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Comparative analysis reveals the underlying mechanism of vertebrate seasonal reproduction

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ABSTRACT

Animals utilize photoperiodic changes as a calendar to regulate seasonal reproduction. Birds have highly sophisticated photoperiodic mechanisms and functional genomics analysis in quail uncovered the signal transduction pathway regulating avian seasonal reproduction. Birds detect light with deep brain photoreceptors. Long day (LD) stimulus induces secretion of thyroid-stimulating hormone (TSH) from the pars tuberalis (PT) of the pituitary gland. PT-derived TSH locally activates thyroid hormone (TH) in the hypothalamus, which induces gonadotropin-releasing hormone (GnRH) and hence gonadotropin secretion. However, during winter, low temperatures increase serum TH for adaptive thermogenesis, which accelerates germ cell apoptosis by activating the genes involved in metamorphosis. Therefore, TH has a dual role in the regulation of seasonal reproduction. Studies using TSH receptor knockout mice confirmed the involvement of PT-derived TSH in mammalian seasonal reproduction. In addition, studies in mice revealed that the tissue-specific glycosylation of TSH diversifies its function in the circulation to avoid crosstalk. In contrast to birds and mammals, one of the molecular machineries necessary for the seasonal reproduction of fish are localized in the saccus vasculosus from the photoreceptor to the neuroendocrine output. Thus, comparative analysis is a powerful tool to uncover the universality and diversity of fundamental properties in various organisms.

1. Introduction

In the temperate zones, organisms experience seasonal changes in the environment, and accordingly, they adapt their physiology and behavior, such as reproduction, migration, hibernation, and molting. Although temperature and precipitation show annual changes, these are not reliable sources of information, because summers can often be cool and/or winters, warm. In contrast, changes in the day length (photoperiod) are very reliable seasonal cues, because solstices and equinoxes always occur at exactly the same times of the year. Therefore, organisms can use changes in the photoperiod as a calendar; this phenomenon is the photoperiodism (Garner and Allard, 1920).

Seasonal reproduction maximizes the survival of offsprings. For example, small mammals and birds whose gestation or incubation periods last only a few weeks mate during spring and summer; they are the so-called long-day (LD) breeders. In contrast, goats and sheep have a gestation period of ~6 months, therefore they mate during fall, and they are the so-called short-day (SD) breeders. In both LD and SD breeders, offsprings are born and raised during spring and summer, when climate is moderate, and food is abundant.

Vertebrate reproduction is regulated by the hypothalamus–pituitary–gonadal (HPG) axis. Gonadotropin-releasing hormone (GnRH) secreted from the hypothalamus regulates the secretion of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) from the pars distalis (PD) of the anterior pituitary gland. In seasonal breeding animals, the HPG axis is activated at a specific time of the year. Here, we review the current knowledge about the vertebrate seasonal reproduction.

2. Signal transduction pathway of the avian seasonal reproduction

In 1925, William Rowan discovered that the gonadal size of Junco is dependent on changes in the day length (Rowan, 1925).

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In contrast with mammals, birds have highly sophisticated photoperiodic mechanisms, and their gonadal size may change more than a hundredfold within a few weeks. Japanese quail (*Coturnix japonica*) is an excellent model for understanding the mechanism of seasonal reproduction in birds, because they show a rapid induction of serum LH and drastic testicular growth in response to changes in photoperiod (Follett et al., 1998). A classic lesion study suggested that the mediobasal hypothalamus (MBH) is the center of seasonal reproduction in birds (Sharp and Follett, 1969).

2.1. Key genes that trigger seasonal reproduction

Recent functional genomics studies have revealed that seasonal reproduction is regulated by the ependymal cells (ECs) lining ventrolateral walls of the third ventricle within the MBH and its adjacent pars tuberalis (PT) of the anterior pituitary gland (Yoshimura et al., 2003; Nakao et al., 2008). LD stimulus induces the production and secretion of thyroid-stimulating hormone (TSH: thyrotropin) in the PT (Fig. 1). Subsequently, PT-derived TSH acts on the ECs within the MBH to induce the expression of type 2 deiodinase (DIO2) and reduce the expression of type 3 deiodinase (DIO3) via TSH receptor (Nakao et al., 2008). *DIO2* and *DIO3* encode thyroid hormone (TH) activating and inactivating enzymes, respectively. In addition, LD-induced DIO2/DIO3 switching locally regulates the bioactive TH concentration within the MBH. It has been demonstrated that the precursor thyroxine (T_4) is transported in the cerebrospinal fluid (CSF) to the ECs by the organic anion transporting polypeptide 1c1 (Oatp1c1) to be converted from T_4 into bioactive triiodothyronine (T_3) by DIO2 (Yoshimura et al., 2003; Nakao et al., 2006). TH regulates the development and plasticity of the central nervous system (Bernal, 2002), and the locally activated TH induces dynamic morphological changes between the GnRH nerve terminals and the glial endfeet in the median eminence (ME) (Yamamura et al., 2004, 2006). Under LD condition, GnRH nerve terminals are in direct contact with the basal lamina located between the ME and the hypophyseal portal vessel. However, under SD condition, GnRH nerve terminals are encased by the glial endfeet. Therefore, these morphological changes regulate or modulate seasonal GnRH secretion from the hypothalamus to the portal capillary (Yoshimura et al., 2003; Yamamura et al., 2004, 2006).

2.2. Deep brain photoreceptors regulating seasonal reproduction

The brains of non-mammalian vertebrates receive direct information from light to regulate seasonal physiology and behavior. In birds, injection of India ink under the scalp, which blocks the penetration of light into the brain, abolishes LD-induced testicular recrudescence (Menaker et al., 1970). Although the photoreceptive avian pineal organ resets the circadian clock of birds, pinealectomy and enucleation of lateral eyes do not affect seasonal response (Siopes and Wilson, 1974), suggesting the existence of other photoreceptors within the brain. Indeed, local illumination of the MBH or the septal region of the telencephalon leads to gonadal growth (Benoit, 1935; Homma et al., 1979). Numerous groups have tried to identify the deep brain photoreceptors involved in the photoperiodic response. Although the expression of various rhodopsin genes and/or proteins was reported within the avian brain, including rhodopsin, VA-opsin, and melanopsin (Silver et al., 1988; Wada et al., 1998; Chaurasia et al., 2005; Halford et al., 2009), there was no direct evidence for their involvement in the photoperiodic response. Recently, the expression of OPN5 was reported in the CSF-contacting neurons of the paraventricular organ (PVO) (Nakane et al., 2010; Yamashita et al., 2010), and the intrinsic photosensitivity of these neurons was demonstrated using slice patch clamp technique (Nakane et al., 2014; Nakane and Yoshimura, 2014). In addition, OPN5-positive CSF-contacting neurons projected to the PT (Nakane et al., 2010), and knockdown of OPN5 attenuated the LD-induction of TSH in the PT (Nakane et al., 2014). Therefore, OPN5 appears to be one of the deep brain photoreceptors that regulate avian seasonal reproduction.

2.3. Mechanism of seasonal testicular regression

As described above, the photoperiodic signal transduction pathway that activates avian seasonal reproduction has been uncovered. However, the underlying mechanism of seasonal testicular regression remained unclear. The discovery of gonadotropin-inhibitory hormone (GnIH) is one of the hot topics of the last decade. GnIH is a neuropeptide synthesized by the neurons of the paraventricular nucleus (PVN), and it has been shown to inhibit gonadotropin secretion (Tsutsui et al., 2000; Ubuka et al., 2006). Numerous studies reported that melatonin has a minor role in avian seasonal reproduction (Gwinner et al., 1997). However, Tsutsui and his colleagues demonstrated that melatonin suppresses the reproductive activity by activating GnIH (Ubuka et al., 2005).

In quail, stimulation with low temperature accelerates SD-induced testicular regression (Oishi and Konishi, 1978; Wada, 1993). Low temperature increases the amount of circulating T_3 to support adaptive thermogenesis. In addition, circulating T_3 induced by low temperature triggers the apoptosis of germ cells by activating genes involved in metamorphosis (Fig. 1, Ikegami et al., 2015). The increased amount of circulating T_3 is produced by DIO2 in the liver through increased food intake (Ikegami et al., 2015).

The role of TH in seasonal reproduction has been suggested for several decades. However, the effect of TH was often contradictory; some studies reported stimulatory effects, while others reported inhibitory effects (Dawson et al., 2001). Therefore, TH was suggested to play a permissive role in seasonal reproduction. A recent report explains these contradictory effects. Central activation of TH results in seasonal testicular growth; however, peripheral activation of TH regulates adaptive thermogenesis and seasonal testicular regression. Therefore, TH has a dual role in the regulation of seasonal reproduction. Interestingly, TH has opposite effects during the metamorphosis of the tadpole; TH induces both the outgrowth of the limb and resorption of the tail (Furlow and Neff, 2006).

3. Regulatory mechanism of the mammalian seasonal reproduction

In mammals, eyes are considered the only photoreceptor organs, and enucleation of the lateral eyes abolishes the photoperiodic response (Reiter, 1980). Light stimulation received by the eyes is transmitted to the pineal gland via the suprachiasmatic nucleus (SCN), which is known as the master circadian pacemaker (Reiter, 1980; Arendt, 1995). Pineal gland secretes melatonin during the night, and the melatonin secretion profile encodes the length of night. Melatonin plays a crucial role in the regulation of seasonal reproduction in mammals, because pinealectomy abolishes seasonal responses; however, melatonin administration restores them in both LD and SD breeders (Hoffman and Reiter, 1965; Reiter, 1980; Arendt, 1995).

3.1. Laboratory mouse as a model of seasonal reproduction

Laboratory mice are regarded as non-seasonal breeders, and therefore, they were not considered as an appropriate model for seasonal reproduction. However, we noticed that mice do not breed well during winter, even though they are kept under constant light-dark and temperature conditions throughout the