Review

The underlying mechanisms of vertebrate seasonal reproduction

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Abstract: Animals make use of changes in photoperiod to adapt their physiology to the forthcoming breeding season. Comparative studies have contributed to our understanding of the mechanisms of seasonal reproduction in vertebrates. Birds are excellent models for studying these phenomena because of their rapid and dramatic responses to changes in photoperiod. Deep brain photoreceptors in birds perceive and transmit light information to the pars tuberalis (PT) in the pituitary gland, where the thyroid-stimulating hormone (TSH) is produced. This PT-TSH locally increases the level of the bioactive thyroid hormone T_3 via the induction of type 2 deiodinase production in the mediobasal hypothalamus, and an increased T_3 level, in turn, controls seasonal gonadotropin-releasing hormone secretion. In mammals, the eyes are the only photoreceptive structure, and nocturnal melatonin secretion encodes day-length information and regulates the PT-TSH signaling cascade. In Salmonidae, the saccus vasculosus plays a pivotal role as a photoperiodic sensor. Together, these studies have uncovered the universality and diversity of fundamental traits in vertebrates.

Keywords: photoperiodism, circadian clock, thyrotropin, thyroid hormone, photoreceptor, opsin

1. Introduction

Organisms living in a seasonal world alter their physiology and behavior to adapt to annual fluctuations in the environment. Animals display a wide variety of responses to the changing seasons, such as alterations in the growth rate, metabolism, and immune function as well as the initiation of molting, migration, nesting, hibernation, and reproductive activity. Anticipating and aligning with periodic, geophysical cycle-generated changes to ensure the precise timing of these annual processes is essential for their survival and reproductive success. A number of environmental factors, such as temperature, rainfall, and day length, vary with seasons. However, seasonal fluctuations in temperature and precipitation are relatively unpredictable because there are occasional warm winter or dry rainy seasons. In contrast, changes in the day length (photoperiod) are the most reliable seasonal cues because solstices and equinoxes occur at almost identical times each year, suggesting that organisms use photoperiod to estimate the time of year. The principal role of photoperiod in the seasonal responses was conclusively demonstrated in various organisms in the 1920s[1)–3)] and these day length-dependent responses are collectively referred to as photoperiodism.

Strategies for reproduction in animals can be classified into the following two categories: seasonal

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and nonseasonal. Nonseasonal reproduction is mainly observed in animals inhabiting tropical areas, where only relatively minor changes in the environment occur throughout the year. Animals in these areas reproduce almost throughout the year. In contrast, most animals living outside the tropics limit their reproductive activity to a specific time of the year. The advantages of seasonal reproduction are obvious; animals can avoid expending energy for reproduction at an inappropriate time of the year (*e.g.*, winter), and the survival of offspring will be maximized if they are delivered and raised in seasons with a moderate climate. For example, most birds breed during spring and summer and are called long-day (LD) breeders. Because the incubation period of most birds lasts only a few weeks, their offspring are born during spring and summer. Conversely, relatively large mammals, such as goats and sheep, breed during autumn and are called short-day (SD) breeders. Because these animals have a gestation period of approximately six months, their offspring are also born and raised during spring and summer (Fig. 1). As a result, the offspring of both LD and SD breeders can grow in favorable conditions with a moderate climate and abundant food.

Reproduction in vertebrates is primarily regulated by the hypothalamic–pituitary–gonadal (HPG) axis. Gonadotropin-releasing hormone (GnRH), released from the hypothalamus, induces the secretion of gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) from the pars

distalis (PD) of the pituitary (also known as the anterior pituitary). Gonadotropins, in turn, activate gonadal function and trigger reproductive activity. In this context, seasonal reproduction is achieved via activation of the HPG axis at an appropriate time of the year. For seasonal breeders, activation of the HPG axis results in a dramatic change in the gonadal size, particularly in birds, in which it increases more than a hundred fold during the breeding season.[4] In addition to this gonadal response, birds have more sophisticated photoperiodic mechanisms than other vertebrate species. They have very short breeding seasons, and the HPG axis is automatically turned off after breeding; the gonads start to regress although the photoperiod still increases, a phenomenon known as photorefractoriness, and gonadal weight is significantly reduced during the nonbreeding season.[5] Such robust responses and a restricted breeding season appear to be adaptations of birds to flight. Accordingly, birds have often been investigated in studies on photoperiodic responses. Among mammals, hamsters and sheep are frequently studied to understand the mechanisms of photoperiodism because they also show robust photoperiodic responses. However, the magnitude of gonadal regression is less dramatic in mammals than in birds and only involves a several-fold change.[6]

2. Models for photoperiodic time measurement

One of the most important questions in the field of photoperiodism is how organisms discriminate
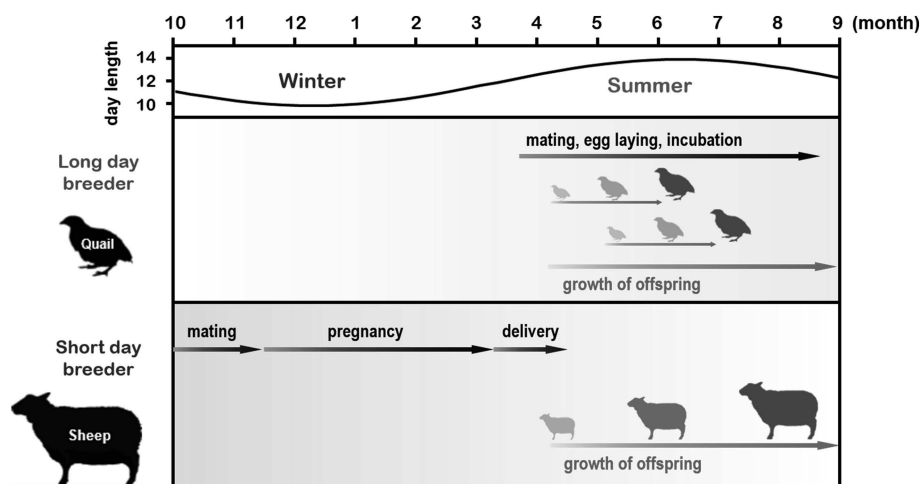

Fig. 1.   (Color online) Calendar of seasonal breeders. Small species with short gestation or incubation periods mate in spring and summer [long-day (LD) breeders]. In contrast, relatively large species with approximately six-month gestation periods mate in fall [short-day (SD) breeders]. Consequently, the offspring of both LD and SD breeders are born and raised in spring/summer. Figure adapted from Shinomiya *et al.* (2014)[104] with permission under the terms of the Creative Commons Attribution License (CC BY) ⓒ 2014 Shinomiya, Shimmura, Nishiwaki-Ohkawa, and Yoshimura.

between LDs and SDs. Organisms show photoperiodic responses when the day length reaches or exceeds the so-called "critical day length". Most seasonal breeders possess a highly accurate mechanism to respond to small changes in photoperiod; for instance, testicular recrudescence (gonadal growth) can only be seen in hamsters transferred from SD to photoperiods of ≥ 12.5 h.[7),8)] In Japanese quail, days that are >11.5 h induce testicular growth.[9)] Somewhere between the receptors receiving environmental day-length information and the HPG axis must be the capacity to measure the photoperiod. The easiest and most intuitive way to conceptualize this is to assume that a substance (chemical or physiological agent) required for a seasonal event (*e.g.*, gonad development) gradually accumulates in response to light (or dark). The seasonal event is then initiated when the level of this substance reaches a critical value or threshold at the appropriate day length.[10)] However, this model, referred to as the hourglass model, has long been refuted because a light pulse given at a specific time of day (called the photoinducible phase) is sufficient to induce testicular development (Fig. 2).[11)] This finding reveals that organisms possess a daily rhythm of light sensitivity and that it is the time point or phase at which the light pulse occurs that matters, rather than the total duration of light exposure. This implicates the
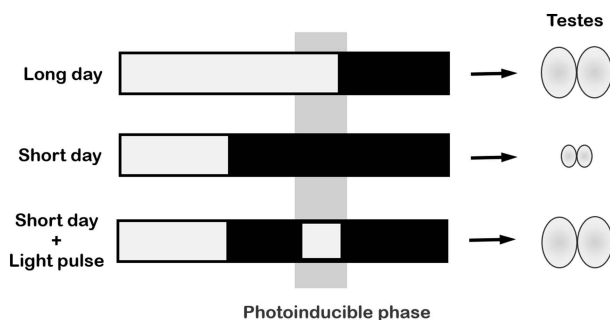

Fig. 2. (Color online) Involvement of the circadian clock in photoperiodic time measurement. A light pulse given at a specific time of the day, called the "photoinducible phase" (highlighted in orange), is sufficient to induce gonadal growth. The circadian clock is thought to be involved in generating this photoinducible phase, but the exact mechanism remains unclear. Figure adapted with permission from RightsLink Permissions Springer Nature Customer Service Centre GmbH: Springer Nature. Avian Reproduction. Advances in Experimental Medicine and Biology, vol 1001. Molecular and Neuroendocrine Mechanisms of Avian Seasonal Reproduction, Tamai T.K., Yoshimura T.,[105)] © Springer Nature Singapore Pte. Ltd. 2017.

involvement of the endogenous circadian clock in photoperiodic time measurement.

Two models, referred to as "external coincidence"[12)] and "internal coincidence",[13)] have been proposed to address the role of the circadian clock in seasonal time measurement. The former model is based on Bünning's hypothesis,[14)] which states that when an external light stimulus is applied during the photosensitive phase (generated by the circadian oscillator), a photoperiodic response is induced. External coincidence refers to the requirement of the concurrence of an external stimulus with an internal rhythm of photosensitivity. Conversely, the internal coincidence model hypothesizes the existence of multiple oscillators, of which one oscillator couples with dawn and the other with dusk, and it also hypothesizes that the phase relationship between the two oscillators changes between seasons. In this model, the coincidence of two (or more) internal oscillators leads to seasonal responses. Although the exact nature of these endogenous rhythms of photosensitivity remains elusive, these theoretical models have helped us to better understand photoperiodism and have promoted the discovery of molecular mechanisms for photoperiodic responses in vertebrates as well as in plants and insects.

Photoperiodic time measurement is a process that describes how environmental light information is perceived, assessed, transduced, and finally translated into a neuroendocrine event in organisms. It consists of three components: (1) a light input pathway that perceives external light/dark information, (2) a biological clock that measures the day length within a 24 h cycle, and (3) a neuroendocrine output pathway that regulates various aspects of physiology and behavior. In the following section, we present an updated overview of the mechanisms that regulate photoperiodism in vertebrates.

3. Mechanism of seasonal reproduction in birds

3.1. Involvement of deep brain photoreceptors in seasonal reproduction in birds.
Organisms detect and transduce light signals through a functional unit known as the photoreceptor. In vertebrates, photoreceptors are light-sensing cells (usually neurons) that contain a photopigment (comprising an opsin protein and a vitamin A derivative, retinal), which is capable of phototransduction.[15)] Classic photoreceptors are the cone and rod cells within the eyes (retina), which are responsible for image formation.[16)] In addition, there are non-image-forming photoreceptors found in the eyes, which are

involved in light entrainment of circadian rhythms.[17] In marked contrast to mammals, in which the eyes are the only photoreceptive structure, nonmammalian vertebrates have extraocular photoreceptors. Apart from the eyes, the pineal gland is the best-known photoreceptive organ; the photopigment pinopsin has been isolated from chicken pineal gland.[18] It was observed that the photoperiodic response is not disrupted by the removal of the eyes and pineal gland in quail,[19] suggesting an extraretinal, extrapineal pathway in mediating photoperiodic light responses. In a number of studies investigating the light input pathway in birds, the involvement of deep brain photoreceptors was suggested. These are photosensitive cells located deep within the brain and are capable of perceiving light penetrating through the scalp. Benoit first demonstrated that blind ducks, capable of photo-induced gonadal development, were incapable of providing photoperiodic responses when black caps were placed on their heads.[20] Moreover, injection of India ink under the scalp of blinded, pinealectomized sparrows blocked the photoperiodic response.[21] Finally, local illumination experiments highlighted the critical importance of deep brain photoreception. The implantation of radium luminous-painted beads into the septal region of the telencephalon or mediobasal hypothalamus (MBH) led to testicular growth in quail under SD conditions, indicating two candidate sites where avian deep brain photoreceptors might exist.[22] Several photopigments identified in a variety of brain regions have been proposed as candidates for deep brain photoreception, including the photopigments rhodopsin,[23),24)] melanopsin,[25)–27)] and vertebrate ancient (VA) opsin.[28),29)] Subsequent identification of OPN5 (also known as Opsin 5 and neuropsin) in quail[30] added another strong candidate for the putative deep brain photopigment-mediating seasonal responses. OPN5 is localized to the cerebrospinal fluid (CSF)-contacting neurons in the paraventricular organ (PVO) within the MBH.[30),31)] Notably, lesions around PVO prevent photoperiodic responses in quail,[32] and CSF-contacting neurons are morphologically similar to photoreceptor cells in the developing retina,[33] implying a potential role for OPN5 in photoperiodism. Functional analysis demonstrated that OPN5 is a short-wavelength-sensitive (SWS) photopigment,[30] and this is consistent with an observation that short-wavelength light, ranging from blue light to UV-B,[34] is sufficient to induce gonadal growth. Despite the argument of ineffective penetration of short-wavelength light into the brain,

it is confirmed that short-wavelength light can penetrate the hypothalamus of quail.[35] These findings suggest that OPN5-positive, CSF-contacting neurons of PVO are the long-sought deep brain photoreceptors that regulate seasonal reproduction in birds. It is noteworthy that Foster *et al.*[34] reported an action spectrum for photoperiodic responses and suggested the involvement of photoreceptors that have a high sensitivity around 480 nm. In this context, it is also possible that the presence of other photopigments, such as melanopsin and/or VA opsin, accounts for the reported sensitivity at 480 nm. Owing to the fact that sunlight comprises a wide range of wavelengths, birds might utilize multiple photopigments and wavelengths to measure the photoperiod.

3.2. Birds have multiple circadian pacemakers. Light information perceived by photoreceptors has to be interpreted or measured, and this process, as described previously, involves the endogenous circadian clock. The existence of a circadian clock has been demonstrated virtually in all tissues and cell types. These cell-autonomous peripheral oscillators are synchronized by the so-called master circadian pacemaker, which is thought to be the site responsible for photoperiodic time measurement. In mammals, the master pacemaker is localized to the suprachiasmatic nucleus (SCN) of the hypothalamus.[36] However, unlike mammals, birds have multiple circadian pacemakers in the pineal organ, eyes, and hypothalamic SCN, but the relative importance of these three pacemakers varies among avian species.[37)–41)] Intriguingly, the photoperiodic response of birds is not affected by the removal of either the eyes[20] or pineal organ[19] or the presence of lesions around the SCN.[42] Therefore, it is still unclear which tissue clocks are responsible for measuring the photoperiodic response. Alternatively, several studies have implicated the MBH in photoperiodic time measurement.[22),32),43)] Moreover, OPN5-positive neurons send projections to the external layer of the median eminence within the MBH,[30] suggesting that light information received by deep brain photoreceptors might be interpreted or measured in this region.

3.3. Local activation of thyroid hormone (TH) in the MBH is critical for the photoperiodic response. A key to understanding the mechanism of photoperiodism in birds came with the discovery of local regulation of TH metabolism in the MBH of quail. In quail, the MBH is considered to be crucial for seasonal reproduction. This is primarily based on

the observations that the MBH lesions disrupt seasonal LH secretion[32),44)] and that LD activates neurons in the MBH, as evidenced by the induction of the neuronal activation marker c-Fos.[45)] As described above, light pulses delivered during the photoinducible phase stimulate testicular development, indicating that key light-regulated events may be taking place within the MBH during this period. By analyzing differentially expressed genes in the MBH during the photoinducible phase, the type 2 deiodinase ($DIO2$) gene was found to be induced by light stimulation.[46)] $DIO2$ encodes a TH-activating enzyme that converts the precursor thyroxine (T_4) to bioactive triiodothyronine (T_3). The expression of $DIO2$ is upregulated under LD and suppressed under SD conditions in the ependymal cells (ECs, also known as tanycytes) that line the ventrolateral walls of the third ventricle within the MBH.[46)] This suggests that a local increase in the T_3 level may contribute to the LD response. Later studies further revealed that $DIO3$, a TH-inactivating enzyme that converts T_4 and T_3 into inactive reverse T_3 (rT_3) and $3,3'$-diiodothyronine (T_2), respectively, is coexpressed with $DIO2$ in ECs. Conversely, the expression of $DIO3$ is upregulated under SD and downregulated under LD conditions.[46),47)] These findings implicate a role of reciprocal switching of DIO2 and DIO3, which, in turn, fine-tunes the local TH concentration within the MBH to regulate seasonal responses. Consistent with this hypothesis is evidence showing that the concentration of T_3 within the MBH is approximately ten-fold higher under LD than under SD conditions, whereas plasma concentrations are similar during both photoperiods.[46)] The functional significance of this locally enhanced TH activity was demonstrated by intracerebroventricular (ICV) infusion of T_3 and a DIO2 inhibitor; T_3 administration under SD conditions induced testicular growth in a dose-dependent manner, whereas the administration of a DIO2 inhibitor under LD conditions attenuated testicular growth.[46)] These studies identifying $DIO2$ as a key regulator are critical because later studies demonstrated that a similar mechanism also underlies the seasonal response in mammals and fish (see Sections 4.2 and 5.1).

The connection between the photoinduction of T_3 in the MBH and activation of the HPG axis is hinted at by its potential target sites, such as the location of its cognate receptors. TH receptors (THRα, THRβ, and RXRα) are expressed in the median eminence[46)] at the base of the hypothalamus,

functioning as a gateway for the release of hypothalamic hormones into the portal capillary that leads to the anterior pituitary. This suggests that T_3 from the MBH is involved in the regulation of GnRH release. It is thought that direct contact of the nerve terminals of GnRH neurons to the pericapillary space (*i.e.*, the basal lamina) is required for secretion of the hypothalamic neurohormone from the hypothalamus into the portal capillary.[48)] Ultrastructural analysis of the quail median eminence revealed that many GnRH nerve terminals are covered by the end-feet of glial processes and do not come into contact with the basal lamina under SD conditions. In contrast, under LD conditions, many GnRH nerve terminals are in close proximity to the basal lamina.[49)] Particularly, local T_3 administration to the MBH under SD conditions mimics these LD-induced morphological changes as well as testicular growth,[49),50)] indicating that the MBH T_3 regulates or modulates seasonal GnRH release by altering neuroglial plasticity in the median eminence.

3.4. Thyrotropin in the pars tuberalis (PT) is a springtime hormone. An increase in the plasma LH level, which reflects the activation of the HPG axis, is observed before the end of the first LD when quails are transferred from SD to LD.[51),52)] This photoperiodic response is the core feature of the so-called "first-day release model" and has been used to unravel the regulatory mechanisms of photoperiodism. Consistent with our working model, the aforementioned reciprocal switching of $DIO2$ and $DIO3$ precedes the photoperiodic induction of LH release from the anterior pituitary by a couple of hours.[47)] The next emerging question was "What is the link between the light stimulus and the T_3-mediated cascade in the MBH?" In other words, it is unclear whether there are events occurring earlier to regulate the switching of $DIO2/DIO3$ and subsequent photoperiodic signaling. A genome-wide gene expression analysis conducted with Japanese quail during the transition from SD to LD conditions revealed a critical role of thyroid-stimulating hormone (TSH, thyrotropin). The $TSHB$ gene, which encodes the TSH β-subunit, was found to be induced 4 h prior to $DIO2/DIO3$ switching (*i.e.*, 14 h after dawn) in PT of the pituitary gland.[53)] PT comprises thin layers of cells and is present at the interface between the median eminence and PD of the pituitary gland. Although $TSHB$ is not expressed in ECs where $DIO2/DIO3$ switching occurs, the fact that TSH is a hormone indicates that it acts on sites remote from PT. Critically, the expression of the TSH receptor

(TSHR) and binding of ^{125}I-labeled TSH were observed in ECs.[53] Furthermore, ICV TSH administration stimulated *DIO2* expression and suppressed *DIO3* expression in ECs even under SD conditions, whereas passive immunization against TSH mitigated LD induction of *DIO2* expression,[53] highlighting the significant role of TSH as a springtime hormone. Notably, the magnitude of testicular growth induced by ICV TSH infusion was nearly identical to that observed in LD-exposed birds, suggesting that LD-induced PT-TSH is a master regulator of seasonal reproduction in birds. Because OPN5-positive neurons project to the external layer of the median eminence adjacent to PT,[30] it appears that PT is an important hub for photoperiodic regulation (Fig. 3).

4. Mechanism of seasonal reproduction in mammals

4.1. Melatonin encodes day-length information. In mammals, removal of the eyes completely abolishes the photoperiodic response,[54,55] clearly demonstrating that the eyes are the only photoreceptive structure/organ to perceive light for seasonal responses. However, the identity of the photoreceptors that mediate this response remains unknown. Seasonal changes in day length are detected by the eyes, which send projections to the master circadian pacemaker in the SCN, where the light information is decoded.[55,56] The SCN readout of the photoperiodic time is then transmitted to the pineal gland via a multisynaptic pathway, resulting in different secretion profiles of melatonin,[55,56] thus converting the photic signal into a rhythmic endocrine message. During periods of darkness (*e.g.*, night), melatonin is synthesized and secreted, whereas exposure to light immediately suppresses the synthesis of melatonin. The resulting rhythmic secretion of melatonin, which closely reflects the duration of the night, provides the biochemical signal for photoperiodic information in mammals. The SCN–pineal melatonin pathway appears to be crucial for mammalian seasonal reproduction because animals that have SCN lesions or are pinealectomized are incapable of generating photoperiodic responses.[55,56] However, the underlying mechanism of how the SCN decodes the photoperiodic information is still unclear.

4.2. Involvement of TH in seasonal reproduction in mammals. It has been known for decades that TH can affect reproduction in mammals and in birds. Thyroidectomy blocks the normal seasonal response,[57–60] whereas thyroxine replacement restores it.[61,62] After the discovery of photoperiodic *DIO2*/*DIO3* switching in birds, photoperiodic regulation of *DIO2* and/or *DIO3* within the MBH was reported in a number of mammalian species, such as hamsters[63,64] and SD breeding sheep[65] and goats.[66] In addition, seasonal changes in the morphology of GnRH neurons and glial cells have also been observed.[67] Thus, the T_3-mediated neuroglial interaction likely regulates or modulates seasonal changes in GnRH secretion in both birds and mammals.

4.3. PT-TSH mediates melatonin signaling for seasonal reproduction in mammals. As mentioned above, melatonin, which encodes day-length information, and the local switching of *DIO2*/*DIO3* both play crucial roles in the photoperiodic regulation of reproduction in mammals. Following secretion by the pineal gland, melatonin is immediately released and travels to target tissues via the bloodstream, where it exerts its action through the G-protein-coupled melatonin receptors. Two types of melatonin receptors, called MT1 and MT2, have been identified in mammals.[68,69] However, the absence of melatonin receptor expression in ECs[70,71] raises the question of how melatonin regulates the seasonal switching of *DIO2*/*DIO3*. Evidence indicates that the vital link is PT-derived TSH. First, the MT1 receptor is highly expressed in the thyrotrophs of PT,[72] and the binding of melatonin is observed in PT in a wide range of seasonally breeding mammalian species.[73] Second, consistent with birds, the expression of PT-TSH in mammals is induced by LD, and TSHR is highly expressed in ECs.[65,74] Moreover, local administration of TSH in the MBH upregulates *DIO2* expression.[65,74,75] Finally, the administration of melatonin has no effect on *DIO2*/*DIO3* expression in *TSHR*-null mice,[74] demonstrating the crucial role of TSH–TSHR signaling in mediating melatonin action on seasonal responses. Notably, some of these discoveries were made with laboratory mice, a well-known, nonseasonal breeding species. Although murine gonads do not exhibit a photoperiodic response and most inbred strains of mice are melatonin deficient,[76] melatonin treatment can mimic the photoperiodic response in gene expression in the MBH.[74] In addition, in the melatonin-proficient CBA mouse, *TSHB*, *DIO2*, and *DIO3* are clearly regulated photoperiodically.[74] These results, along with the availability of genetic modification techniques, suggest that mice are a valuable model for the study of the molecular mechanisms of
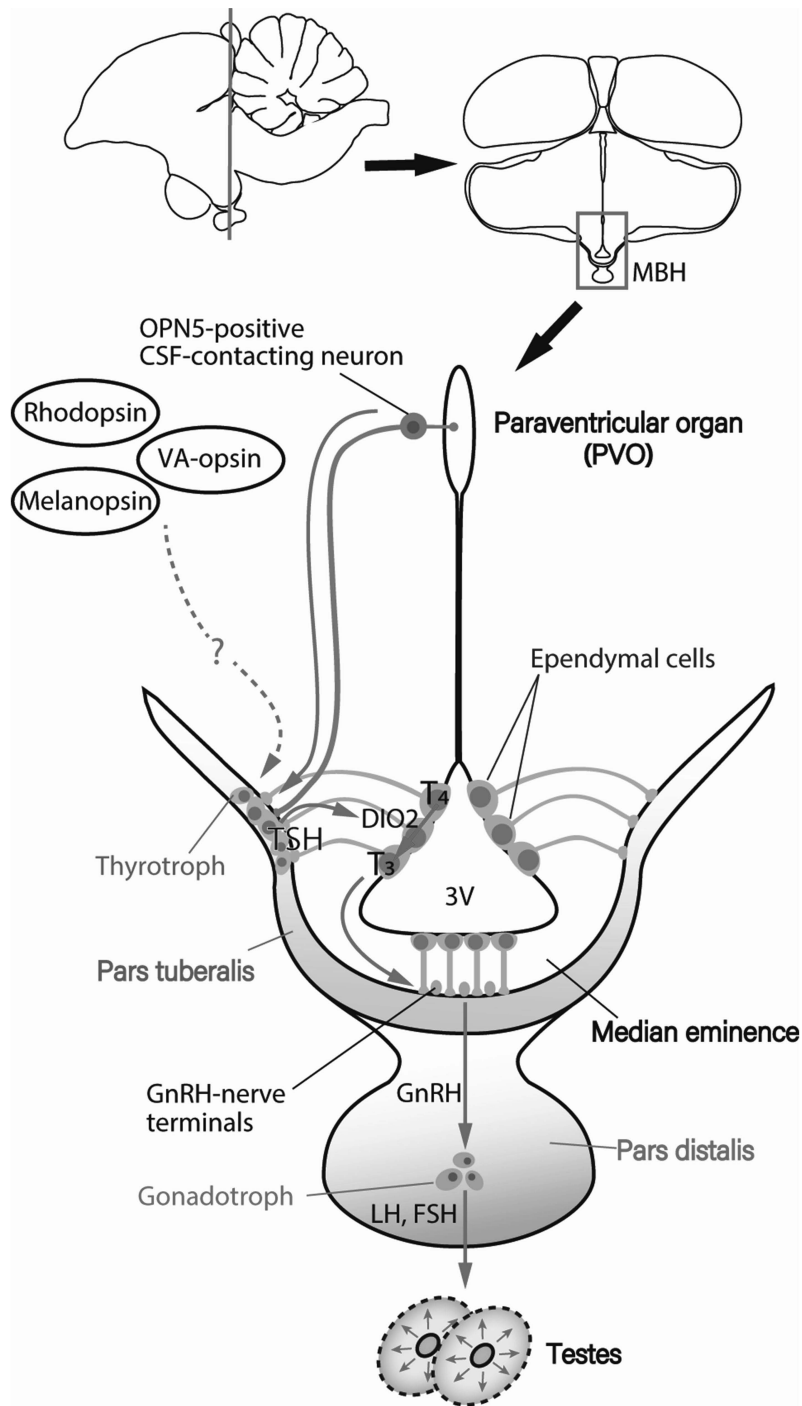
Fig. 3. (Color online) Photoperiodic signal transduction cascade for seasonal reproduction in birds. Light information received by deep brain photoreceptors, such as OPN5-positive cerebrospinal fluid (CSF)-contacting neurons, is transmitted to the pars tuberalis (PT) of the pituitary gland, inducing thyroid-stimulating hormone (TSH). PT-derived TSH then acts on the ependymal cells to induce a thyroid hormone-activating enzyme, type 2 deiodinase (DIO2), which converts the thyroid hormone precursor T_4 into the active form T_3. T_3 regulates morphological changes in GnRH nerve terminals and glial processes, thereby facilitating GnRH secretion, resulting in the secretion of gonadotropin and gonadal development. Figure reproduced from Nakane and Yoshimura (2014)[106] with permission under the terms of the Creative Commons Attribution License (CC BY) © 2014 Nakane and Yoshimura. Abbreviations: 3V, third ventricle; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; MBH, mediobasal hypothalamus.

photoperiodism at the hypothalamic–pituitary level. Taken together, the studies on mammals suggest that the photoperiodic signaling pathway, which is formed by TSH, $DIO2/DIO3$ switching, and the resultant local activation of T_3 in the MBH, appears to be conserved between birds and mammals, despite the differences in their light input mechanisms. In addition, although remarkable strides have been made, an interesting question remains regarding the discrepancy in T_3 action between LD and SD breeders. As the LD-induced, PT-TSH-mediated mechanism has also been reported in SD breeders, such as sheep,[65] the mechanism by which the resultant local T_3 activation shows opposite effects in LD and SD breeders (*i.e.*, stimulates the HPG axis in LD breeders and suppresses the HPG axis in SD breeders) needs to be assessed. Further studies are required to determine the underlying mechanism because they may provide new critical insights into the regulation of seasonal reproduction.

4.4. Tissue-specific glycosylation prevents functional crosstalk between TSHs.   It is well known that TSH is a hormone secreted by PD (PD-TSH) and that it stimulates the thyroid gland to synthesize and secrete THs, which, in turn, regulate growth and metabolism in the body. However, the aforementioned PT-derived TSH is secreted in response to melatonin signaling and acts on the adjacent ECs to regulate seasonal physiology. Thus, it has been a great mystery how the two TSHs trigger distinct biological processes without interfering with one another. Results of mass spectrometric analysis show that both PT-TSH and PD-TSH have the same protein structure, but each is glycosylated differently.[77] PD-TSH has sulfated, biantennary carbohydrate chains, which are easily metabolized. In contrast, PT-TSH has sialylated, multibranched carbohydrate chains, which are easily trapped and inactivated by the immunoglobulin and albumin present in the blood.[77] Thus, tissue-specific glycosylation in PT and PD differentiates the two TSHs, preventing functional crosstalk within the body.

4.5. Involvement of kisspeptin and RFamide-related peptides in mammalian seasonal reproduction.   Kisspeptin is encoded by *Kiss1*, and three RFamide-related peptides (RFRPs) are encoded by the *Npvf* gene and cleaved from propeptides, which belong to the RFamide superfamily.[78],[79] These peptides are suggested to be involved in the regulation of the reproductive activity. Kisspeptin induces GnRH release via the G-protein-coupled receptor GPR54, which is ex-

pressed in GnRH neurons, resulting in the activation of the HPG axis. In LD-breeding rodents, melatonin treatment (as an SD signal) suppresses the secretion of kisspeptin from the hypothalamic arcuate nucleus,[80],[81] whereas the administration of kisspeptin restores reproductive function in SD conditions,[80],[82] suggesting a role of kisspeptin in activating the HPG axis downstream of melatonin signaling. The RFRP-1 and RFRP-3 peptides were originally identified as mammalian orthologs of the gonadotropin inhibitory hormone, which inhibits the HPG axis in birds.[79] In mammals, the effects of RFRPs on seasonal reproduction vary among species. The injection of RFRP-3 suppresses the activity of GnRH neurons in sheep[83] but induces secretion of GnRH under the control of melatonin in Syrian hamsters.[84] In addition, the effect of RFRP appears to be photoperiod-dependent in Siberian hamsters, in which it inhibits LH release in LD conditions but stimulates LH release in SD conditions.[85] There is no consistent evidence suggesting a role for RFRP in the photoperiodic signaling mechanism. Additional work is required to clarify whether these peptides are the direct targets of inhibitory melatonin signaling or they lie downstream of the TSH–TH signaling cascade.

5. Mechanism of seasonal reproduction in fish

5.1. Saccus vasculosus (SV) is the seasonal sensor in Salmonidae.   Fish show robust seasonal changes in physiology and behavior, akin to terrestrial species;[86] for example, Japanese medaka fish (*Oryzias latipes*) are seasonal breeders that undergo gonadal development in response to LDs. In contrast, Salmonidae fish are SD seasonal breeders that swim upstream to their home river in autumn for spawning. Based on the observation that removal of the eyes and pineal gland has a limited effect on photoperiodic responses, it has been suggested that deep brain photoreceptors might also exist in fish.[86] However, the photoreceptors mediating photoperiodicity have long been unknown in fish. In addition, there is no conclusive evidence that melatonin plays a major physiological role in seasonal reproduction in fish.[86] Moreover, fish do not possess an anatomically distinct PT,[87] which is a regulatory hub for seasonal reproduction in birds and mammals. Thus, the signal transduction pathway for seasonal reproduction in fish remains unclear.

In a study on the masu salmon (*Oncorhynchus masou masou*), it was revealed that the key elements involved in vertebrate seasonal reproduction, such as photopigments, TSH, TSHR, and DIO2, may be

integrated into a fish-specific organ known as SV.[88] The role of SV in fish physiology has long been a mystery since its discovery in 1685.[89] SV is located at the floor of the hypothalamus, posterior to the pituitary gland. Anatomical study showed that SV comprises coronet, CSF-contacting, and supporting cells.[88] Coronet cells have a crown-like morphology with globule-tipped cilia protruding from the cell bodies. Immunohistochemical analysis revealed that TSH and the photopigments SWS1 (SWS opsin 1) and melanopsin are expressed in the globules of cilia, whereas the DIO2 protein is expressed in the cell bodies,[88] implying that SV plays a pivotal role as a photoperiodic sensor in fish. Subsequent work supports this hypothesis; isolated SV shows photoperiodic changes in gene expression, and removal of SV prevents photoperiodically induced gonadal development.[88] Notably, not all fish have SV; therefore, how fish that lack an SV, such as medaka and zebrafish, measure and process photoperiodic time information is currently under investigation.

5.2. Seasonal regulation of color perception in medaka. In addition to gonadal development, other physiological processes related to reproductive success also exhibit seasonal responses; for example, during the breeding season, medaka develop black stripes and spots on their fins, and their orange-red color becomes much more intense.[90] This phenomenon, known as nuptial coloration, implies that medaka are attracted to orange-red mates. Recent work using virtual fish generated by 3D computer graphics revealed that color perception in medaka was influenced by the seasons; only breeding (spring/summer) medaka exhibited a preference for virtual fish with nuptial coloration, whereas nonbreeding (winter) medaka showed no such preference.[91] Consistent with these findings, the long-wavelength-sensitive (LWS) opsin, which is potentially responsible for the perception of the orange-red color,[92] was found to be upregulated in summer medaka.[91] Knockout of *LWS* attenuated the preference for virtual fish with nuptial coloration under summer conditions,[91] suggesting that summer-induced LWS opsin is crucial for the emergence of mate preference.

6. Domestication and the photoperiodic signaling pathway

Seasonal reproduction is one of the critical rate-limiting factors in the production of animals. In this context, the photoperiodic signaling pathway represents a potential target that can facilitate human-driven domestication. An obvious example of this is

laboratory mice, of which most inbred strains lack the enzyme activity for melatonin biosynthesis.[76),93),94] Evidence of selective sweeps has also been found at the *TSHR* locus in all domestic chickens,[95] implicating a role of *TSHR* as a domestication locus in this species. Therefore, genes involved in the photoperiodic signaling pathway emerge as useful selection targets for the domestication of wild animals and improvement of livestock production in agriculture.

7. Conclusions and perspectives

The mechanisms of vertebrate seasonal reproduction have long been a mystery; however, recent comparative studies have uncovered signal transduction pathways that regulate seasonal reproduction across various vertebrate species. The results of these studies have revealed the universality and diversity of these photoperiodic mechanisms. The molecules (TSH, DIO2, and THs) involved are conserved, but the tissues/organs responsible for these seasonal effects appear to be different (Fig. 4).

Although humans are not considered seasonal, changes in various physiological processes and susceptibility to external agents of disease have been observed in different seasons. The incidence of multiple types of diseases, such as infectious diseases, heart diseases, cerebrovascular diseases, and lung cancer, has been suggested to be seasonal.[96] Furthermore, the seasons also affect our mood and behavior and are strongly associated with the occurrence of depression, mania, and suicide.[97)–99] Seasonal affective disorder (SAD) is a syndrome characterized by recurrent depression that begins and ends at approximately the same time every year,[100] usually appearing from late fall to winter and disappearing during spring and summer. The susceptibility of humans to SAD or other seasonally related syndromes continues to be a much discussed, but poorly understood, topic. Understanding the biological process of seasonality in animals may help us better understand seasonality in humans.

An emerging theme in chronobiology is the development of compounds that interfere with the circadian clock. Several small molecules that act directly on clock proteins to lengthen the circadian period have been discovered,[101] and extended efforts have been made to develop novel period-shortening molecules by conducting structure–activity relationship analyses.[102] Furthermore, via a drug-repurposing approach, several circadian clock modulators have been identified from existing drugs.[103] Clock-
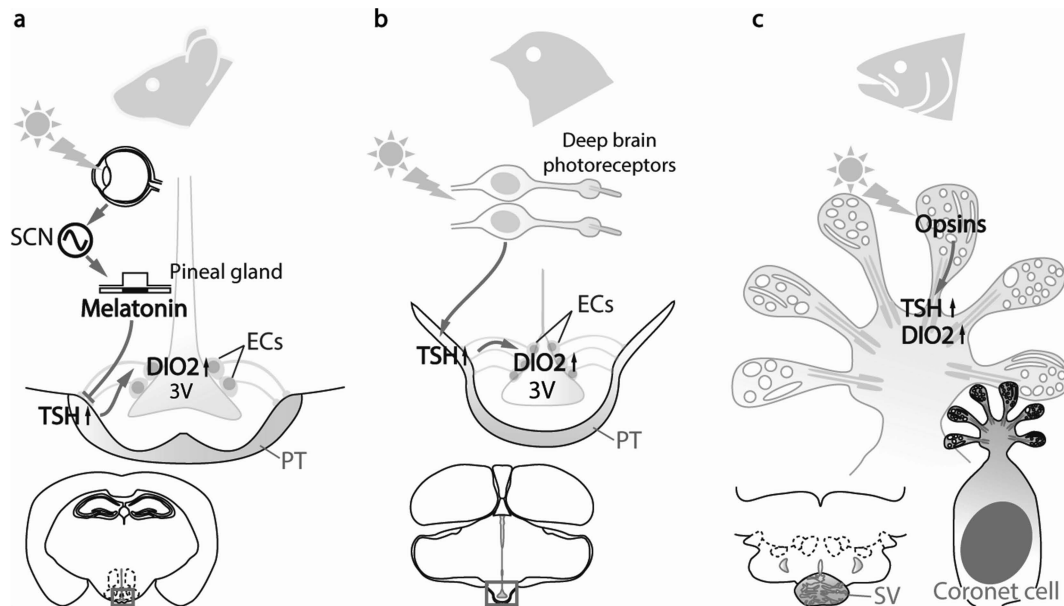
Fig. 4. (Color online) Universality and diversity in the photoperiodic signal transduction pathways in vertebrates. (a) In mammals, light information is detected via the eyes and transmitted through the suprachiasmatic nucleus (SCN) to the pineal gland. The profile of melatonin secretion from the pineal gland encodes photoperiodic information and regulates the thyroid-stimulating hormone (TSH) in the pars tuberalis (PT) of the pituitary gland. (b) In birds, light information is directly received by deep brain photoreceptors and is then transmitted to PT to trigger TSH secretion. (c) In fish, all of the key elements required for seasonal reproduction (from photoreceptors to neuroendocrine output) are integrated within the coronet cells located in saccus vasculosus (SV). Figure reproduced from Nakane and Yoshimura (2014)[106] with permission under the terms of the Creative Commons Attribution License (CC BY) © 2014 Nakane and Yoshimura. Abbreviations: 3V, third ventricle; DIO2, type 2 deiodinase; ECs, ependymal cells.

modulating compounds will provide useful tools for understanding how the circadian clock regulates seasonal reproduction, particularly for studies on nonmodel species, in which genetic modification approaches are not yet applicable. Moreover, because disruption of the circadian clock has been reported in patients with SAD, these compounds might help develop better treatments for these patients.

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Profile

Ying-Jey Guh was born and brought up in Taiwan. He earned his B.S. degree in Animal Science, M.S. degree in Animal Science, and Ph.D. degree in Life Science from the National Chung Hsing University, National Taiwan University, and National Defense Medical Center, respectively, in Taiwan. Thereafter, he began his postdoctoral training at Academia Sinica, Taiwan. He received the JSPS Postdoctoral Fellowship and moved to Japan in 2017, where he was employed in the Nagoya University and National Institute for Basic Biology under the supervision of Prof. Takashi Yoshimura. His research interest is environmental physiology, with primary focus on understanding the modulation of physiological mechanisms in aquatic animals to cope with the changing environment, such as changes between seasons as well as perturbations in ambient salinity, pH, or temperature. He is currently working as a postdoctoral research fellow in the WPI Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University.

Profile

Takako Katherine Tamai was born in California in 1960 and graduated from the University of California, Davis, in 1986. She received her Ph.D. degree in Biological Chemistry from the University of Michigan, Ann Arbor, in 1993 and worked as a postdoctoral research fellow in Germany and France. She moved to London in 2001 and worked at University College London as a senior scientist in the laboratory of Prof. David Whitmore, where she investigated circadian rhythms and tissue light sensitivity in zebrafish. She then moved to Japan in 2015 to work with Prof. Takashi Yoshimura at the WPI Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, where she screened for circadian clock modulators and studied seasonal rhythms in the medaka fish.

Profile

Takashi Yoshimura was born in Shiga Prefecture in 1970 and graduated from Nagoya University. He received his Ph.D. degree from Nagoya University in 1999 and is currently a Professor in the WPI Institute of Transformative Bio-Molecules (WPI-ITbM) and the Graduate School of Bioagricultural Sciences, Nagoya University. He was appointed as a Visiting Professor in the National Institute for Basic Biology from 2013 to 2019. Work conducted in Yoshimura's laboratory is focused on understanding the molecular mechanism of seasonal adaptation in vertebrates. The uniqueness of his research lies in the use of various vertebrate species, such as the Japanese quail, chicken, hamster, mouse, salmon, and medaka, together with an interdisciplinary approach. He currently serves as the Vice President of the Japanese Society for Chronobiology and is a fellow of the Royal Society of Biology.