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Regulation of seasonal reproduction by hypothalamic activation of thyroid hormone

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Organisms living outside the tropics measure the changes in the length of the day to adapt to seasonal changes in the environment. Animals that breed during spring and summer are called long-day breeders, while those that breed during fall are called short-day breeders. Although the influence of thyroid hormone in the regulation of seasonal reproduction has been known for several decades, its precise mechanism remained unknown. Recent studies revealed that the activation of thyroid hormone within the mediobasal hypothalamus plays a key role in this phenomenon. This localized activation of the thyroid hormone is controlled by thyrotropin (thyroid-stimulating hormone) secreted from the pars tuberalis of the pituitary gland. Although seasonal reproduction is a rate-limiting factor in animal production, genes involved in photoperiodic signal transduction pathway could emerge as potential targets to facilitate domestication.

Keywords: seasonal reproduction, mediobasal hypothalamus, ependymal cell, pars tuberalis, thyrotropin, thyroid hormone, iodothyronine deiodinase

INTRODUCTION

Orbiting of the earth around the sun causes changing seasons. To adapt to the seasonal changes in the environment, animals alter their physiology and behavior, which is characterized by the changes in growth, metabolism, immune function, reproductive activity, migration, hibernation, and molting. Most of the organisms use the changes in the length of the day (photoperiod) as a calendar, because temperature and precipitation varies throughout each year and are unreliable when compared with the length of the day. This phenomenon is called "photoperiodism" (1). Among the various seasonally regulated phenomena, the mechanism of seasonal reproduction has been extensively studied. Small mammals and birds breed during the spring and summer. Therefore, they are called long-day (LD) breeders. The gestation or incubation period of these animals last only a few weeks and their offspring are born during the spring and summer. In contrast, larger mammals, such as goats and sheep, breed during fall. Therefore, they are called short-day (SD) breeders. These animals have a gestation period of approximately 6 months. Therefore, their offspring are also born and raised during spring and summer. Accordingly, the offspring of both LD and SD breeders grow when the climate is moderate and food is abundant (**Figure 1**).

Seasonal reproduction of vertebrate species is regulated by the hypothalamic–pituitary–gonadal (HPG) axis. The secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus induces the secretion of gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] from the anterior pituitary gland, which in turn activates gonadal activity. In other words, the HPG axis of seasonally breeding animals is only activated during the breeding season. Among the various vertebrate species, birds show the most dramatic changes in gonadal size (typically more than a 100-fold) (2). Therefore, birds have a highly sophisticated photoperiodic mechanism in comparison to other vertebrate species (3). In addition to the robust gonadal responses, most of the birds have very short breeding seasons, as the HPG axis is automatically switched off and their gonads start to regress even though the length of the day is still increasing. This phenomenon is known as photorefractoriness (4, 5). The length of the breeding season tends to be shorter in higher latitude due to the short benign season in higher latitude. Among mammals, hamsters and sheep are extensively studied, because they show dramatic photoperiodic responses. However, the magnitude of the seasonal gonadal development and regression is less robust in mammals than in birds, as their gonads change only by a few-folds.

INFLUENCE OF THYROID HORMONE IN THE SEASONAL CHANGES

It has been known for many decades that thyroid hormone is somehow involved in the regulation of seasonal reproductive function in various organisms including fish, birds, and mammals (2, 6, 7). In some species, thyroidectomy prevents the transition to reproductive state (i.e., seasonal testicular development and/or regression) (8–11), and thyroxine (T_4) treatment mimics the effects of a long photoperiod (12–14). However, photo-stimulated gonadal

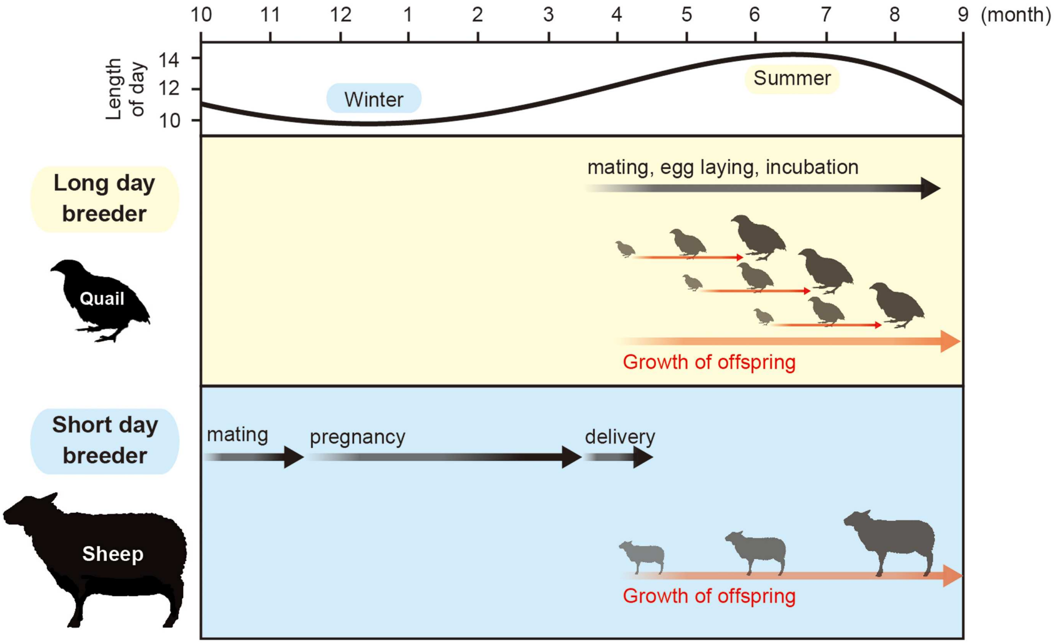

FIGURE 1 | Calendar of seasonal breeding animals. Most animals mate in a specific time of a year. Small animals with short gestation or incubation period mate in spring and summer, while large animals that have a 6-month gestation period mate in fall to give birth in spring.

maturation appears to have been largely unaffected by thyroidectomy in some species (2). Therefore, the reported effects of thyroidectomy on seasonal breeding are often contradictory and the role of T_4 is thought to be permissive. Although the requirement of T_4 for an appropriate response to photoperiod has been documented (15), the mechanism by which thyroid hormone regulates seasonal reproduction remained unknown for several decades.

PHOTOPERIODIC CHANGES IN TYPE 2 AND TYPE 3 DEIODINASES WITHIN THE HYPOTHALAMUS

The Japanese quail (*Coturnix japonica*) is an excellent model for studying photoperiodism, because of its rapid and robust responses to changing photoperiods (3). Local illumination of the mediobasal hypothalamus (MBH) by radioluminous-painted beads induce testicular growth (16), and lesions of MBH blocks the photoperiodic response of LH secretion and gonadal development (17, 18). In addition, expression of c-Fos, a marker of neuronal activation, is induced in the MBH by LD stimulus (19). The MBH is therefore considered central for the seasonal reproduction in quail. By using differential subtractive hybridization analysis, LD-induction of type 2 deiodinase gene (*DIO2*) and LD-suppression of type 3 deiodinase gene (*DIO3*) were observed in the ependymal cells (also known as tanycytes) that line the ventrolateral walls of the third ventricle within the MBH [Ref. (20, 21), **Figure 2**]. *DIO2* encodes the thyroid hormone-activating enzyme that converts the prohormone T_4 to bioactive triiodothyronine (T_3) (22), while *DIO3* encodes thyroid hormone-inactivating enzyme that metabolizes T_4 and T_3 to inactive reverse T_3 (rT_3) and 3,3′-diiodothyronine (T_2), respectively. The reciprocal switching of *DIO2* and *DIO3* appears to regulate the local thyroid hormone concentration precisely within the MBH. Moreover, T_3 concentration within the MBH is about 10-fold higher under LD conditions than under SD conditions, even though plasma concentrations are similar to both photoperiods (20). The functional significance of this locally activated thyroid hormone has been demonstrated by pharmacological analyses. Intracerebroventricular (i.c.v.) infusion of T_3 in SD conditions induced testicular development while infusion of a DIO2 inhibitor (iopanoic acid) in LD conditions attenuated testicular development (20). Photoperiodic regulation of *DIO2* and/or *DIO3* has also been confirmed in a number of other avian species, such as the tree sparrow (23), chicken (24), great tits (25), and canary (26). Similarly, photoperiodic regulation of thyroid hormone metabolism in the MBH has been confirmed in various mammalian species, including LD breeders like Siberian hamsters (27–30), Syrian hamsters (31, 32), rats (33, 34), mice (35), and SD-breeding goats (36) and sheep (37). Activation of thyroid hormone within the MBH decodes the LD information. Therefore, daily T_3 subcutaneous injections induce testicular development (28) and chronic replacement of T_3 in the hypothalamus prevents the onset of testicular regression (27) in LD-breeding Siberian hamsters. In contrast, in the SD breeders, LD-induced DIO2 appears to convert T_4 to T_3 to terminate the breeding season (37). In addition, LD stimulus induces the expression of *DIO2*, and T_4 administration terminates the breeding season via a decrease in serum LH (38, 39).

THYROID HORMONE TRANSPORT TO THE EPENDYMAL CELLS

Due to their lipophilic nature, thyroid hormones are believed to traverse plasma membranes by passive diffusion. However,

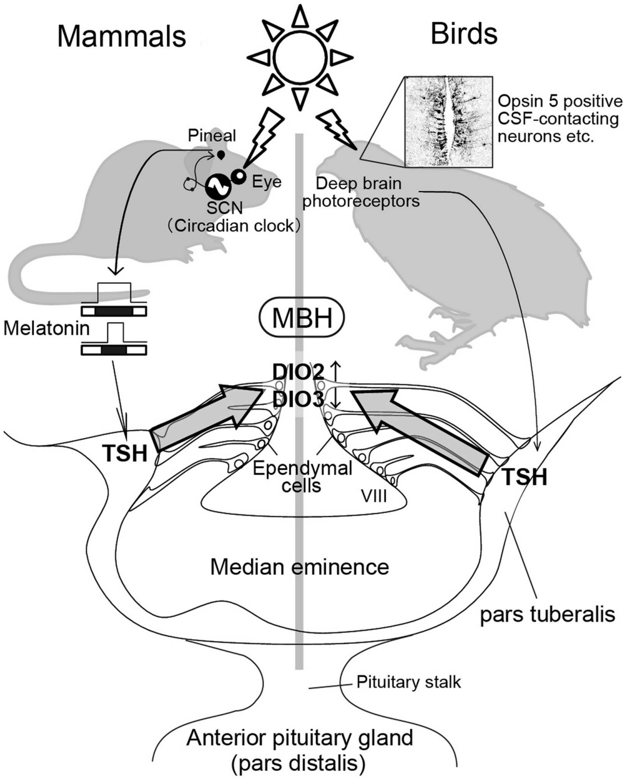

FIGURE 2 | Photoperiodic signal transduction pathway in mammals and birds. In mammals, light information is received by the eye and transmitted to the pineal gland via the circadian pacemaker, the suprachiasmatic nucleus (SCN). The duration of the pineal melatonin signal encodes the length of night and regulates TSH secretion in the pars tuberalis. The pars tuberalis TSH acts on TSH receptor expressed in the ependymal cells lining ventrolateral walls of the third ventricle (VIII) to induce DIO2 and reduce DIO3. Local thyroid hormone activation within the mediobasal hypothalamus (MBH) by DIO2/DIO3 switching plays a key role in the regulation of seasonal reproduction. In contrast, light information received by deep brain photoreceptors induces TSH secretion from the pars tuberalis in birds. Nevertheless, melatonin is not involved in the seasonal reproduction of birds. The schematic is a modified version of illustration published by Ikegami and Yoshimura (40).

involvement of a membrane transport system for thyroid hormone has been reported recently and a mechanism that facilitates the transport of thyroid hormone into the ependymal cells was examined. Some members of the organic anion transporting polypeptide (Oatp) family have been shown to transport thyroid hormones in mammals (41, 42) and the involvement of a member of this family in transporting T_4 into the quail brain has been investigated (43). Oatp1c1, which is expressed in the ependymal cells within the MBH, has been demonstrated to be a highly specific transporter of T_4. In addition to Oatp1c1, another thyroid hormone transporter, monocarboxylate transporter 8 (MCT8), has been found in the ependymal cells within hamster MBH (29). Although MCT8 appears to be involved in the regulation of photoperiodism, its expression is upregulated under SD conditions, which does not require thyroid hormone.

REGULATION OF HYPOTHALAMIC DEIODINASES BY THE PARS TUBERALIS TSH

When quail are transferred from SD conditions to LD conditions, an increase in plasma gonadotropin (LH) is observed 22 h after the dawn of the first LD (3, 44, 45). As discussed previously, reciprocal switching of *DIO2* and *DIO3* plays a critical role in the regulation of seasonal reproduction in birds and mammals. In quail, the reciprocal switching of *DIO2* and *DIO3* precedes photoperiodic induction of gonadotropin release by roughly 4 h (21). Genome-wide gene expression analysis during the transition from SD conditions to LD conditions in Japanese quail (45) identified the induction of two genes 4 h prior to *DIO2/DIO*3 switching (i.e., 14 h after dawn) in the pars tuberalis of the pituitary gland. The pars tuberalis consists of thin layers of cells surrounding the median eminence (**Figure 2**). One of these genes encode the thyroid-stimulating hormone β subunit (*TSHB*) and the other encode the transcriptional co-activator eyes absent 3 (*EYA3*). Although EYA3 is a transcriptional co-activator, the expression sites of *EYA3* and *DIO2*/*DIO3* are different (i.e., *EYA3* in the pars tuberalis and *DIO2/DIO3* in the ependymal cells). Therefore, it appears that EYA3 is not involved in the regulation of *DIO2*/*DIO3* switching. On the other hand, the expression of TSH receptor (TSHR) and binding of ^{125}I-labeled thyroid-stimulating hormone (TSH) were observed in the ependymal cells where *DIO2* and *DIO3* are expressed. In addition to these, i.c.v. TSH administration induced *DIO2* expression and reduced *DIO3* expression in the ependymal cells even under SD conditions, while passive immunization against TSH attenuated LD-induction of *DIO2* expression (45). The involvement of TSHR-Gsα-cAMP signaling pathway in this TSH regulation of *DIO2* expression was demonstrated by the promoter analysis. Considering that the magnitude of testicular growth induced by i.c.v. TSH infusion was almost similar to that observed in birds exposed to LD stimulus, the LD-induced pars tuberalis TSH appears to be a major factor regulating the seasonal reproduction in birds.

In birds, eyes are not necessary for the regulation of seasonal reproduction because deep brain photoreceptors are involved in this process (46, 47). Although pineal organ is a photoreceptive organ in non-mammalian vertebrates (48, 49), pineal organ is not involved in the regulation of seasonal reproduction (50, 51). In contrast, local illumination of the septal region of the telencephalon or the MBH using radioluminous-painted beads caused testicular growth in quail, suggesting the existence of deep brain photoreceptors in these regions (16). Localization of several rhodopsin family proteins (rhodopsin; OPN4: melanopsin; OPN5: neuropsin and VA opsin: vertebrate ancient opsin) are reported in these brain regions and projections that link some of these photoreceptor cells to the pars tuberalis have also been reported (52–62). These photoreceptors are therefore thought to be involved in the seasonal regulation of reproduction in birds (**Figure 2**).

In a marked contrast to avian species, eyes are the only photoreceptive organ in mammalian species (63–69). Therefore, removal of the eyes abolishes the photoperiodic response (64, 68). Light information received by the eye is transmitted to the pineal gland through the suprachiasmatic nucleus (SCN), where the circadian pacemaker is localized (68, 70–74). The duration of night corresponds to the nocturnal secretion profile of melatonin, which plays a crucial role in the regulation of seasonal reproduction in mammalian species. For example, in both LD and SD breeders, pinealectomy abolishes seasonal responses, while melatonin administration restores them (68, 74, 75). Melatonin acts via melatonin receptors and there are two subtypes of melatonin receptors (MT1 and MT2) in mammals (76, 77). However, these melatonin receptors are not expressed in the ependymal cells where *DIO2* and *DIO3* are expressed (78, 79). The MT1 receptor is reportedly expressed in the thyrotroph cells of the pars tuberalis (80, 81). Therefore, pars tuberalis TSH likely mediates the influence of melatonin in the *DIO2*/*DIO3* switching in mammalian species. Although it is generally considered that laboratory mice are non-seasonal breeders, many researchers noticed that mice do not breed well during the winter (e.g., small litter size) even though they are kept under standardized conditions. To determine whether pars tuberalis TSH mediates the influence of melatonin in the *DIO2/DIO3* switching, laboratory mice were analyzed as experimental models. Two key enzymes, arylalkylamine *N*-acetyltransferase (AA-NAT) and hydroxyindole-*O*-methyltransferase (HIOMT) are involved in melatonin biosynthesis from serotonin (74). However, most inbred mice genetically lack the ability to produce these enzymes, resulting in minimal melatonin generation (82, 83). Therefore, it was predicted that melatonin-producing strains would have the capacity to respond to photoperiodic changes, while melatonin-deficient strains would be resilient to such changes. As expected, clear photoperiodic regulation of *TSHB*, *DIO2*, and *DIO3* was observed in the melatonin-producing CBA strain, while such responses were not observed in the melatonin-deficient C57BL strain (35). In addition, daily intraperitoneal (i.p.) melatonin injections mimicked the effect of SD conditions on the expression of these genes (35). To test the involvement of the TSH–TSHR signaling pathway in the melatonin-mediated regulation of *DIO2*/*DIO3* expression, the effects of melatonin administration were examined in TSHR-null mice (35). The TSHR-null mice failed to respond to melatonin administration. This result clearly suggested the involvement of a TSH–TSHR signaling pathway in the melatonin-mediated regulation of *DIO2*/*DIO3* in mammals. In addition, the analysis of mice that lacked the MT1 and MT2 melatonin receptors revealed the involvement of MT1 melatonin receptors in this regulation (84). It is also interesting to note that TSH is involved in the LD-induction of *DIO2* in SD-breeding sheep (37). Thus, pars tuberalis TSH appears to relay the seasonal information in both LD and SD-breeding animals and sensitize them for spring.

THYROID HORMONE ACTION WITHIN THE HYPOTHALAMUS

Thyroid hormone is involved in the development and plasticity of the central nervous system (22). The expression of thyroid hormone receptors (*THR*α, *THR*β, and *RXR*α) in the median eminence suggested that the median eminence is the target site of action for the photo-induced increase in T_3 in the quail MBH (20). To understand the action of thyroid hormone within the MBH, the ultrastructure of the median eminence was examined under SD and LD conditions using electron microscopy. Dynamic morphological changes were observed between the GnRH nerve terminals and glial endfeet within the median eminence (85). In SD conditions, many GnRH nerve terminals are encased by the endfeet of glial processes and do not contact the basal lamina, while many GnRH nerve terminals are in close proximity to the basal lamina under LD conditions (**Figure 3**). It has been proposed that the nerve terminals of hypothalamic neurons are required to directly contact the pericapillary space for the secretion of the hypothalamic neurohormone from the hypothalamus into the portal capillary (86). Morphological changes between the GnRH nerve terminals and endfeet of glial processes are observed in SD quail treated with T_3 to stimulate testicular growth (87). Therefore, these morphological changes appear to regulate or modulate the seasonal GnRH secretion from the median eminence. It is also interesting to note that the seasonal plasticity within the GnRH system is reported in ewes (88).

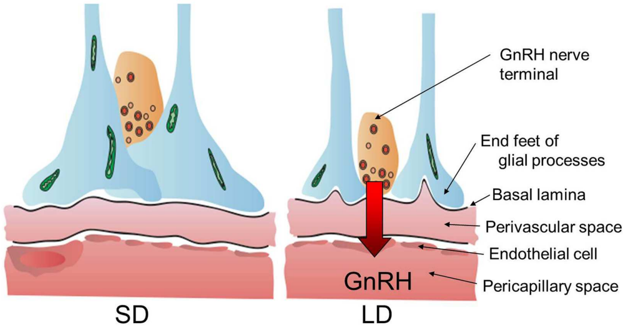

FIGURE 3 | Neuro–glial interaction between GnRH nerve terminals and glial endfeet. Locally activated thyroid hormone within the MBH regulates neuro–glial interaction in the median eminence and these morphological changes appear to regulate or modulate seasonal GnRH secretion from the hypothalamus to portal capillary. The illustration has been modified from that published by Yoshimura (89).

PHOTOPERIODIC SIGNALING PATHWAY AND DOMESTICATION

Seasonal reproduction is a rate-limiting factor for the animal procreation. The photoperiodic signaling pathway could also be a potential target that facilitates human-driven domestication process. As discussed previously, most laboratory mice lack the enzyme activity of melatonin biosynthesis pathway (82, 83, 90, 91). In addition, occurrence of selective sweeps was found at the TSHR locus in all domestic chickens (92). This observation suggests that the TSHR may be a domestication locus in chicken (92). Although we still do not know the correlation with domestication, it is interesting to note that photoperiodic regulation of *DIO3* is absent in Syrian hamster (27). Thus, genes involved in the photoperiodic signaling pathway could emerge as useful targets for the domestication of wild animals.

CONCLUSION

Involvement of thyroid hormone in the regulation of seasonal reproduction has been suggested in the past several decades. Recent comparative studies clearly reveal that the local activation of thyroid hormone within the hypothalamus is a key factor in the regulation of seasonal reproduction in a number of mammalian and avian species. It is important to note that this mechanism is also conserved in fish (93) and is universal among various vertebrate species. Although thyroid hormone influences both LD and SD breeders, the mechanism that differentiates LD breeders from SD breeders remains unknown. Presumably, the responsiveness of pathways downstream of T_3 activity (e.g., responsiveness of T_3 target genes to LD-induced T_3 etc.) differs in LD and SD breeders. The switching mechanism of LD breeder and SD breeder needs to be clarified in the future studies.

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