

## Review

## Thyroid hormone and seasonal regulation of reproduction

Takashi Yoshimura\*

Laboratory of Animal Physiology, Graduate School of Bioagricultural Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan  
 Institute of Transformative Bio-molecules (WPI-ITbM), Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan  
 Avian Bioscience Research Center, Graduate School of Bioagricultural Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan  
 National Institute for Basic Biology, 38 Nishigonaka, Myodaiji, Okazaki 444-8585, Japan

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## ABSTRACT

Organisms living outside the tropics use changes in photoperiod to adapt to seasonal changes in the environment. Several models have contributed to an understanding of this mechanism at the molecular and endocrine levels. Subtropical birds are excellent models for the study of these mechanisms because of their rapid and dramatic response to changes in photoperiod. Studies of birds have demonstrated that light is perceived by a deep brain photoreceptor and long day-induced thyrotropin (TSH) from the pars tuberalis (PT) of the pituitary gland causes local thyroid hormone activation within the mediobasal hypothalamus (MBH). The locally generated bioactive thyroid hormone,  $T_3$ , regulates seasonal gonadotropin-releasing hormone (GnRH) secretion, and hence gonadotropin secretion. In mammals, the eyes are the only photoreceptor involved in photoperiodic time perception and nocturnal melatonin secretion provides an endocrine signal of photoperiod to the PT to regulate TSH. Here, I review the current understanding of the hypothalamic mechanisms controlling seasonal reproduction in mammals and birds.

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## 1. Introduction

Organisms living outside the tropics experience seasonal changes in the environment, and accordingly adapt their physiology and behavior, including flowering, growth, migration, hibernation, and molt. Temperature and precipitation show robust annual changes. Therefore, it has been assumed that organisms use such information as a calendar. However, Garner and Allard used soy and tobacco plants to demonstrate that daylength (photoperiod) is the dominant cue for seasonal responses (Garner and Allard, 1920). Therefore, aforementioned responses to changes in daylength are referred to as photoperiodism. Although temperature and precipitation vary throughout each year, this information is unreliable because there are occasionally warm winter or dry rainy seasons. In contrast, changes in daylength are the most reliable seasonal cue, because solstices and equinoxes occur at almost identical times each year. Therefore, it is plausible that organisms might use changes in photoperiod as a calendar. After the discovery of photoperiodism by Garner and Allard, similar phenomena were soon described in insects (Marcovitch, 1923), birds (Rowan, 1925), and mammals (Baker and Ranson, 1932). Adaptation to the seasons also involves seasonal reproduction because seasonal reproduction maximizes the survival of offspring. For example, small mammals and birds breed during the spring and summer

and 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, and are therefore called short-day (SD) breeders. Because these animals have a gestation period of ~6 months, their offspring are also born and raised during spring and summer. Thus, the offspring of both LD and SD breeders can grow when the climate is benign and food is abundant.

Seasonal breeders experience annual cycles of reproductive quiescence and recrudescence, and in vertebrates this seasonal reproduction is regulated by the hypothalamic–pituitary–gonadal (HPG) axis. Gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus induces the secretion of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) from the anterior pituitary gland and gonadotropin activates gonadal activity. Thus, the HPG axis is activated during the breeding season, resulting in a dramatic increase in gonadal size, particularly in birds (Dawson et al., 2001). In birds, gonadal size changes more than a hundred-fold. Therefore, birds are considered to have highly sophisticated photoperiodic mechanisms that drive changes in hpg activity of very large amplitude in comparison to other vertebrate species (Follett et al., 1998). In addition to the dramatic gonadal response, birds have very short breeding seasons. After breeding, the HPG axis is automatically switched off and the gonads start to regress even though the photoperiod is still increasing. This phenomenon is known as

\* Fax: +81 52 789 4056.

E-mail address: [takashi@agr.nagoya-u.ac.jp](mailto:takashi@agr.nagoya-u.ac.jp)

photorefractoriness and the gonadal weight is significantly reduced during the non-breeding season (Hahn and MacDougall-Shackleton, 2008; Nicholls et al., 1988b). Such robust responses, and this restricted breeding season appear to be adaptations of birds to flight. Accordingly, birds have often been used to study photoperiodism. Among mammals, hamsters and sheep are often used 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 change of several-fold. It is demonstrated that the number of apoptotic cells is about 10-fold larger in birds than in seasonally breeding mammals. Therefore, differences between birds and mammals in the occurrence of apoptosis has been suggested as the reason for the difference in gonadal changes between these groups of animals (Young et al., 2001).

## 2. Models for photoperiodic time measurement

Organisms show photoperiodic responses when daylength reaches or exceeds a photoperiod with so-called “critical daylength.” Most seasonally breeding organisms have a highly accurate mechanism for photoperiodic time measurement and show dramatic changes in seasonal response to small changes in photoperiod. For example, testicular recrudescence can be seen only in those hamsters transferred from SD to photoperiods of 12.5 h or longer (Elliott, 1976; Goldman, 2001). In Japanese quail, days that are longer than 11.5 h induce testicular growth (Follett and Maung, 1978). These animals can recognize changes in daylength that are as small as 30 min. To accomplish this, the photoperiodic time measurement systems consist of three components, as is the case for circadian time keeping systems. These components are: (1) a light input pathway that perceives external light–dark information, (2) a biological clock that measures daylength, and (3) an output pathway that regulates various aspects of physiology and behavior.

### 2.1. Bünning’s hypothesis

In 1936, Erwin Bünning proposed the concept of circadian clock-based photoperiodic time measurement (Bünning, 1936). In his hypothesis, he proposed a ~12-h photophil (light-requiring phase) and a ~12-h scotophil (dark-requiring phase) that together comprised ~24 h. When animal experience light only during photophil, an SD response is induced, while light exposure during scotophil causes an LD response. In this hypothesis, light entrains the circadian clock in addition to inducing seasonal responses. Bünning’s hypothesis was ground-breaking in that it predicted the involvement of a circadian clock in photoperiodic time measurement. The involvement of a circadian clock in photoperiodic responses was experimentally demonstrated using non-24-h light–dark cycles. These experiments are also known as the Bünsow protocol (Bünsow, 1953) and the Nanda–Hamner resonance experiment (Nanda and Hamner, 1958). In house finches and quail, a 6-h light period coupled with dark periods of varying duration (resonance light cycles) does not cause photoperiodic responses when the duration of each cycle is a multiple of 24 h (e.g., 6 h light, 18 h dark: 6L18D, 6L42D, 6L66D). However, cycle lengths that are not multiples of 24 h (6L30D, 6L54D) cause a photoperiodic response (Hamner, 1963; Follett and Sharp, 1969). In these experiments, the 6 h of light exposure would fall at the same phase of day in cycles that were multiples of 24 h, while the 6-h light exposure would fall at different phases of the day in non-24 h-light–dark cycles. Similar observations were also reported for mammalian species such as golden hamsters (Elliott et al., 1972).

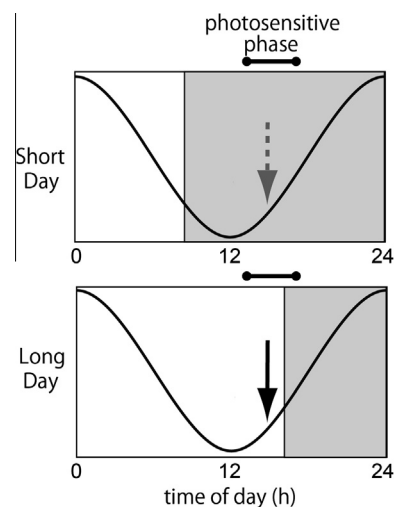
### 2.2. External coincidence model and Internal coincidence model

In the 1960s, Colin Pittendrigh and his colleague proposed two models called the “external coincidence model” (Fig. 1; Pittendrigh and Minis, 1964) and the “internal coincidence model” (Fig. 2; Pittendrigh, 1972). In the external coincidence model, light has two effects as in the Bünning’s hypothesis (i.e., entrainment of the circadian clock and induction of seasonal responses). However, in this model, a photosensitive phase, also known as photoinducible phase, was hypothesized instead of a simple photophil and scotophil. When external light stimulus is coincident with the photosensitive phase, a photoperiodic response is induced (Fig. 1). In contrast, the internal coincidence model hypothesized the existence of multiple oscillators. When one oscillator couples with dawn and the other with dusk, the phase relationship between the two oscillators changes between seasons (Fig. 2). In this model, coincidence of two (or more) internal oscillators causes seasonal responses. These theoretical models aided understanding of the molecular mechanisms of photoperiodism in plants, insects, and vertebrates.

## 3. Mechanism of mammalian seasonal reproduction: the input pathway and the oscillator

### 3.1. Input pathway of mammalian seasonal reproduction

In mammals, all of the experimental evidence suggests that the eye is the only photoreceptor organ (Groos and van der Kooy, 1981; Legan and Karsch, 1983; Lockley et al., 1998; Meijer et al., 1999; Nelson and Zucker, 1981; Reiter, 1980; Yamazaki et al., 1999), and removal of the eyes abolishes the photoperiodic response (Legan and Karsch, 1983; Reiter, 1980). There are rod and cone photoreceptors within the eye for image formation (Dowling, 1987). Melanopsin (OPN4) expressed in the ganglion cell layer of the retina is required for non-image functions, such as resetting the circadian clock and the pupillary reflex (Berson et al., 2002; Hattar et al., 2002, 2003; Lucas et al., 2003; Panda et al., 2002, 2003; Provencio et al., 2002; Ruby et al., 2002). However, the identity of photoreceptor(s) that mediates photoperiodic time measurement remains unclear. In mammals, the master circadian pacemaker is localized in the suprachiasmatic nucleus (SCN)



**Fig. 1.** External coincidence model for photoperiodic time measurement. When light falls on a photosensitive phase (arrow), a photoperiodic response is observed. In this model, light has two effects: resetting the circadian clock and induction of the photoperiodic response.

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