Molecular basis for regulating seasonal reproduction in vertebrates

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Abstract

Animals that inhabit mid- to high-latitude regions exhibit various adaptive behaviors, such as migration, reproduction, molting and hibernation in response to seasonal cues. These adaptive behaviors are tightly regulated by seasonal changes in photoperiod, the relative day length vs night length. Recently, the regulatory pathway of seasonal reproduction has been elucidated using quail. In birds, deep brain photoreceptors receive and transmit light information to the pars tuberalis in the pituitary gland, which induces the secretion of thyroid-stimulating hormone. Thyroid-stimulating hormone locally activates thyroid hormone via induction of type 2 deiodinase in the mediobasal hypothalamus. Thyroid hormone then induces morphological changes in the terminals of neurons that express gonadotropin-releasing hormone and facilitates gonadotropin secretion from the pituitary gland. In mammals, light information is received by photoreceptors in the retina and neurally transmitted to the pineal gland, where it inhibits the synthesis and secretion of melatonin, which is crucial for seasonal reproduction. Importantly, the signaling pathway downstream of light detection and signaling is fully conserved between mammals and birds. In fish, the regulatory components of seasonal reproduction are integrated, from light detection to neuroendocrine output, in a fish-specific organ called the saccus vasculosus. Various physiological processes in humans are also influenced by seasonal environmental changes. The findings discussed herein may provide clues to addressing human diseases, such as seasonal affective disorder.

Key Words
- photoperiodism
- seasonal reproduction
- thyroid hormone
- thyroid-stimulating hormone
- type 2 deiodinase

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Introduction

In mid- to high-latitude regions of the world, environmental factors such as temperature, day length and precipitation drastically change throughout the year. Organisms living in these regions anticipate seasonal changes using intrinsic timing mechanisms and adapt their physiology to the forthcoming seasons. In chipmunks, for example, seasonal hibernation is regulated by a circannual clock that oscillates with a period of approximately 1 year (Kondo *et al.* 2006). Many organisms use photoperiod, or relative day length, as a cue to initiate seasonal adaptations. The circadian

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clock, an oscillator with a period of approximately 24 h, is thought to be responsible for measuring the day length in a phenomenon called photoperiodism (Bünning 1969). Many biological processes are photoperiodic, for example, flowering and dormancy in plants (Heino *et al*. 2010, Izawa 2010, Putterill *et al*. 2010), as well as reproduction, diapause (Saunders 2010), migration (Saunders 2010) and molting (Fischer *et al*. 2008) in animals. Here, we focus on the mechanisms underlying photoperiodic regulation of reproduction in vertebrates, in which this phenomenon has been extensively studied.

Seasonal reproduction in animals

Reproductive mechanisms in animals can be classified into two categories: seasonal and nonseasonal reproduction. Nonseasonal reproduction is mainly observed in animals inhabiting tropical areas, where annual environmental changes are relatively small. Animals in these areas exhibit reproductive behavior all year round. In contrast, seasonal breeders develop gonads and display reproductive behavior during specific times of the year in order to limit the delivery of offspring between spring and early summer. These seasons are optimal for raising offspring because the climate is moderate and sufficient food is available. A critical factor in determining the timing of mating is the length of the period of gestation or incubation of fertilized eggs (Lincoln & Short 1980).

Animals can be categorized as long-day (LD) breeders and short-day (SD) breeders based on when they are fertile relative to day length. LD breeders are fertile during spring when the days are longer, whereas SD breeders display reproductive behaviors during autumn when the day length shortens. For example, the breeding behavior of birds and rodents is observed from spring to early summer because their incubation/gestation period lasts only a few weeks. Similarly, mating of large animals with gestation periods of approximately 1 year also occurs in spring. However, SD breeders, such as goats and sheep, with gestation periods of approximately half a year breed during autumn and early winter.

The critical day length refers to the threshold value of light phase duration that is required to trigger a photoperiodic response. Reproductive behaviors in LD breeders are observed when the light phase lasts longer than the critical day length and vice versa in SD breeders (Bünning 1969). During the process of domestication, animals that show a nonseasonal reproduction phenotype have been artificially selected because of their higher yield of offspring and animal products. Therefore, understanding the mechanism of seasonal reproduction will contribute to increased productivity in livestock farming (Lincoln & Short 1980). In this review, we first describe the current knowledge of the regulatory mechanism of seasonal reproduction from studies using Japanese quail as an avian model. Secondly, we show that a similar mechanism exists in mammals and fish. We conclude with a discussion about the evolution of seasonal reproduction.

Roles and metabolic pathway of thyroid hormone

Thyroid hormone (TH) is a tyrosine-based hormone that was originally known to promote the maturation of juvenile animals and maintain the basal metabolic rate (Joseph-Bravo *et al*. 2015). There has been increasing evidence that TH is responsible for seasonal reproduction (Dawson *et al*. 2001). Furthermore, removal of the thyroid gland prevents seasonal development/regression of gonads in several avian species and in sheep (Moenter *et al*. 1991, Dawson 1993, 1998, Parkinson & Follett 1995). Administration of TH ameliorates the effect of thyroidectomy and mimics exposure to light conditions that induce gonadal development (Follett & Nicholls 1985, Goldsmith & Nicholls 1992, Wilson & Reinert 2000).

It is well established that TH negatively regulates its own production through the hypothalamic–pituitary–thyroid (HPT) axis. Thyrotropin-releasing hormone (TRH) secreted from the hypothalamus induces the pars distalis of the anterior pituitary gland to release thyroid-stimulating hormone (TSH), which in turn stimulates the thyroid gland to synthesize and release TH. Thyroxine (T_4) and 3,5,3′-triiodothyronine (T_3) are the precursor and active forms of THs, respectively (Fig. 1) (Joseph-Bravo *et al*. 2015). Both T_4 and T_3 are produced in the follicle cells of the thyroid gland by proteolytic liberation from thyroglobulin, a large iodinated glycoprotein, and released into circulation (Dunn & Dunn 2004). In target tissues, THs are transported across the membrane into cells by transporter proteins, such as monocarboxylate transporter 8 (MCT8) (Friesema *et al*. 2003, Herwig *et al*. 2009) and organic anion-transporting peptide 1c1 (Oatp1c1) (Abe *et al*. 2002, Hagenbuch & Meier 2004). Once inside the cell, T_4 is converted into active T_3 by type 2 deiodinase (DIO2) by elimination of an iodine residue at the 5′ position (Fig. 1). DIO2 locally activates TH at the cellular level without affecting the HPT axis.

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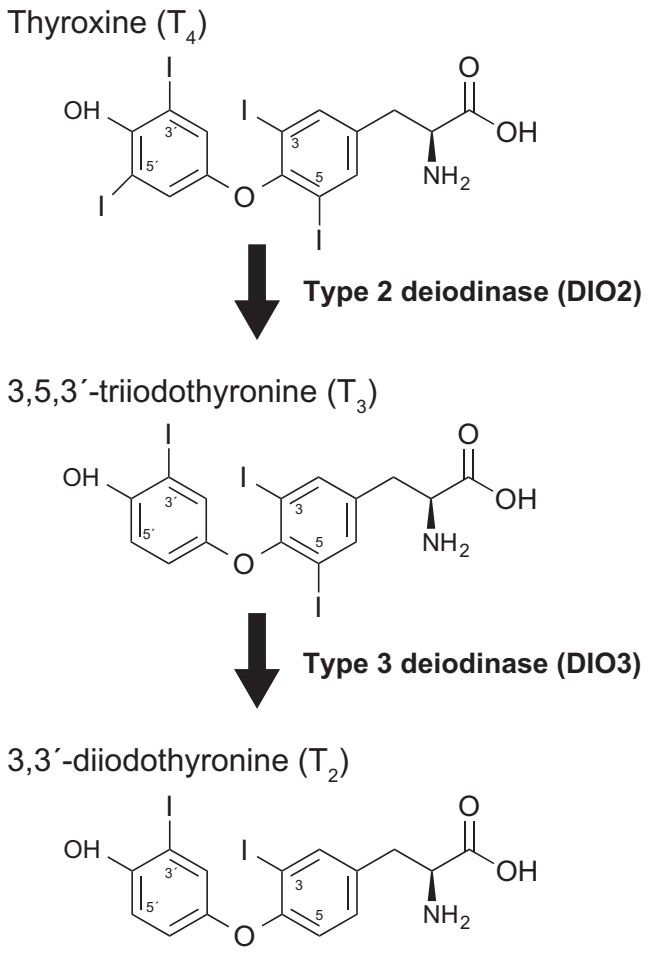

Figure 1
Activation and inactivation of thyroid hormones by iodothyronine deiodinases. Thyroxine (T_4), the thyroid hormone precursor, is converted into the active form, 3,5,3′-triiodothyronine (T_3), by deiodination at the 5′ position mediated by DIO2. DIO3 inactivates T_3 by releasing the C-5 iodine to form the T_2.

TH in the mediobasal hypothalamus regulates seasonal reproduction in quail

Japanese quail (*Coturnix japonica*) is a LD breeder belonging to the family Phasianidae that includes chicken and pheasant. Gonadal development and regression in quail shows a clear photoperiodic response. Under SD conditions, gonads are kept undifferentiated; however, 1 day after transfer into LD conditions, serum gonadotropin levels increase and within 2 weeks, and the weight of testis increases by 100 times. Interestingly, continuous illumination during the daytime is not necessary, but a light pulse during the critical time window (photoinducible phase) is sufficient to induce a photoperiodic response. In quails, 15 min of light given 14 h after dawn triggers gonadal development (Follett & Sharp 1969). The mediobasal hypothalamus (MBH) is thought to be the regulatory center for seasonal reproduction in birds. MBH lesions block light-induced gonadal development even under LD conditions (Sharp & Follett 1969). Moreover, electrical stimulation of MBH increases the concentration of LH in plasma (Konishi *et al*. 1987) and testicular growth (Ohta *et al*. 1984). Furthermore, c-Fos, a neuronal activation marker, is induced in the MBH in response to a single LD stimulus (Meddle & Follett 1995, 1997). Collectively, these phenomena support the notion that the MBH plays central roles in regulating seasonal reproduction.

In order to identify the components of the photoperiodic signaling cascade, genes differentially expressed in the MBH between LD and SD conditions were explored by subtractive hybridization. Expression of the *DIO2* gene is significantly induced by a 1-h light pulse during the photoinducible phase (Yoshimura *et al*. 2003). In contrast to *DIO2* induction, expression of type 3 deiodinase gene (*DIO3*), the product of which inactivates T_3 by releasing C-5 iodine (Fig. 1), is repressed under LD conditions (Yasuo *et al*. 2005). These results suggest that local activation of TH in the MBH plays a key role in the regulation of seasonal reproduction. In fact, the concentration of T_3 in the MBH is 10 times higher in LD conditions than in SD conditions (Yoshimura *et al*. 2003). MBH *DIO2* mRNA is localized to the ependymal cells around the third ventricle (Yoshimura *et al*. 2003). Chronic intraventricular administration of T_3 in quail stimulates testicular development even in SD conditions (Yoshimura *et al*. 2003). These results confirm that the local concentration of T_3 at the MBH is increased by induction and repression of *DIO2* and *DIO3*, respectively, and facilitates photoperiodic gonadal development.

Locally activated TH induces neuronal plasticity in the MBH

In vertebrates, gonadal development is regulated by the HPG axis. Gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus and stimulates the release of gonadotropins, such as luteinizing hormone and follicle-stimulating hormone, from the anterior pituitary gland. These hormones act on the testis and ovary to facilitate gonadal development and the production of steroid hormones, including androgen, estrogen and progesterone. Therefore, seasonal breeders activate the HPG axis only in the breeding season.

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TH is involved in neural development and plasticity in the central nervous system (Bernal 2002), raising the possibility that locally activated T_3 in the MBH promotes the development of testis via modification of neuroendocrine pathways. TH receptors exist in the median eminence of the MBH where terminals of GnRH neurons project (Yoshimura *et al*. 2003). Electron microscopy revealed that terminal morphology of GnRH neurons varied according to the photoperiod. GnRH nerve terminals are wrapped with endfeet of glial processes in SD conditions, whereas in LD conditions, the terminals contact the basal lamina of capillary vessels and allow GnRH secretion into the bloodstream (Yamamura *et al*. 2004). It is possible that these morphological changes induced by MBH-localized T_3 allow gonadal development only in LD conditions.

TSH is the master regulator of seasonal reproduction

In order to elucidate the signaling pathway between light stimulus and *DIO2* induction, the regulatory network of genes activated in the MBH upon light stimulus was analyzed using a chicken genome microarray. Quails housed under SD conditions (6L18D) were transferred to LD conditions (20L4D), and then time series samples of MBH were subjected to genome-wide expression analysis. At 14 h after the SD-to-LD transition, a gene encoding the β-subunit of thyroid-stimulating hormone (*TSHB*) is induced, and 4 h later, the expression of a second wave of genes, including *DIO2*, is increased (Nakao *et al*. 2008). TSH is a glycoprotein hormone that consists of α- and β-subunits (Magner 1990, Vassart & Dumont 1992). *TSHB* mRNA is localized in the pars tuberalis (PT) (Nakao *et al*. 2008) of the anterior pituitary gland that surrounds the median eminence. Intracerebroventricular administration of TSH increases the testis size to the same degree as seen in the LD condition (Nakao *et al*. 2008).

TSH receptor (TSHR) is highly expressed in ependymal cells that coexpress DIO2. These results suggest that induction of TSH in the PT (PT-TSH) triggers a photoperiodic response and stimulates the expression of *DIO2*. TSHRs are G protein-coupled receptors that induce genes flanked by cAMP-responsive elements (CREs) via activation of Gsα–cAMP signaling pathway (Magner 1990, Vassart & Dumont 1992, Walton & Rehfuss 1992). The quail *DIO2* gene possesses CRE sequences in its 5′-flanking region. A luciferase reporter gene containing the *DIO2* upstream region is induced by TSH administration, and mutations in the CRE sequences abolish luciferase expression (Nakao *et al*. 2008). These results demonstrate that PT-TSH is a master regulatory factor of the photoperiodic response downstream of photoreception.

The induction of TSH in the pars distalis (PD-TSH) of the anterior pituitary is known to stimulate the thyroid gland to synthesize and release TH, which results in increasing basal metabolic rates (Magner 1990, Joseph-Bravo *et al*. 2015). Uncovering how PT-TSH and PD-TSH avoid functional crosstalk after release into the circulation was an important issue. In mice, PT-TSH and PD-TSH are subjected to tissue-specific glycosylation; PD-TSH contains sulfated biantennary *N*-glycans and is rapidly degraded in the liver (Magner 1990, Ikegami *et al*. 2014). However, PT-TSH is modified with sialylated multibranched *N*-glycans and forms a macro-TSH complex with immunoglobulin or albumin in the blood, which inactivates circulating PT-TSH and prevents stimulation of the thyroid gland (Ikegami *et al*. 2014).

Photoreceptors regulating avian photoperiodism

In addition to photoreceptors in the retina, nonmammalian vertebrates have extraretinal photoreceptors located in the pineal gland (Okano *et al*. 1994) and the brain; deep brain photoreceptors are thought to be responsible for avian photoperiodism (Benoit 1935, Menaker *et al*. 1970). As expected, photoperiodicity is not disrupted by the removal of the eyes or pineal gland in quail (Siopes & Wilson 1974). Among the 12 opsin superfamily genes in the chicken genome, *OPN5* is localized to the cerebrospinal fluid (CSF)-contacting neurons in the hypothalamic paraventricular organ (PVO) (Nakane *et al*. 2010). Cell bodies of these neurons project dendrites to the third ventricle, and their axons terminate in the vicinity of the PT (Nakane *et al*. 2010). In *Xenopus* oocytes with forced OPN5 expression, exposure to light ranging from ultraviolet (UV)-B to blue activates a membrane current under voltage clamp conditions, demonstrating that OPN5 is a short-wavelength-sensitive photopigment (Nakane *et al*. 2010). Testicular growth is observed in eye-patched, pinealectomized quail upon exposure to light in the UV-to-blue region of spectrum, supporting the hypothesis that OPN5 is a deep brain photoreceptor that regulates photoperiodicity in quail (Nakane *et al*. 2010). Furthermore, OPN5-positive CSF-contacting neurons in the PVO located in the quail MBH are intrinsically photosensitive (Nakane *et al*. 2014). The current understanding of the signal transduction pathway for photoperiodicity is summarized in Fig. 2.

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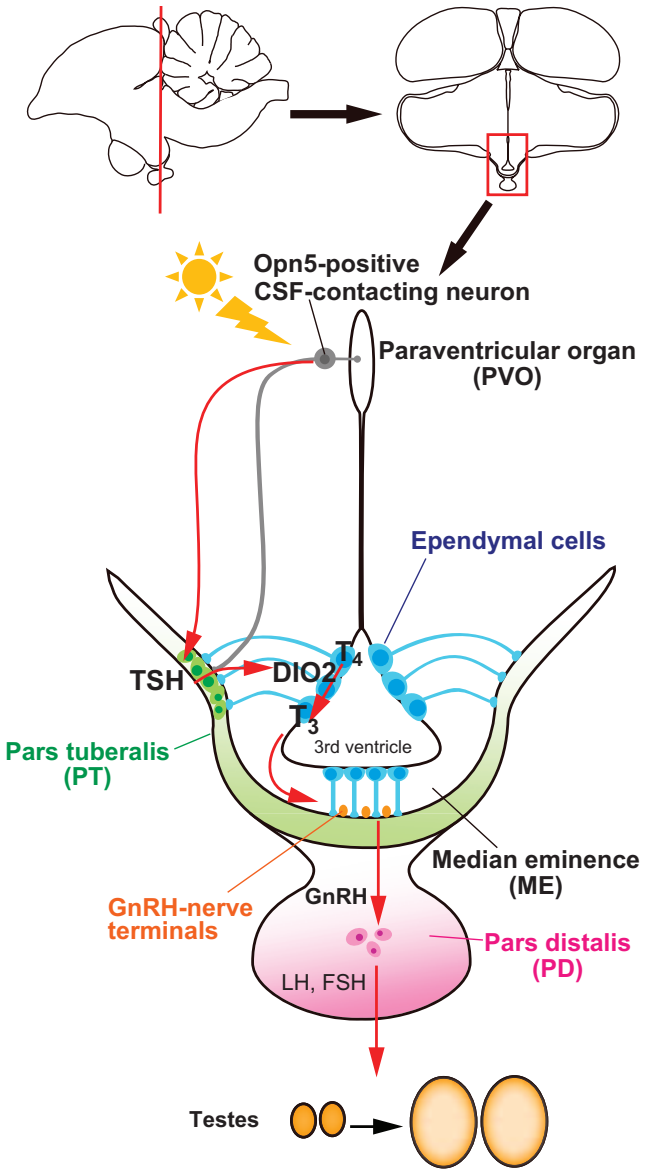

Figure 2
A schematic diagram of the signal transduction cascade for seasonal reproduction in birds. Light information is received by deep brain photoreceptors, such as OPN5, and then transmitted to the pars tuberalis (PT) of the pituitary gland, where TSH is induced. TSH acts on ependymal cells to induce DIO2, which converts the TH precursor T_4 into the active form T_3. T_3 induces morphological changes in GnRH nerve terminals and glial processes, thereby facilitating GnRH secretion, resulting in gonadal development.

Regulatory mechanism for mammalian seasonal reproduction

The retina is the only photoreceptive organ in mammals. Light information from the retina is transmitted to the pineal gland via the suprachiasmatic nucleus (SCN), which is the location of the master circadian clock (Morin *et al.* 1977). Pinealectomy disrupts photoperiodic responses in reproduction (Pévet 1988), suggesting that the pineal gland relays photoperiodic information. Melatonin is a serotonin-derived hormone produced in the pineal gland (Reiter 1980). Upon synthesis, melatonin is immediately released into circulation. Melatonin synthesis and secretion shows a clear day–night variation with high levels at night and trace amounts during the day (Klein & Moore 1979), which is directly regulated by arylalkylamine *N*-acetyltransferase (AANAT) activity in the pineal. AANAT is a rate-limiting enzyme of melatonin synthesis catalyzing acetylation of serotonin, which is rapidly degraded by light exposure (Klein & Moore 1979). Additionally, the circadian clock activates the transcription of *AANAT* mRNA during the night via an upstream CRE (Foulkes *et al.* 1997). Therefore, information regarding environmental light–darkness cycles is physiologically represented by the duration of melatonin synthesis and secretion by the pineal gland.

Melatonin receptors are highly expressed in the PT (Dardente *et al.* 2003), which is consistent with the notion that melatonin mediates photoperiodic information. LD stimuli induce *DIO2* expression in ependymal cells in hamsters (Watanabe *et al.* 2004). Intraperitoneal injection with melatonin inhibits *DIO2* expression and regression of the testis even under LD conditions (Watanabe *et al.* 2004). Although most of inbred mouse lines are genetically deficient in melatonin synthesis, CBA/N is one of the few melatonin-proficient strains of mice. In the CBA/N mouse brain, expression of *TSHB* and *DIO2* is upregulated by exposure to long light periods (Ono *et al.* 2008). Although these genes are not photoperiodically regulated and they are not increased even under LD conditions in the melatonin-deficient C57BL/6J strain, intraperitoneal injection of melatonin reduces the expression of *TSHB* and *DIO2* (Ono *et al.* 2008). Moreover, *DIO2* inhibition by melatonin injection is not observed in a TSHR-deleted strain (Ono *et al.* 2008), nor in melatonin receptor MT1 null mice (Yasuo *et al.* 2009). It is important to note that the phototransduction mechanism is different in mammals and birds, but the downstream signaling pathway regulating seasonal reproduction is conserved among avian and mammalian species (Fig. 3). *TSHB* functions as a master control gene of seasonal reproduction in both mammals and birds.

TH is involved in seasonal reproduction also in SD breeding mammals. In Saanen goats (*Capra hircus*), *DIO2* expression and T_3 content in the MBH are suppressed in LD conditions, which is opposite to the LD breeders (Yasuo *et al.* 2006). By contrast, PT-TSH expression in

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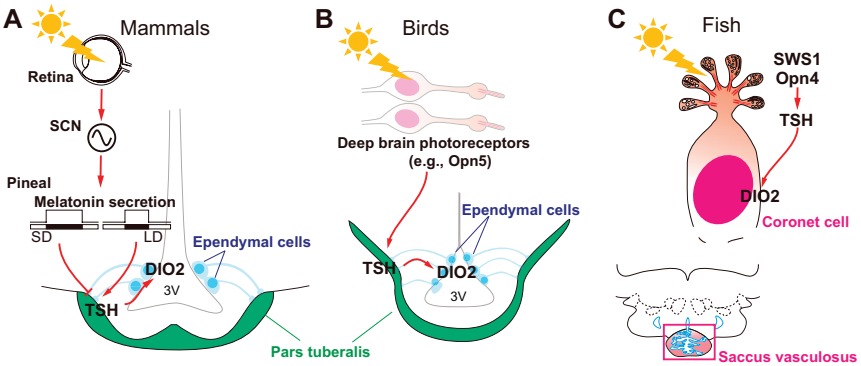

Figure 3
Universality and diversity of photoperiodic signaling mechanisms in vertebrates. In mammals, light information received in the retina is transmitted to the pineal gland via the SCN, the location of the master circadian clock. Melatonin synthesis and secretion in the pineal gland is a reflection of photoperiod, because light and the circadian clock regulate its production, which is higher in the night than in the day. Melatonin inhibits the induction of TSH in the PT; therefore, the signaling cascade downstream of TSH is activated only under long-day conditions (A). In birds, light signals received by deep brain photoreceptors directly induce TSH in the PT (B). In fish, the entire photoperiodic signaling machinery is integrated in the coronet cells located in the fish-specific SV (C).

Soay sheep (*Ovis aries*) is stimulated under LD conditions followed by *DIO2* expression in MBH (Hanon *et al*. 2008). The photoperiodic TSH–TH signaling pathway is widely conserved; however, the downstream events may be different among species.

Kisspeptin and RFRPs (RFamide-related peptides), which belong to the RFamide superfamily, are involved in the regulation of reproductive activity (Tsutsui *et al*. 2010). Kisspeptin stimulates GnRH release via G protein-coupled receptor GPR54 located at the surface of GnRH neurons resulting in activation of the HPG axis (Oakley *et al*. 2009). In LD breeding rodents, melatonin inhibits secretion of kisspeptin from the hypothalamic arcuate nucleus (Revel *et al*. 2006, Ansel *et al*. 2010), and administration of kisspeptin restores the reproductive activity in SD conditions (Revel *et al*. 2006, Ansel *et al*. 2011). RFRP-1 and -3 peptides were originally identified as mammalian orthologs of gonadotropin inhibitory hormone (GnIH) that inhibits the HPG axis in birds (Tsutsui *et al*. 2013). In mammals, the effects of RFRPs on seasonal reproduction are different among species. Administration of RFRP-3 inhibits the activity of GnRH neurons in sheep (Clarke *et al*. 2008), whereas in Syrian hamsters, RFRP-3 stimulates GnRH secretion under the control of melatonin (Ancel *et al*. 2012). In Siberian hamsters, the effect of central administration of RFRP peptide is dependent on the photoperiod; it inhibits and stimulates LH release in LD and SD conditions, respectively (Ubuka *et al*. 2012). It is controversial whether these peptides are the primary targets of inhibitory melatonin signaling or the indirect ones located at the downstream of TSH-TH signaling cascade (Simonneaux *et al*. 2013). Further studies are required to clarify this issue.

In the photoresponsive rat strain Fischer 344, the retinoic acid (RA) signaling pathway is also activated in LD conditions (Helfer *et al*. 2012, Tavolaro *et al*. 2015). As the temporal expression profiles of TH signaling- and RA signaling-related genes are similar (Tavolaro *et al*. 2015), it is possible that these two pathways coordinately regulate seasonal reproduction.

Regulation of seasonal reproduction in fish

Seasonal reproduction is widely observed in fish. For example, medaka is an LD breeder that develops gonads from spring to summer (Koger *et al*. 1999). Salmonidae fish are SD breeders that swim upstream to their home river in autumn for spawning. Despite lacking an anatomical site homologous to PT, TH is known to affect the reproduction of fish (Cyr *et al*. 1988). In masu salmon, *TSHB* and *DIO2* mRNAs were localized in the saccus vasculosus (SV), a circumventricular organ located caudal to the pituitary gland (Nakane *et al*. 2013). The removal of SV results in loss of photoperiodicity, which confirms that SV functions as a regulatory center for seasonal reproduction (Nakane *et al*. 2013). The photoreceptor that is responsible for photoperiodicity had long been unknown in fish. The removal of the eyes and pineal gland has limited effect on photoperiodicity, suggesting that deep brain photoreceptors might also exist in fish (Borg 2010). As expected, four rhodopsin family genes, *RH1*, *SWS1*, *LWS* and *OPN4* are expressed in the SV (Nakane *et al*. 2013). The SV consists of coronet cells, CSF-contacting cells and supporting cells. Coronet cells have a crown-like morphology with globule-tipped cilia protruding from cell bodies (Fig. 3). Within coronet cells, the TSHβ, SWS1 and OPN4 proteins are localized in the globules of cilia, whereas DIO2 protein is expressed in cell bodies (Nakane *et al*. 2013), indicating that light information received at the globules regulates expression of TSH and DIO2.

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Although the regulation of seasonal reproduction seems to be conserved in vertebrates, the anatomical regions responsible for photoperiodic signal transduction differ across the classes of vertebrates. The mammalian photoperiodic response is initiated by light signals received by the retina, which are then transmitted to the hypothalamus where TSH secretion and TH activation by DIO2 take place. In birds, photoreception as well as TSH secretion and DIO2 induction also occur in the hypothalamus. In fish, which are evolutionarily lower than mammalian and avian species, all components of the photoperiodic signaling are integrated into a single anatomical region, the SV. This is analogous to the functional differences in the pineal gland for circadian systems. The mammalian pineal gland is an endocrine organ that synthesizes and releases melatonin under the control of photic input from the retina and the circadian clock in the SCN (Morin *et al*. 1977), whereas the pineal gland of nonmammalian species contains an entire circadian clock system consisting of the input (photoreceptor), oscillator (circadian clock), and output (synthesis and release of melatonin) (Takahashi *et al*. 1980, Menaker & Wisner 1983). It is interesting to note that a recent developmental study identified common transcription factors in the SV and pituitary gland of rainbow trout (Maeda *et al*. 2015).

Measurement of day length using the circadian clock

The idea that the circadian clock is involved in the photoperiodic regulation of seasonality was first proposed over 50 years ago (Bünning 1960). This has since been demonstrated to be true in both white-crowned sparrow (Follett *et al*. 1974) and quail (Follett & Sharp 1969), where the photoinducible phase occurs in a circadian manner. However, how the circadian clock determines the specific photoinducible phase remains elusive. Historically, researchers have proposed two theories: the internal and the external coincidence models (Pittendrigh *et al*. 1972). In the external coincidence model, the photoinducible phase is determined by a circadian oscillator, and light entrains the oscillations as well as triggers the photoperiodic response. However, the internal coincidence model predicts that photoperiodic responses are induced when two or more oscillations are in a certain phase relationship. In this model, light serves only to entrain oscillations. It is widely accepted that the circadian clock generates an oscillation with a period of approximately 24 h by a transcriptional–translational feedback loop, in which translational products of clock genes inhibit their own transcription (Hardin & Panda 2013).

In mammals, photoperiodicity is likely regulated by the circadian clock located in the SCN, because lesions of the SCN disrupt photoperiodic responses (Rusak & Morin 1976). In mammals and birds, the core oscillator of the circadian clock is composed of the clock genes *Period* (*Per*), *Cryptochrome* (*Cry*), *Bmal1* and *Clock*. These genes are expressed rhythmically not only in the SCN but also in brain regions responsible for photoperiodicity, such as the MBH, PT and pineal gland (Yasuo *et al*. 2003, Johnston *et al*. 2005, Tournier *et al*. 2007). Changes in photoperiod affect the phase relationship between the expression profiles of ovine *Per1* and *Cry1* in the SCN and PT, implying that these genes function as an internal coincidence timer (Lincoln *et al*. 2002); however, this is not the case in mice (Ikegami *et al*. 2013). Furthermore, disruption of *Per2* abolishes rhythmic locomotor activity and the expression of other clock genes, but it does not affect photoperiodic induction of Tshb, Dio2 and Dio3 (Ikegami *et al*. 2013). Therefore, further studies are necessary to fully elucidate the involvement of not only known clock genes but also novel clock factors in the photoperiodic time measurement.

To achieve this, a chemical biology approach might be useful. Recently, small molecules that affect circadian parameters, such as period and amplitude, have been identified by cell-based high-throughput chemical library screening (Wallach & Kramer 2015). By this method, small compounds that lengthen the circadian period by acting directly on the clock protein CRY have been discovered (Hirota *et al*. 2012). We have extended this study by performing structure–activity relationship (SAR) analyses, and as a result, we have developed novel period-shortening molecules (Oshima *et al*. 2015). Clock-modulating compounds might be useful tools to understand how the circadian clock regulates seasonal reproduction by *in vivo* administration of these molecules. Moreover, these compounds might be applied to treatment of human seasonal disorders, such as seasonal affective disorder (SAD, see next).

Seasonal rhythms in humans

Various physiological activities in humans show seasonal fluctuations. Temporal profiles of more than 4000

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protein-coding mRNAs in white blood cells and adipose tissue show seasonal variations, which differ between Europeans and Africans. Expression of genes related to immunity and risk biomarkers for cardiovascular and psychiatric diseases increase in winter in Europeans (Dopico *et al*. 2015).

SAD is a disease that is characterized by depression-like symptoms from autumn to winter with remission or slight hypomania from spring to summer (Rosenthal *et al*. 1984). A recent study revealed more frequent depression-like behavior in mice kept in SD conditions compared with those kept in LD conditions (Otsuka *et al*. 2014). The level of serotonin in the brain is also decreased in LD conditions (Otsuka *et al*. 2014). Together, these results raise the possibility that the mouse model recapitulates human seasonal affective disorder. The relationship between TH and depression has long been discussed (Wiersinga 2014); therefore, understanding the mechanism that animals use to sense seasonal changes may help humans address and possibly treat seasonal disorders.

Concluding remarks

Studies in the past two decades have uncovered an evolutionarily conserved mechanism for photoperiodic signal transduction. At the same time, species-specific aspects have also become apparent. These findings have contributed to a greater understanding of seasonal reproduction and photoperiodism, and might be useful in developing strategies to increase animal production in livestock farming, as well as therapies for human seasonal disorders. Additional interdisciplinary approaches, such as chemical biology or molecular epidemiology, might also be helpful in achieving these aims.

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

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