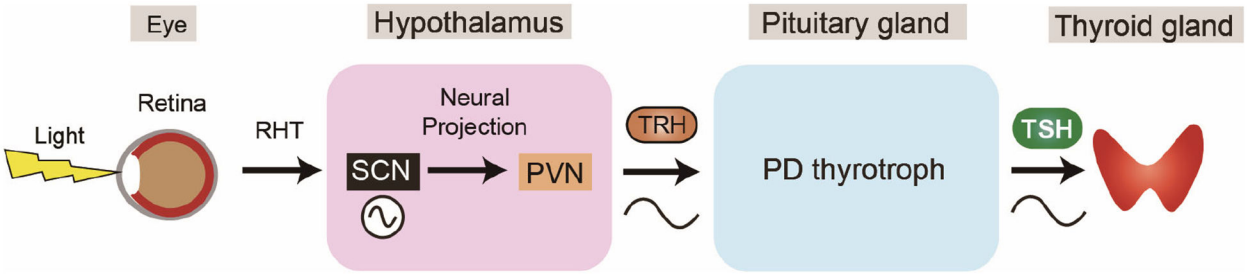

Figure 2. The hypothalamic–pituitary–thyroid axis is under circadian regulation.

The suprachiasmatic nuclei (SCN) receives light information from the retina through the retino-hypothalamic tract (RHT) and outputs the circadian signal to hypothalamic paraventricular nucleus (PVN) via neural connections[20,21]. In humans, thyrotropin-releasing hormone (TRH) and TSH secretions exhibit circadian rhythms[34,35].

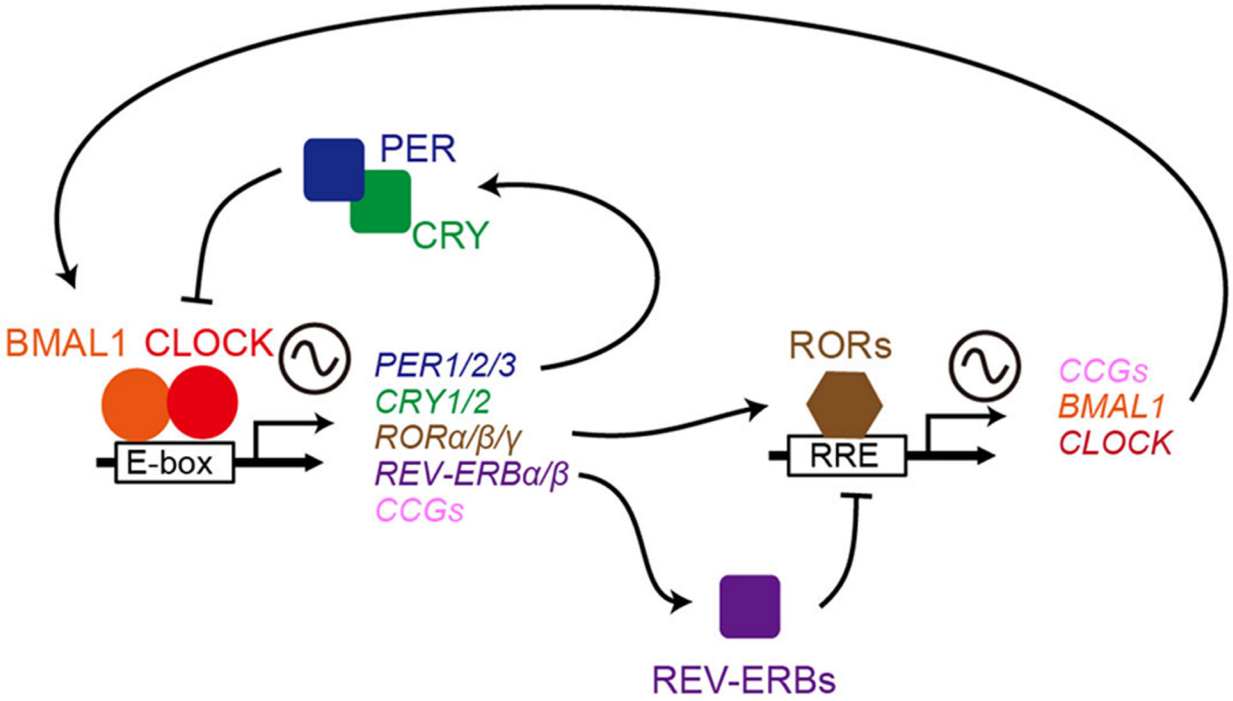

Figure 3. The circadian transcriptional and translational feedback loop machinery in mammals.

In the core loop, the CLOCK–BMAL1 complex binds E-boxes in promoters of target genes (*PER1, PER2* and *PER3*, and *CRY1 and CRY2*, and clock-controlled genes [*CCGs*]) and activates their transcription. PERs and CRYs form complexes to inhibit CLOCK–BMAL1-mediated transcription. A second loop involves additional pairs of transcription factors such as Reverse strand of Erbα (REV-ERBα) and REV-ERBβ and retinoic acid receptor-related orphan receptor-α (RORα), RORβ and RORγ. CLOCK–BMAL1 also induces REV-ERB proteins and RORs, which regulate *CLOCK* and *BMAL1* through ROR-elements (RREs) but exert opposite effects on transcription[27].

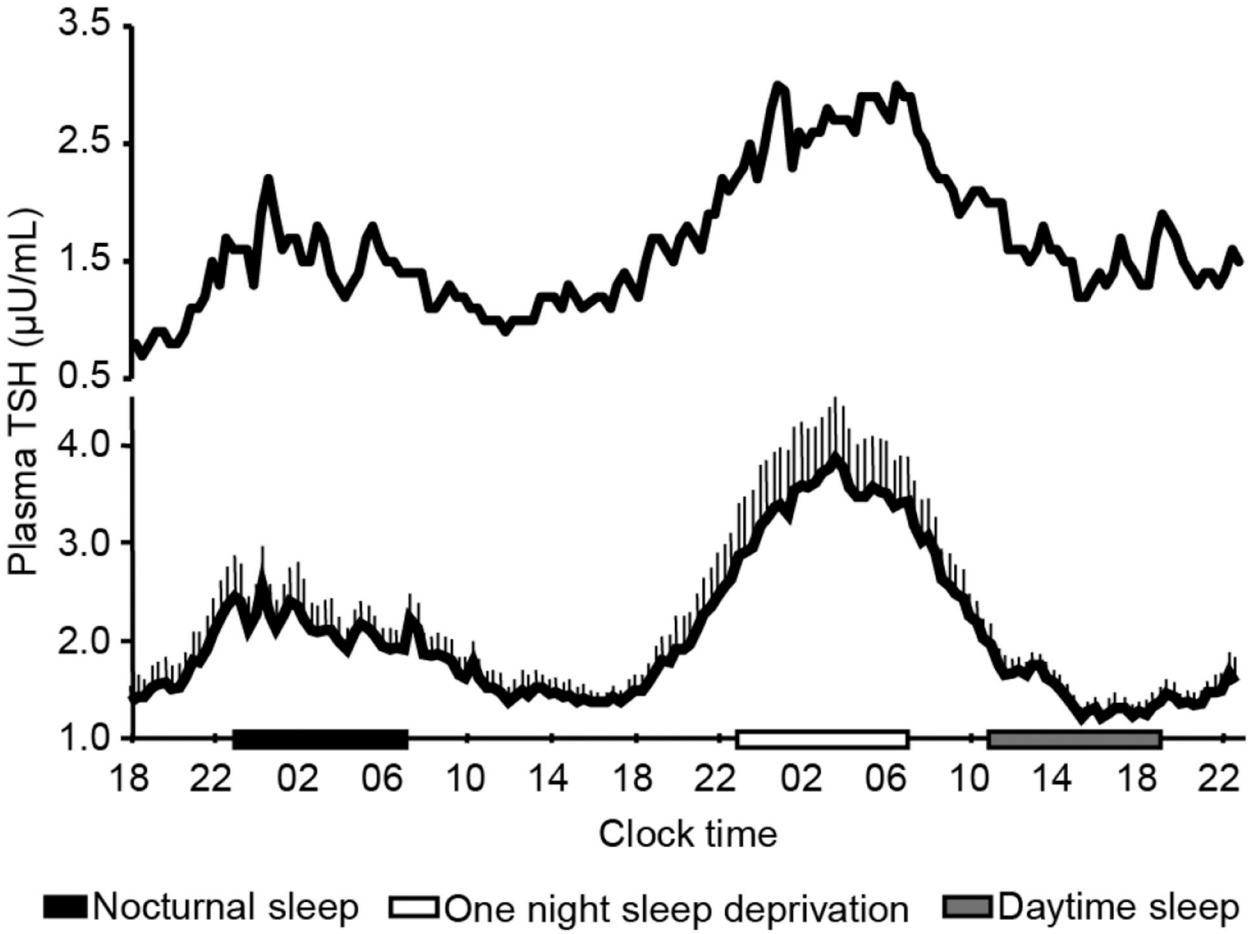

Figure 4. Temporal changes of plasma TSH in human.

Upper panel shows an individual profile of plasma TSH sampled at 20-min intervals for 53 h in a healthy young male volunteer. The sampling period included one night of nocturnal sleep (black bar), one night of total sleep deprivation (open bar) and one 8-h period of daytime recovery sleep (grey bar). Note that sleep deprivation was associated with a near twofold rise in nocturnal TSH levels, uncovering an inhibitory effect of sleep under normal condition. Pulsatile TSH variations are apparent throughout the sampling period. Lower panel shows mean (plus standard error of the mean) levels of plasma TSH from 11 healthy young men. The symbols are the same as in upper panel. Note that daytime recovery sleep did not suppress TSH below the daytime levels. Modified from previous data[36].

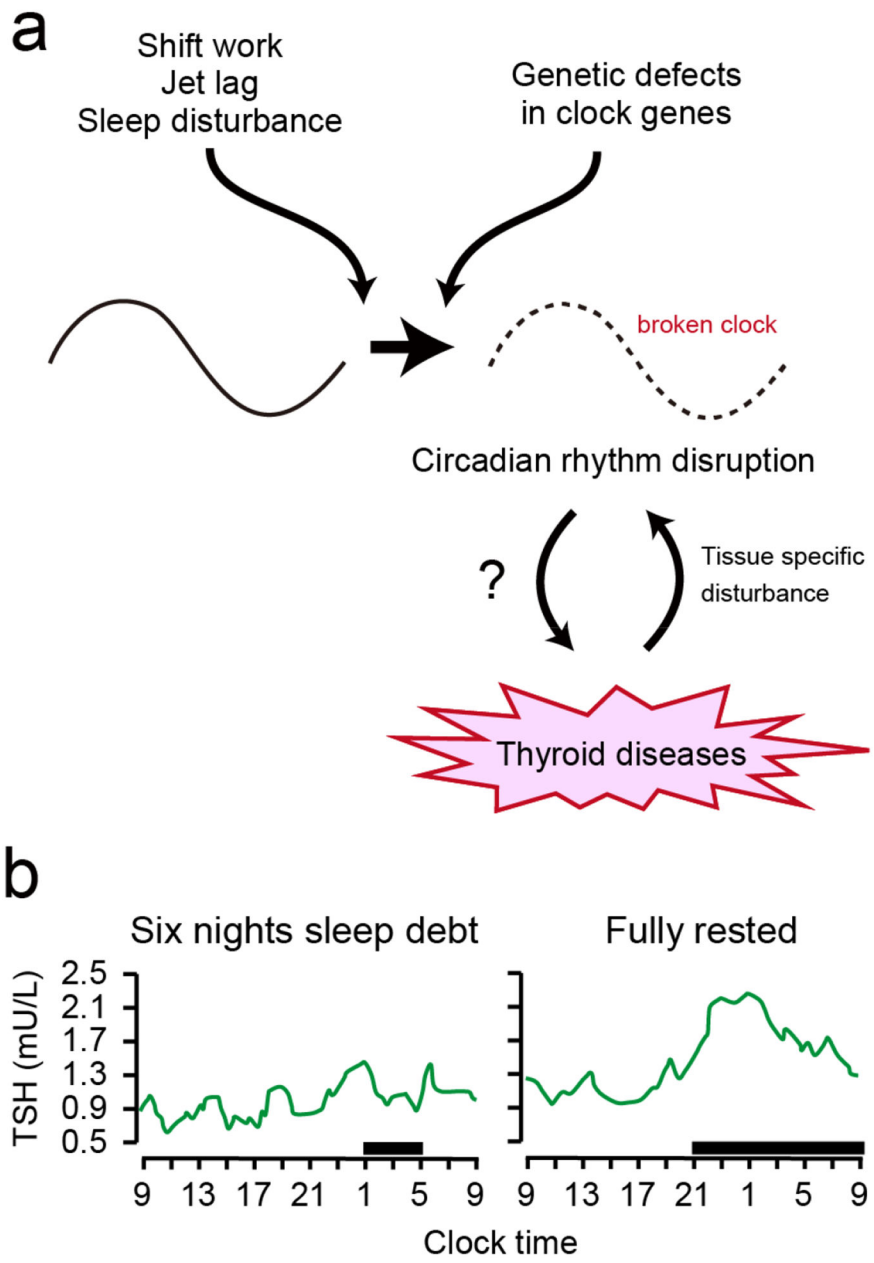

Figure 5. Circadian disruption can drive thyroid diseases.

(**a**) Endogenous factors, such as genetic defects, and exogenous factors such as chronic shift work, jet lag and sleep disturbance, disrupt the endogenous circadian timing system. A faulty circadian clock is thought to increase the risk of thyroid diseases[7,8]. Thyroid diseases also perturb the circadian system in a tissue-specific manner[68]. (**b**) Effects of a sleep debt achieved by six nights of bedtime restriction to 4 h per night and a fully rested condition on TSH concentration (modified from Ref[37]). Shaded areas show bedtime periods.

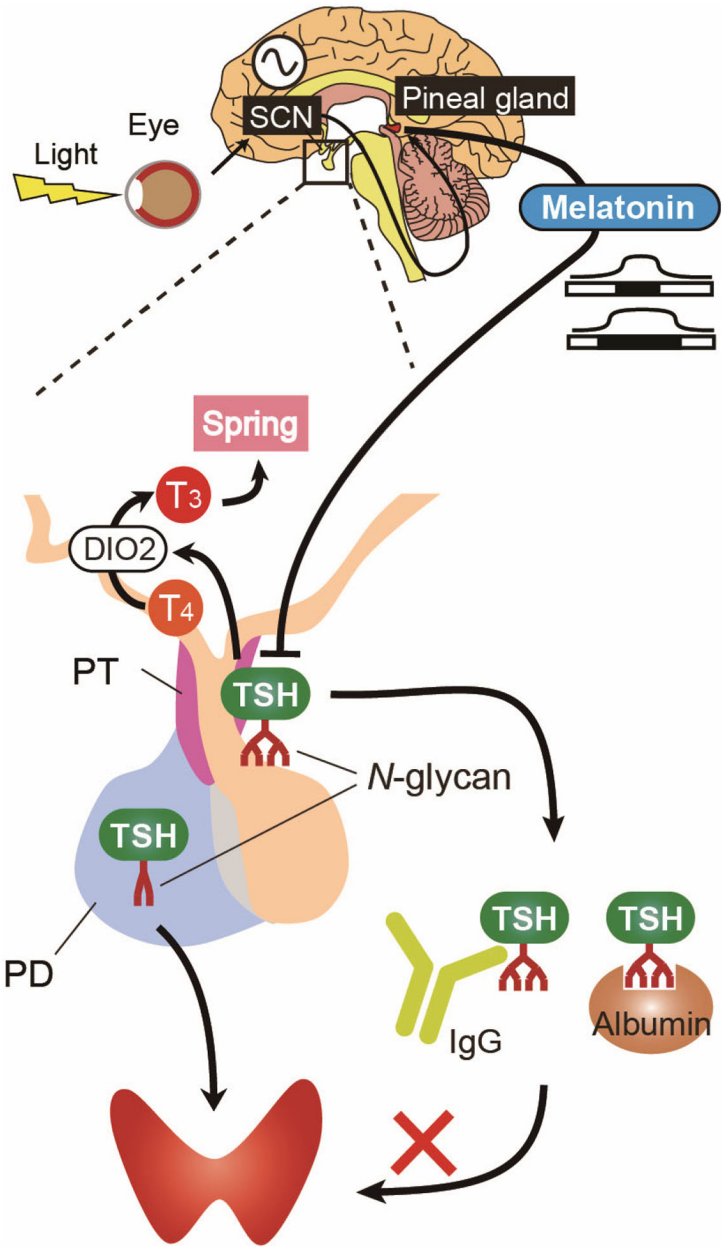

Figure 6. Pars tuberalis-derived TSH regulates seasonal thyroid hormone function.

Light information received by the eyes is transmitted to the pineal gland via the suprachiasmatic nuclei (SCN). Pineal melatonin secretion pattern reflects the length of nights and suppresses pars tuberalis-derived TSH expression. Long days increase production of pars tuberalis-derived TSH, which acts on ependymal cells in the hypothalamus to induce type 2 iodothyronine deiodinase (DIO2) expression through the TSH receptor–Gsα–cAMP signaling pathway. DIO2-induced thyroid hormone activation, through the generation of T_3 from T_4, transmits the springtime signal[128,132]. Pars distalis-derived TSH stimulates the thyroid gland. Pars tuberalis-derived TSH has tissue-specific *N*-glycans and forms macro-TSH complexes with immunoglobulin (IgG) and albumin in the circulation. The macro-TSH complexes are unable to stimulate the thyroid gland, and this feature prevents functional

crosstalk between the two TSHs, thus preventing the production of seasonal thyroid gland overactivity[73].

Table 1

Effect of circadian clock on thyroid function.

Circadian status	Intervention	species	Effect on thyroid function	references
Intact	None	Human	Rhythmic TSH secretion	34,35,38
Pacemaker ablation	SCN lesion	Rat	Rhythmic TSH secretion abolished and rhythmic Trα expression abolished	53,54
Circadian disruption	Recurrent sleep restriction	Human	Decreased TSH rise at night	37
Clock molecules	Increased expression of DEC1	Human	Promoting thyroid cancer aggressiveness	107
Clock molecules	Rev-erbα	Mouse	Circadian regulation of *Tshb* expression	56

Table 2

Effect of thyroid status on the circadian system.

Thyroid status	Symptoms or treatment	species	Effect on the circadian system	references
Hypothyroidism	Thyroidectomy	Rat	Shortened free-running period of locomotor activity rhythm, decreased amplitude of clock genes *(Bmal1, Per2, Nr1d1* and *Rora)* in heart, and altered Per2 expression (in the bed nucleus and amygdala, not in the SCN)	83,84,88,89
Hyperthyroidism	T_4 administration	Rat	Lengthened free-running period of locomotor activity rhythm	84
Hyperthyroidism	Thiourea administration	Hamster	Lengthened free-running period of locomotor activity rhythm	85
Hyperthyroidism	T_3 administration	Mouse	Altered clock gene *(Bmal1, Nr1d1* and *Rora)* expressions in heart	88
Thyroid cancer	Cancer	Human	Abnormal clock gene expressions	113