

Thyroid hormones and seasonal reproductive neuroendocrine interactions

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Abstract

Many animals that breed seasonally measure the day length (photoperiod) and use these measurements as predictive information to prepare themselves for annual breeding. For several decades, thyroid hormones have been known to be involved in this biological process; however, their precise roles remain unknown. Recent molecular analyses have revealed that local thyroid hormone activation in the hypothalamus plays a critical role in the regulation of the neuroendocrine axis involved in seasonal reproduction in both birds and mammals. Furthermore, functional genomics analyses have revealed a novel function of the hormone thyrotropin. This hormone plays a key role in signaling day-length changes to the brain and thus triggers seasonal breeding. This review aims to summarize the currently available knowledge on the interactions between elements of the thyroid hormone axis and the neuroendocrine system involved in seasonal reproduction.

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Photoperiodism

Many animals inhabiting regions in the temperature zone limit their reproductive activity to specific seasons in order to maximize the survival of their offsprings. Species that have a short incubation or gestation period, such as birds and small mammals, produce young during spring and summer; therefore, they are known as long-day breeders. By contrast, species that have a gestation period of about 5 or 6 months, such as sheep, goats, and deer, enter breeding in the autumn; therefore, they are known as short-day breeders. These seasonal breeding animals use the changes occurring in the day length (photoperiod) as a calendar and accordingly regulate many of their physiological and behavioral processes, including reproduction, migration, molting, hibernation, and body weight alterations. In long-day breeders, the increase in the photoperiod during spring stimulates the secretion of the gonadotropin-releasing hormone (GnRH) from the hypothalamus and the subsequent release of gonadotropins (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)) from the pituitary gland. By contrast, the decrease in the photoperiod during autumn stimulates the secretion of these hormones in short-day breeders. This phenomenon is termed as 'photoperiodism'. Prolactin secretion is also known to be photoperiodically regulated (reviewed by Morgan & Williams 1996). However, its release is not

driven by thyroid hormones (Dahl *et al.* 1994). Furthermore, previous studies have revealed that the blockade of seasonal reproductive functions due to lesions or hypothalamo-pituitary disconnection does not affect the seasonal secretion of prolactin (Juss 1993, Lincoln 2002). Therefore, we do not focus on prolactin in the present review.

Melatonin and seasonality

In all vertebrates, melatonin is secreted on a daily basis by the pineal gland under the control of the circadian system; its secretion peaks during the subjective night and ceases during the day. The duration of melatonin secretion tracks night length and in mammal this humoral signal is considered a crucial component of the mechanism governing mammalian photoperiodism (Reiter 1993, Goldman 2001). In mammals, light signals are received by the eye and are then transmitted to the circadian pacemaker in the hypothalamus, i.e., the suprachiasmatic nucleus (SCN). The SCN drives the nocturnal rhythm of melatonin secretion by the pineal gland, and a lesion in the SCN abolishes the circadian rhythms that govern the production and secretion of this hormone (Scott *et al.* 1995, Tessonnaud *et al.* 1995). Hamsters and sheep have been shown to develop photoperiodic blindness following pinealectomy (Hoffman & Reiter 1965, Bittman *et al.* 1983). In addition,

melatonin secretion for a long duration (i.e., short-day pattern) suppresses gonadotropin secretion in hamsters (Bartness *et al.* 1993) but stimulates it in sheep (Bittman & Karsch 1984). Melatonin is considered to act on its membrane-bound receptors that are involved in the regulation of a various seasonal responses. Specific melatonin-binding sites have been identified by using 125 I-labeled melatonin, and a study wherein lesions were created in melatonin-binding sites revealed that the mediobasal hypothalamus (MBH) is essential for the melatonin-mediated photoperiodic control of reproduction in hamsters (Maywood *et al.* 1996). It has also been reported that microimplants of melatonin introduced into the MBH of sheep regulate seasonal reproduction; this suggests that the MBH plays an important role in the photoperiodic mechanisms that operate in mammals (Lincoln 1992, Lincoln & Maeda 1992, Malpoux *et al.* 1993). Although melatonin plays a critical role in the photoperiodic mechanisms as mentioned above, the downstream pathway involved in its functioning remains unknown.

Birds, just like mammals, secrete a daily rhythm of melatonin that tracks night length but, surprisingly, melatonin is not involved in the photoneuroendocrine axis regulating gonadotropin secretion and seasonal breeding (Kumar *et al.* 1993). Light is detected directly within the brain of birds via deep brain photoreceptors, and eyes are not required for this process. Despite the marked differences that exist between the mammalian and avian light input pathways for the regulation of photoperiodism, the MBH is considered the center for photoperiodic time measurement in both mammals and birds. This is because lesions in the MBH block photoinduced LH release (Sharp & Follett 1969, Davies & Follett 1975) even though the GnRH neurons are left intact (Juss 1993) and deep brain photoreceptors are thought to be localized in this region (Silver *et al.* 1988, Saldanha *et al.* 1994). In addition, circadian clock genes are expressed in the MBH, and the circadian clock they regulate appears to be the long-sought biological clock responsible for photoperiodic time measurement (Ball & Balthazart 2003, Yasuo *et al.* 2003).

Thyroid hormones and seasonality

For many decades, it has been known that interference with the thyroid glands (or exogenous treatment with thyroid hormones) has a wide range of effects upon seasonal reproduction in birds (recently summarized by Dawson & Thapliyal 2001). Two major sets of effects have been described. First, exogenous treatment with thyroid hormones has been shown to mimic the effects of long-day conditions. Additionally, thyroid gland removal stops the development of photorefractoriness (i.e., insensitivity to previous stimulatory day-length) in birds and if carried out during the refractory period leads to its spontaneous dissipation (Follett & Nicholls 1988,

Goldsmith & Nicholls 1992, Wilson & Reinert 1995, Bentley *et al.* 1997). Most of the molecular analyses described below have focused upon the involvement of thyroid hormones in long-day induced gonadotropin secretion and it is still unclear exactly how the thyroid is involved in refractoriness (refer to Dawson 1993, Dawson *et al.* 2001).

Fascinatingly, studies have shown that the thyroids are also involved in mammalian seasonal responses. In sheep, thyroidectomy stops the development of refractoriness in ewes (Nicholls *et al.* 1988) and rams (Parkinson & Follett 1994, 1995). Work from Michigan and New Zealand groups suggests that then thyroid hormones are probably involved in the alterations in the responsiveness of the GnRH axis to the negative feedback effects of estrogen during the transition to anestrus (Moenter *et al.* 1991, Anderson *et al.* 2002). Although possible homologies between the avian and mammalian photoperiodic systems have been discussed, the precise role played by thyroid hormones in the regulation of seasonal reproduction has remained unclear for many decades.

The Japanese quail – an excellent model for studying photoperiodism

Although the mouse is a superb vertebrate model for many physiological processes, this is not true for seasonality and so work has focused upon species showing far stronger photoperiodic responses (quail, starlings, and white-crowned sparrows; sheep and hamsters). The Japanese quail (*Coturnix japonica*) offers some advantages when studying real-time photoperiodic changes. Quail respond to a single long day. Put briefly, photoperiodic induction occurs when light coincides with one particular phase of a circadian based rhythm of photoinducibility (Follett & Sharp 1969). In quail, the most sensitive phase of this rhythm begins about 11 h after dawn and runs until about 1600 h. If light occurs during this period (as in a long day) then a wave of gonadotropin secretion is triggered. The first detectable changes in LH, FSH, and GnRH secretion begin at about 2200 h of the first long day and a wave of secretion builds up over the next few days (Follett *et al.* 1977, Nicholls *et al.* 1983).

Molecular analysis of photoperiodic time measurement

We offered the hypothesis that in quail given light pulses during the photoinducible phase there would be molecular events induced within the MBH where the center for photoperiodic time measurement is localized. Based on this assumption, a differential subtractive hybridization analysis was performed by using the MBH of a quail that received light pulse and no light

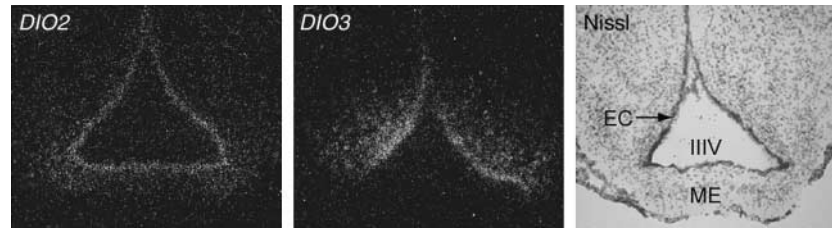


Figure 1 Expression of *DIO2* and *DIO3* in the MBH. Dark-field photomicrographs of the *DIO2* and *DIO3* expressions and a light-field photomicrograph of the Nissl-stained sections are shown. The images of *DIO2* and *DIO3* expressions were obtained from continuous long- and short-day stimulated birds respectively. EC, ependymal cell layer lining the ventrolateral walls of the third ventricle; ME, median eminence; and IIIV, third ventricle.

pulse at the photoinducible phase. From the analysis emerged one key gene encoding type 2 iodothyronine deiodinase (*DIO2*; D2) (Yoshimura *et al.* 2003). Acute induction of *DIO2* expression by light was observed in the dorsal MBH, around the paraventricular organ. Furthermore, upregulation of *DIO2* was observed in the ependymal cells lining the ventrolateral walls of the third ventricle and the infundibular nucleus (which is anatomically homologous to the mammalian arcuate nucleus) by the continuous long-day stimulus (Fig. 1). These observed photoinduced expression sites of *DIO2* were in agreement with the results of lesion studies performed by Sharp & Follett (1969). This suggests that *DIO2* expression in both regions is potentially important for the induction of photoperiodic responses in the gonads (Yoshimura *et al.* 2003).

Local activation of thyroid hormone is the key for the photoperiodic response

A further discovery was that the expression of type 3 iodothyronine deiodinase (*DIO3*) was downregulated under long-day conditions at the same time as *DIO2* was upregulated (Yasuo *et al.* 2005). The timing of the inverse changes was precise and began at about 16–18 h on the first long day to which the quail were exposed. This was some 4 h prior to first detectable rise in LH secretion. A strong argument that the *DIO2*/*DIO3* changes were related to photoinduction came from finding that the gene changes lasted for a number of days after quail had been exposed to just one long photoperiod, just as occurred in the case of LH secretion. The enzyme *DIO2* (D2) catalyzes the removal of an outer ring iodine from the prohormone thyroxine (T_4) and thus converts it into the bioactive form, i.e., 3,3',5-tri-iodothyronine (T_3). By contrast, the enzyme *DIO3* (D3) catalyzes the removal of an inner ring iodine from T_4 and T_3 and thus converts them into reverse T_3 (rT_3) and T_2 respectively (Fig. 2; Leonard & Visser 1986). Thus, both these enzymes play essential roles in the local control of the T_3 levels via mechanisms that operate under a various conditions to maintain the T_3 concentrations within a narrow range (Bernal 2002). Overall, it appeared as if the *DIO2*/*DIO3*

changes had the capacity to produce locally high concentrations of the T_3 , the active thyroid hormone. Support for this idea came from finding that the T_3 concentrations in the MBH of the quail were found to be approximately ten times higher under long- than short-day conditions, while these concentrations in the plasma and other parts of the brain, such as the optic tectum and cerebellum, did not differ with the exposure conditions (Yoshimura *et al.* 2003).

Next, to validate the physiological significance of this local activation of the thyroid hormone, the effects of i.c.v. infusion of T_3 , T_4 , and a *DIO2* inhibitor were investigated. Although the effects of T_4 infusion on testicular growth were minimal, T_3 administration under short-day conditions mimicked the effects of long-day conditions on testicular growth. In addition, i.c.v. infusion of a *DIO2* inhibitor, namely iopanoic acid, impaired testicular growth under long-day conditions (Yoshimura *et al.* 2003). These results clearly indicated that the local activation of the thyroid hormone within the MBH, induced by long-day conditions, plays a key role in the regulation of seasonal reproduction.

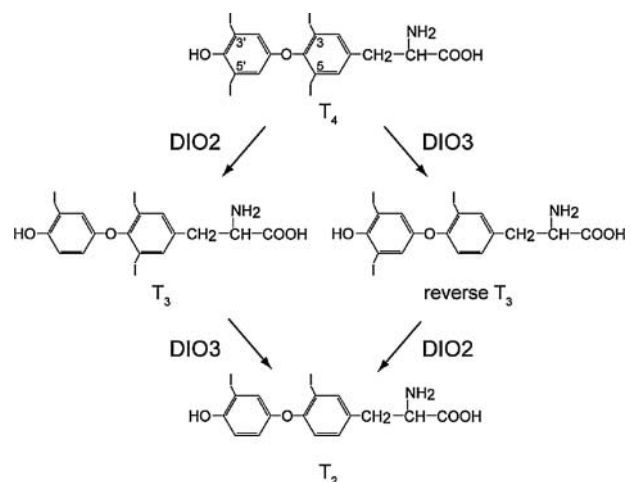


Figure 2 Structures and interrelationships between the principal iodothyronines in activated or inactivated form. Type 2 deiodinase (*DIO2*) generates active T_3 from T_4 by outer ring deiodination, whereas type 3 deiodinase (*DIO3*) catalyzes the conversion of both T_3 and T_4 to inactive form by inner ring deiodination.

Extension of findings to photoperiodic mammals

At this point, a number of studies were undertaken by both ourselves and others that indicated that the *DIO2/DIO3* discoveries may also apply in a number of photoperiodic mammals. Although some interspecies differences exist with regard to the relative importance of *DIO2* and *DIO3* in photoperiodism, the photoperiodic regulation of *DIO2* and/or *DIO3* expression has been confirmed in various mammalian species, including the Djungarian (Siberian) hamster (Watanabe *et al.* 2004, 2007, Barrett *et al.* 2007, Freeman *et al.* 2007), Syrian hamster (Revel *et al.* 2006, Yasuo *et al.* 2007a), rat (Yasuo *et al.* 2007b), and goat (Yasuo *et al.* 2006). Further, T_3 administered exogenously under short-day conditions was observed to mimic the effects of long-day conditions on gonadal growth in hamsters (Barrett *et al.* 2007, Freeman *et al.* 2007). In addition, it has been reported that the expressions of *DIO2* and *DIO3* are regulated by melatonin in mammals (Watanabe *et al.* 2004, Revel *et al.* 2006, Barrett *et al.* 2007, Yasuo *et al.* 2007a). It is also noteworthy that in goats, which breed under short-day conditions, a long-day stimulus suppressed the expression of *DIO2*; this effect was contrary to that observed in species that breed under long-day conditions (Yasuo *et al.* 2006). In the ewe, the function of the thyroid hormone in suppressing seasonal activity is known to be limited to a specific seasonal window (Thrun *et al.* 1997, Billings *et al.* 2002), and the long-day suppression of *DIO2* expression may provide a mechanism that accounts for the lack of responsiveness to T_4 during the mid to late anestrus (Yasuo *et al.* 2006).

Thyroid hormone uptake in the MBH

For a long time, it was believed that the thyroid hormone traverses the plasma membrane via passive diffusion due to its lipophilic nature. However, recent studies have revealed the existence of thyroid hormone transporters. Prendergast *et al.* (2002) reported that the expression patterns of thyroid hormone transporters such as transthyretin, T_4 -binding globulin, and albumin in Siberian hamsters differ following exposure to short- and long-day conditions. These transporters may be involved in the regulation of seasonal breeding in mammalian species. However, genes encoding these transporters were not observed to be expressed in the MBH of quail. On the contrary, in quail, organic anion transporting polypeptide 1c1 (OATP1C1) has been demonstrated to transport T_4 from the cerebrospinal fluid (CSF) in the third ventricle to the ependymal cells lining the ventrolateral walls of the third ventricle, where *DIO2* and *DIO3* are expressed (Nakao *et al.* 2006). This indicates that OATP1C1 may play a role in the cellular uptake of T_4 from the CSF to ependymal cells. Following this uptake, T_4 is intracellularly

converted either into active T_3 due to the high *DIO2* expression induced by long-day conditions or into inactive rT_3 due to the high *DIO3* expression induced by short-day conditions.

Downstream events of thyroid hormone action

Thyroid hormone exerts its effects via its nuclear receptors. In quail, weak mRNA expression of the thyroid hormone receptors α (*THRA*) and β (*THRB*) and strong mRNA expression of the retinoid X receptor α (*RXRA*) have been observed in the basal tuberal hypothalamus (BTH), which includes the median eminence and infundibular nucleus (Yoshimura *et al.* 2003); this indicates that the BTH is the target site for T_3 action. Thyroid hormones are known to be critically involved in the development, plasticity, and functioning of the central nervous system (CNS; Bernal 2002). Therefore, immunoelectron microscopy of the median eminence was performed for quail under both short- and long-day conditions. The nerve terminals of the GnRH neurons were observed to be in close proximity to the basal lamina under long-day conditions, while they were encased by the endfeet of the glial processes under short-day conditions (Yamamura *et al.* 2004). The administration of T_3 into the brain brought about similar morphological changes and induced testicular growth under short-day conditions (Yamamura *et al.* 2006). In the glial cells of the median eminence, Fos-like immunoreactivity is induced by long-day stimulus, and this suggested that GnRH release may be controlled by the glial cells at the level of the nerve terminal (Meddle & Follett 1997). Thus, morphological changes in the GnRH neurons and glial processes may regulate the seasonal secretion of GnRH.

A functional genomics analysis of photoperiodic induction in quail

The chicken genomic sequence data, which have recently been made available, have permitted the expansion of studies on avian species from single-gene to genome-wide transcriptional analyses. To analyze the system dynamics and network structure in the MBH involved in regulating the photoperiodic activation of the thyroid hormone in the quail, which is a galliform bird closely related to the chicken, functional genomics analysis was performed using a chicken high-density oligonucleotide microarray (Affymetrix Chicken Genome Array) during the photo-induction process in quail exposed to an abrupt shift from short to long days (Nakao *et al.* 2008). The analysis (Fig. 3) identified two waves of gene expression. As found previously, there was upregulation of *DIO2* and downregulation of *DIO3*, which began at about 1800–1900 h. This wave of gene change was accompanied by alterations in another nine genes including

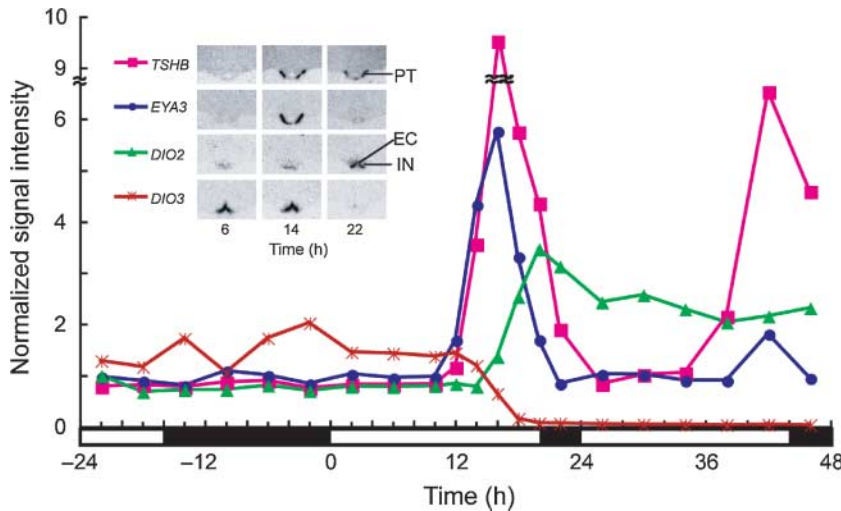


Figure 3 Identification of waves of gene expression during the photoinduction process. Induction of the first wave genes comprising the *TSHB* and *EYA3* genes was followed by induction of the second wave genes, which included the *DIO2* and *DIO3* genes. Data were normalized such that the median signal strength for each gene over all time points was 1.0. The average signal strength at each point was then displayed as a ratio relative to the median signal strength of that gene. Expression of the first wave genes was observed in the pars tuberalis (PT), whereas that of the second wave genes was observed in the ependymal cell (EC) and the infundibular nucleus (IN). The time of 0 h corresponds to the dawn of the first long day.

ICER, *NR4A3*, and *CEBPB*. Of particular interest, however, was a wave of gene expression that began a few hours earlier at about 1400 h of the first long day. In particular two genes, thyroid-stimulating hormone β (*TSHB*) and eyes absent 3 (*EYA3*), rose rapidly (Fig. 3) on the first long day and showed another wave of induction on day 2. The timing of these two first wave genes is fascinating since it coincides with the phase of photoinducibility (Nicholls *et al.* 1983, Follett *et al.* 1998) while earlier experiments had indicated that by 1400 h a quail understands that it has been exposed to a long day even if LH secretion has not yet begun (Follett *et al.* 1977). A spatio-temporal expression analysis of the genes that produced the first and second expression waves revealed that these genes are localized in the pars tuberalis of the pituitary gland and in the ependymal cells lining the ventrolateral walls of the third ventricle in the MBH respectively. The pars tuberalis is a part of the adenohypophysis and is a highly vascularized multicellular tube of cells that surrounds the hypophyseal stalk (Stoeckel & Porte 1984). Although *EYA3* encodes a transcriptional coactivator, it seems unlikely that it regulates the expression of the second wave genes because its localization in the pars tuberalis is distinct from those of the second wave genes in the ependymal cells. On the other hand, *TSHB* encodes the β -subunit of TSH. Functional TSH requires two noncovalently linked subunits, a common pituitary glycoprotein α -subunit (CGA) and TSH β . In addition to *TSHB* expression, CGA expression was observed in the pars tuberalis, and the photoinduction of TSH β -like immunoreactivity was confirmed in the pars tuberalis. The expression of TSH receptor (*TSHR*) was observed in the ependymal cells lining the ventrolateral walls of the third ventricle, where the second wave genes are expressed, and the binding of ^{125}I -labeled TSH was confirmed in this region. Since the median eminence is located outside the blood-brain barrier, it can be hypothesized based on our results that TSH induced

in the pars tuberalis by long-day conditions acts on the TSHR localized on the ependymal cells in the MBH, where the second wave genes are expressed.

Pars tuberalis TSH triggers *DIO2* expression

The hypothesis that TSH triggers the expression of second wave genes was tested by i.c.v. injection of TSH and an anti-TSH β antibody. TSH administration induced the expression of the second wave genes, including *DIO2*, in a dose-dependent manner, whereas the immunoneutralization of TSH by the administration of anti-TSH β IgG impaired their expression that had been induced by long-day conditions. These results clearly indicated that TSH released in the pars tuberalis induces the expression of second wave genes. TSH is known to function via the TSHR-Gs α -cAMP signaling pathway. When the promoter sequences of the second wave genes, including *DIO2*, *ICER*, *NR4A3*, and *CEBPB*, were determined in the quail and chicken, cAMP responsive elements were found to be highly conserved among these genes in both species. In addition, promoter analysis performed using the luciferase reporter revealed that TSH released in the pars tuberalis triggers the second wave gene expression via the TSHR-cAMP signaling pathway.

By subsequent microarray analysis, 183 genes were identified, whose expression patterns in the MBH differed between short- and long-day conditions. Among these genes, *TSHB* and *CGA* were observed to be markedly upregulated under long-day conditions. Therefore, the effects of chronic TSH administration on testicular growth were investigated. As expected, this TSH administration induced *DIO2* expression and testicular growth. These results suggest that TSH released in the pars tuberalis under long-day conditions is important not only for the process of photoinduction but also for the maintenance of reproductive functions.

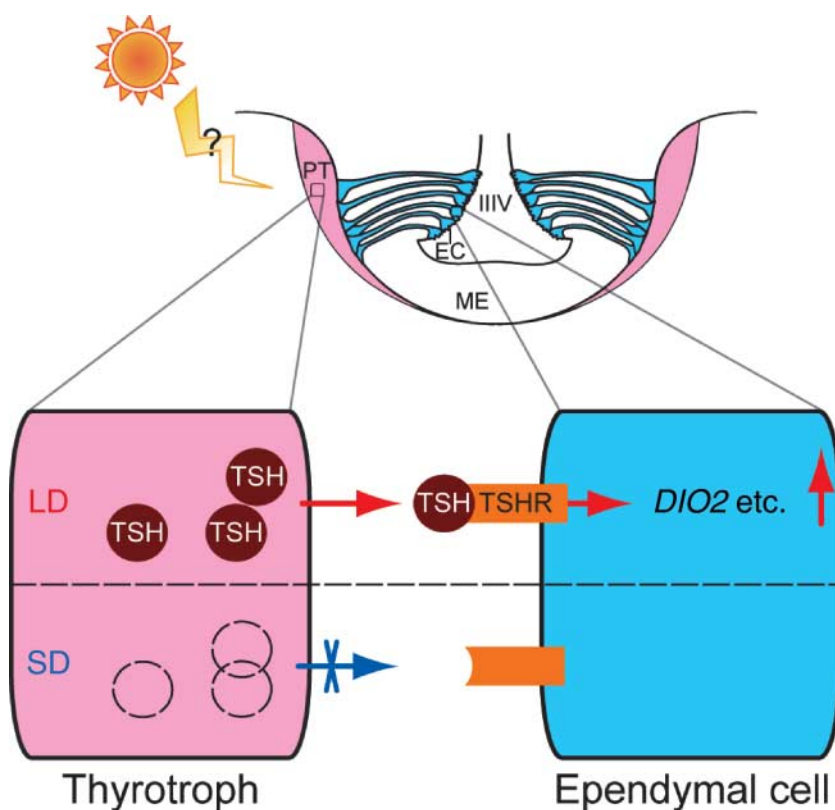


Figure 4 A model depicting a possible mechanism whereby thyroid hormones can regulate the photoperiodic response in birds. Light information received by the deep brain photoreceptors induces the expression of *TSHB* in the pars tuberalis (PT) of the pituitary gland. The light input pathway to the PT remains unknown. Long-day-induced *TSHB* and cycling CGA (common pituitary glycoprotein α -subunit) form TSH in the PT and act on the TSH receptor (TSHR) localized in EC. Expression of the second wave genes that include *DIO2* is induced by TSH through the TSHR-cAMP signaling pathway.

Conclusion

Although the involvement of the thyroid hormone in the regulation of seasonal reproduction has long been recognized, its localization and the manner in which it exerts its function in this regard have remained unclear. Recent molecular analyses have revealed that local activation of the thyroid hormone by *DIO2* and *DIO3* in the MBH plays a critical role in the regulation of seasonal reproduction in both birds and mammals.

It has been reported that the expression of CGA and *TSHB* in the mammalian pars tuberalis are photoperiodically regulated (Wittkowski *et al.* 1988, Bockmann *et al.* 1996, 1997). Furthermore, the expression of TSH has been detected in the CSF and CNS (Schaub *et al.* 1977, Hojvat *et al.* 1982) of mammals. In addition, *TSHR* has been reported to be expressed in the mammalian brain. The localization of melatonin receptors on the pars tuberalis suggests a photoperiodic function of the pars tuberalis in mammals (Morgan & Williams 1996). However, the functional significance of TSH induction in the pars tuberalis with regard to the control of photoperiodic responses has remained unclear for many decades. Recent functional genomics analyses have demonstrated that TSH expression induced in the pars tuberalis by light stimuli triggers *DIO2* expression in the MBH in birds (Fig. 4). These findings shed light on an entirely novel function of the pituitary hormone TSH and provide deeper insights into

the functional significance of the pars tuberalis in birds. Future studies should aim to confirm whether TSH released in the pars tuberalis mediates the melatonin signal to *DIO2/DIO3* expression in mammals. Further, the primary objective of immediate future research should be to identify the photoperiodic signaling pathway that activates the TSH in the avian pars tuberalis.

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