Role of Pineal and Melatonin in the Avian Circadian and Photoperiodic Systems

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Abstract

The pineal gland is an important component of the multioscillatory avian circadian timekeeping system. The other principal clock components reside in the retinae of the eyes and the hypothalamus. The best known output signal from the pineal gland is melatonin, which is a lipophilic molecule. The presence of melatonin is however not limited to the organisms having a pineal gland. Melatonin is present from plants to protozoa to humans. Melatonin seems to have been evolutionarily conserved as an adaptive molecule of darkness of the daily day-night environment. In birds, the major physiological roles of pineal melatonin are in its involvement in the daily and seasonal timekeeping as well as photoperiodic time measurement. Birds use daily rhythm in melatonin secretion to decode the time-of-day as well as the time-of-year information. Besides, melatonin performs other physiological roles, namely in the immune function, free radical scavenging, etc. Avian pineal (melatonin) directly regulates several circadian behaviors, but intriguingly not the circadian rhythm-mediated photoperiodic induction of gonadal development. Melatonin, however, may act as an endocrine modulator of seasonal reproduction. In this article, we describe briefly the avian timekeeping system and then discuss the potential roles of pineal gland and melatonin in daily and seasonal timing of physiology in birds, particularly in songbirds.

Keywords: Bird, circadian, melatonin, pineal, photoperiod

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine molecule, discovered by Aron Lerner and collaborators[1] in the vertebrate pineal gland (an unpaired appendage of the brain called epiphysis in most vertebrates) as its principal hormone. Interestingly, melatonin is secreted only during night, irrespective of the habitat of the organism and the site of synthesis and secretion, and elevated levels of melatonin reflect the nighttime; and therefore, is called the "darkness hormone". It is also called the "nature's sleeping pill" because it promotes sleep at night. Another name given to melatonin is "circadian glue" since its importance has increasingly been realized in the regulation of circadian (*circa* – about; *dian* – day) and circannual (*circa* – about; *annum* – year) functions of the body.

The presence of melatonin has been widely reported from plants and protozoa to humans[2]. During evolution, melatonin is presumed to have mediated the adaptation to the day-night (light-dark, LD) cycle of the environment; organisms may have used the daily nighttime pulse of melatonin in transducing photoperiodic message of the environment. One of the potential reasons for the presence of melatonin across the living systems appears to be its chemical nature. It is a lipophilic molecule and so can diffuse into all kinds of cell types without facing any biological barrier. It also performs the role of an antioxidant and, therefore, cells use this molecule as a free-radical scavenger.

Among birds, the main site of melatonin production is the pineal gland which, in most species, is situated within the recess formed by the two cerebral hemispheres and the cerebellum (Figure 1(a)). Each pineal cell (pinealocyte) synthesizes and secretes melatonin; cultured pineal cells exhibit significant rhythm in melatonin production, similar to that exhibited by the pineal gland[3,4]. Several reports suggest a significant amount of melatonin production by the retinae of the lateral eyes, Harderian gland, and Gastrointestinal Tract (GIT). The circulating melatonin levels are a reflection of the total melatonin production by the organism. However, relative

contributions of different melatonin producing tissues to the blood melatonin level can vary from species to species. In this aspect, the roles of the eyes and the pineal have been investigated in a few species. In house sparrows *(Passer domesticus)* most, if not all, blood melatonin is secreted by the pineal gland. This conclusion is based on the experiments in which surgical removal of pineal gland rendered individuals with undetectable levels of melatonin[5,6]. On the other hand, in Japanese quail *(Coturnix coturnix japonica)* and pigeon *(Columba livia)*, only a little over half of blood melatonin comes from the pineal gland; the remaining, a little less than half of blood melatonin, comes from the retinae and other undefined tissues[7,8].

2. Regulation of Melatonin Synthesis and Secretion

The regulation of melatonin synthesis and secretion has been studied in the avian pineal gland. Several studies have established that day-night cycle of the environment controls the time and duration of melatonin synthesis and secretion[2]. Figure 1(b) represents a schematic diagram of melatonin biosynthesis. Briefly, during the day, amino acid tryptophan is taken up from the bloodstream and hydrolyzed to 5-hydroxytryptophan (5-HTRP) in the presence of the enzyme tryptophan hydroxylase (TrH). Then, it is converted to 5-hydroxytryptamine (5HT, serotonin) by the action of the enzyme, Aromatic Amino Acid Decarboxylase (AAADC). During the night, serotonin is acted upon by the enzyme Arylalkylamine *N*-Acetyltransferase (AANAT) forming the N-acetylserotonin. The latter undergoes O-methylation by the action of the enzyme Hydroxyindole-*O*-Methyltransferase (HIOMT) producing melatonin, the final product of the biosynthesis. All melatonin synthesized is released into circulation since it is a lipophilic molecule. But at any given time, the concentration of melatonin within the pineal gland is several folds higher than that of the blood, suggesting that there may be some mechanism, hitherto unidentified, involved in the release of melatonin.
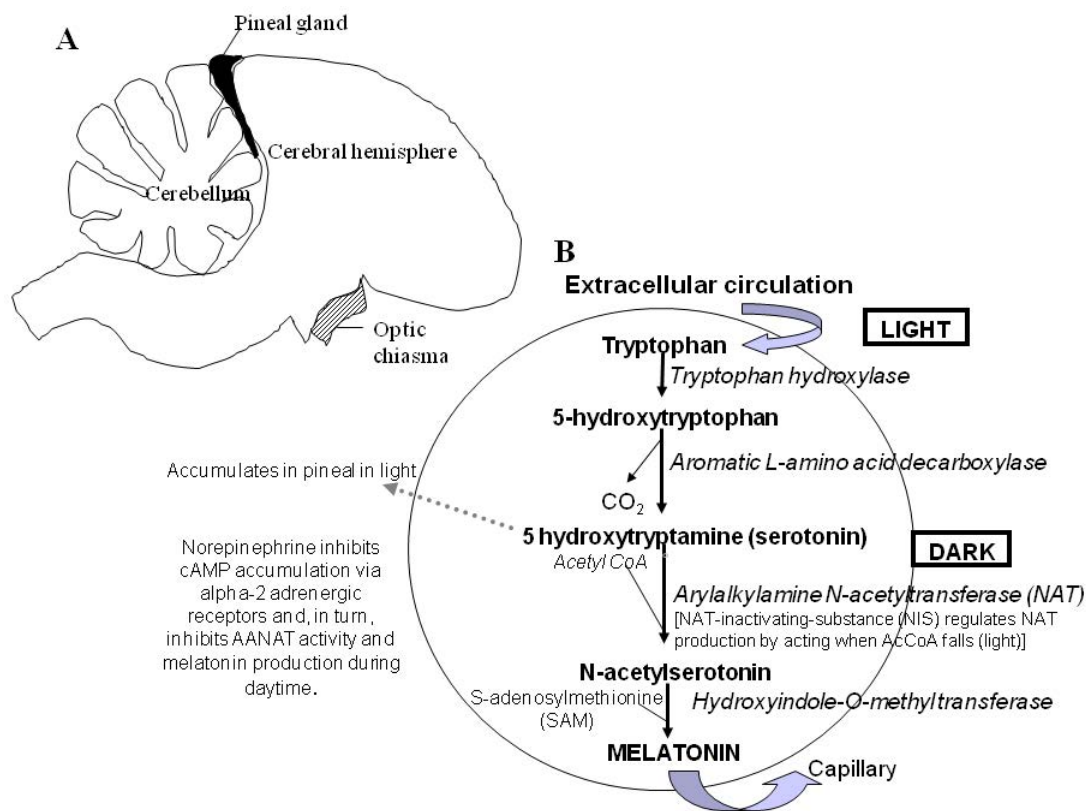

Figure 1. **(a)** Location of the pineal gland within the brain in a passeriform species (diagrammatic). **(b)** Schematic pathway of melatonin biosynthesis (important steps, diagrammatic).

Microarray studies of the pineal gland show the presence of genes encoding hormone-binding proteins, like transthyretin[9]. Neuronally, Norepinephrine (NE) is shown to be involved in the regulation of melatonin biosynthesis but its role in birds appears to be different from what is known from the biosynthesis of melatonin from the mammalian pineal gland in which NE acts mainly on beta-adrenergic receptors and activates melatonin production by the pinealocytes at night. In birds, norepinephrine inhibits cAMP accumulation via alpha-2 adrenergic receptors and, in turn, inhibits AANAT activity and melatonin production during daytime.

2.1 Melatonin Secretion is a Circadian Rhythm

Melatonin is produced rhythmically; circulating levels are low during the day and high at night. The rhythmicity continues both *in vivo* and *in vitro* under constant conditions of darkness (DD) or dim light (LL_{dim}) with a period close to 24 h suggesting it to be a circadian rhythm[10–12], although the degree of persistence of rhythmicity could vary between birds[11,13–16]. Furthermore, advancing or delaying the zeitgeber (zeit = time; geber = giver) conditions (e.g., LD-cycle) produces corresponding phase shifts of the melatonin rhythm, and this phase shift is seen even when the animal is subjected to DD, suggesting that the underlying circadian oscillator was entrained[14,15]. A further confirmation that the properties of the melatonin rhythm are consistent with the melatonin oscillator comes from T-experiments (non 24 h LD cycles with varying periods, e.g., 22 h, 24 h, 26 h, etc.). Exposure to T-photocycles produces changes in the phase of melatonin rhythm[10,17] as one would predict from the oscillatory theory. Consistent with this, the biochemical pathway involved in the synthesis of melatonin has been shown to be under circadian clock control. This seems to be operating both at the transcriptional (as seen in the rhythmic expression of TrH, AANAT and HIOMT mRNAs) and posttranscriptional (AANAT) activity parallels the presence and absence of AANAT mRNA level[4,18,19]. Thus, the pinealocytes appear to be equipped with all the genes, which are implicated in the generation of circadian rhythmicity in other tissues including the hypothalamic clock[4].

3. Pineal and Melatonin: Circadian and Photoperiodic Systems

Two major physiological roles of melatonin have been established in vertebrates. First, melatonin is involved in the circadian system. Secondly, melatonin is critical for the photoperiodic system to operate; organisms use daily melatonin rhythm to monitor the photoperiodic message, the LD cycle of the environment.

3.1 Pineal and Melatonin in the Circadian System

A circadian system is conceptualized as comprising three components: an input pathway, a central clock with an intrinsic capacity of generating precise oscillations, and an output pathway (Figure 2(a)). In birds the circadian system is highly complex, as it comprises several independent clocks (Figure 2(b)). Each clock has its own input and output pathways. Thus, birds perceive light environment by the retina of the lateral eyes, by the pineal gland, and by the photoreceptors in the hypothalamus. Circadian oscillators are present at all the three levels, and they all have independent outputs. However, it appears that these clocks interact with one another before producing the final output (Figure 2(b)). Melatonin is a known output of at least two of them, the pineal gland and the eyes. Interestingly, however, circadian clock(s) in the retina seems to be independent of the pineal gland in songbirds. A recent study[20] has shown that the removal of pineal gland did not affect the development of migratory phenotype under photostimulatory long days (shown by intense night activity and wing whirring during migratory state, called Zugunruhe) but caused decay of the circadian rhythm in Zugunruhe as well as in mRNA expression of circadian clock genes in the hypothalamus, but not in the retina, of migratory redheaded buntings (*Emberiza bruniceps*). These authors found variable effects of the absence of pineal gland in the peripheral tissue circadian gene oscillations, notably in the persistence of circadian mRNA oscillations of period 2 and cryptochrome 1 genes in the non-hypothalamic brain areas and liver in pinealectomized redheaded buntings[20].
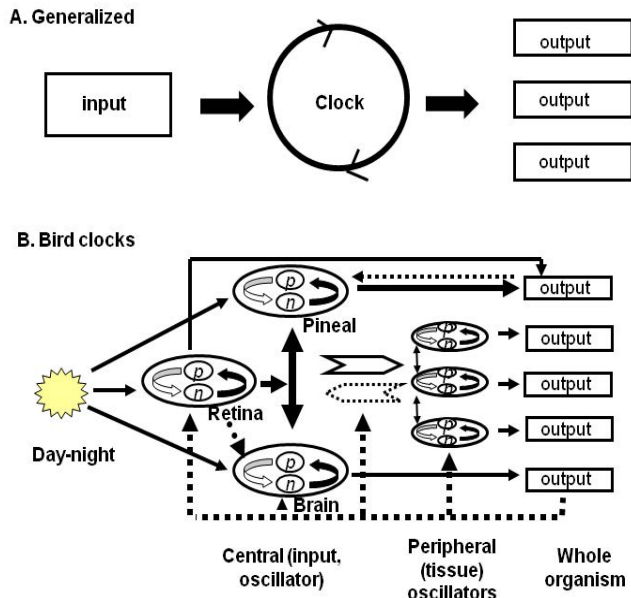
Figure 2. Conceptualized clock system in vertebrates. **(a)** Generalized. **(b)** Birds (adapted from[23,32]).

At the functional level, the two roles of melatonin, although with species-specific importance, have been widely described. First, melatonin is a potential clock component. The retinal and pineal clocks control their circadian outputs via the melatonin rhythm. Therefore, the absence of melatonin rhythm leads to arrhythmicity. Secondly, melatonin acts as a coupling agent. It affects either the frequency of one or more oscillators or the strength of coupling among different oscillators, or both[21–23]. Any change that occurs in melatonin profile will therefore induce changes in the circadian system functions. A high-amplitude melatonin will strengthen the mutual coupling resulting in an increase of the self-sustainment of the clocks and hence decrease their susceptibility to photoperiodic noise. Reduced melatonin amplitude will weaken the mutual coupling, resulting in decrease of the self-sustainment of the clocks thereby facilitating the adjustment of the circadian system to changing zeitgeber conditions[24].

Most studies have measured the effects of pineal melatonin on circadian system regulating behavioral rhythms, especially locomotion and feeding activities. Surgical removal of the pineal (pinealectomy) disrupts circadian rhythmicity of locomotor activity[25], body temperature[26], and feeding[22] in house sparrows. However, the same effect is not achieved by neural disconnection of the pineal gland or by chemical sympathectomy[27], suggesting that some humoral substance (melatonin) is

involved. The pineal (melatonin) contains the circadian information since arrhythmic pinealectomized house sparrow becomes re-rhythmic when the pineal gland from another individual is transplanted in its eye[28]. Periodically applied exogenous melatonin by infusion or in drinking water also restores rhythmicity in arrhythmic pinealectomized house sparrows and pigeons[29,30], confirming that the clock properties of the pineal are achieved through the secretion of melatonin. Also, the duration of melatonin altered by providing exogenous melatonin in drinking water has been shown to regulate seasonal changes in song control nuclei, independent of the melatonin effects on gonads and circadian entrainment in the house sparrow[31]. The effect of pineal removal on circadian activity rhythms has also been shown in the Indian weaver bird *(Ploceus philippinus)*. When weaver birds were exposed to a 12L: 12D zeitgeber conditions, all of them showed good entrainment. Then, half of them were pinealectomized and the other half were sham-operated, and the absence of pineal led to gradual loss of circadian rhythmicity[32,33], similar to that reported in the house sparrow[26,34].

The effect of pineal removal though is not uniform in the avian world. In European starlings (*Sturnus vulgaris*), the role of pineal gland in the control of circadian behavioral rhythms is only partial. Pinealectomy impairs activity, but not feeding rhythm[35]. In chickens (*Gallus domestics;*[36]) and Japanese quail[37], the removal of pineal has no effect on circadian activity rhythms. Rather, the removal of the eye (enucleation) impairs circadian rhythmicity in quails. Since enucleation of quail, achieved by sectioning the optic nerve, leaves the rhythm in melatonin secretion intact[38,39], melatonin is not responsible for enucleation-induced arrhythmicity in quails. In the case of pigeons, pinealectomy together with blinding produces arrhythmicity, but either of the two alone could not achieve this. Cyclic melatonin infusions restored rhythmicity in arrhythmic individuals[40].

The other evidence of melatonin being part of the avian circadian system comes from studies, which have manipulated the rhythm of melatonin. A change in the amplitude of melatonin, for example, will have consequential effects on the properties of avian circadian system, as one would predict from the general principles of the oscillator theory[41]. The persistence of circadian rhythms under constant conditions, the range of entrainment (i.e., the range of zeitgeber periods to which rhythmicity can be synchronized), and the time

required to re-synchronize following phase shifts of the zeitgeber should change by the absence of melatonin rhythm. Several recent studies clearly support this idea. In house sparrows, the elimination of the rhythm in plasma melatonin by pinealectomy which removed the elevated nighttime melatonin levels, or by melatonin implants which enhanced both the daytime and nighttime levels to supra-physiological levels, resulted in (i) loss of circadian rhythmicity in locomotion and feeding[22,42], (ii) an increase in the range of entrainment[43], and (iii) a decrease in the duration required for resynchronization following phase shifts[6,44,45].

Changes and differences in specific features of melatonin signal from the pineal gland can also be found to vary under a variety of natural environmental conditions. For example, pinealectomy abolished circadian rhythmicity in house sparrows when they were kept under constant conditions and free-run, but not when they were kept under LD and synchronized. Further, there was always a residual rhythmicity for-a-while in pinealectomized sparrows[25]. On the other hand, lesions of the hypothalamic pacemaker resulted in severe impairment of rhythmicity in sparrows although they had their pineal intact[46]. Collectively, this means that melatonin interacts with at least one oscillator other than its source to regulate avian circadian rhythmicity. In the absence of melatonin signal, hypothalamic oscillator functions as a damped oscillator. In the presence of light, however, hypothalamic oscillator continues to function as a self-sustained pacemaker even if the melatonin signal is absent.

3.2 Melatonin Rhythm Encodes Photoperiodic Information

The duration of nocturnal melatonin production reflects night length, and hence day length[10]. On the other hand, the peak amplitude melatonin levels also appear to reflect the seasons; the levels are high in summer, low in winter and intermediate in spring[12]. Similarly, the amplitude of plasma melatonin rhythm is significantly reduced during migratory seasons in migratory garden warblers, *Sylvia borin*[47], and during summer months in Adelie penguin, *Pygoscelis adeliae*[48,49] and Arctic svalbard ptarmigan, *Lagopus mutus hyperboreus*[50]. A significant relatively recent result from the study on house sparrows also suggested that the pineal gland could store and retain photoperiodic information[11]. Implication of these findings is that melatonin rhythm provides to the birds

a calendar based on the photoperiodic information of the environment. The capacity of storing biologically meaningful information about time by the pineal may enable birds to compare and measure the day length, as season progresses, and to buffer the effects of adverse environmental conditions, when photoperiodic measurement may be tampered temporarily.

3.3 Melatonin and Photosensitivity

Because melatonin is part of the avian circadian system, it may be assumed to be involved in the regulation of photoperiodic effects at one or the other levels (Figure 3(a)). However, melatonin signal appears to be redundant in many bird species as far as photoperiodic effects on gonadal growth and development are concerned. The list of birds includes European starling *Sturnus vulgaris*[51], spotted munia *Lonchura punctulata*[52], American tree sparrow *Spizella arborea*[53], Japanese quail[10], blackheaded bunting *Emberiza melanocephala*[54] and Red-headed bunting *E. bruniceps*[55]. The absence of a role for melatonin in photoperiodic induction of gonadal growth and development in birds could be explained by a study of Saldanha and collaborators (2001) on ring doves, *Streptopelia roesogrisea.* This study shows direct innervation of GnRH neurons by deep brain photoreceptors (DBPs[56]). This might mean that DBPs, which are necessary and sufficient for the detection of changes in day length that regulates avian reproduction, are not linked to the reproductive axis via the circadian system. Alternatively, these brain photoreceptors also contain the clock, a speculation that needs to be investigated further.

The effects of pinealectomy or melatonin injections are shown nonetheless in some birds, including domestic duck *Anas platyrhynchos*[57], Indian weaver bird[58] (but see also[55] authors therein have reported the absence of melatonin effects in certain phases of the gonadal growth and development cycle), Indian jungle bush quail *Perdicula asiatica*[59], rose-ringed parakeets *Psittacula krameri*[60] and lal munia *Estrilda amandava*[61]. In our more recent experiments, we have also shown the effects of melatonin as modulator of testicular growth and development. In one of the studies, we implanted melatonin-filled or empty silastic capsules subcutaneously in blackheaded buntings that were subjected to 11.75 h light per day (11.75L: 12.25D) under red or white light. Those exposed to red light and melatonin-filled capsules had grown significantly larger testes (Figure 3(b)). These

results are consistent with the hypothesis that elimination of melatonin rhythm probably altered the perception of day length. In another study, Trivedi et al., investigated the modulatory role of melatonin in endocrinology of photoperiodic induction of testicular growth in the redheaded bunting[62]. In redheaded buntings exogenous injections of prolactin attenuates the induction of a photoperiodic response under long days[63]. A part of the results of the experiment presented in Figure 3(b) suggests that pretreatment with melatonin blocks the suppressive effects of prolactin on photoperiodic induction of testicular growth and development in the redheaded bunting[62].

4. Conclusion and Perspective

Birds possess a highly complex and diverse, yet plastic, clock system, the properties of which may vary from species to species. A species-specific circadian timing could have tremendous ecological implications, and may be part of the survival strategy of birds. This may enable, for example, species sharing the same environment to have different temporal strategies in order to perform optimally. Pineal is an important part of the avian timekeeping, and melatonin appears to be a key component of the clockwork at the mechanistic level. In the absence of melatonin, all bird clocks may become incapable of showing self-sustained circadian oscillations. We are still far away, however, from understanding how melatonin exactly meets the demands of a multioscillatory avian circadian system to adjust in the temporal environment. Furthermore, the effect of melatonin on many aspects of bird behavior (e.g., singing, nesting, parental care, etc.) is yet to be investigated thoroughly. This may be essential to understand more comprehensively the effect of melatonin on bird life processes. Finally, most data on the effects of melatonin come from laboratory studies, and whether laboratory observations will hold good for the wild population remains to be investigated.
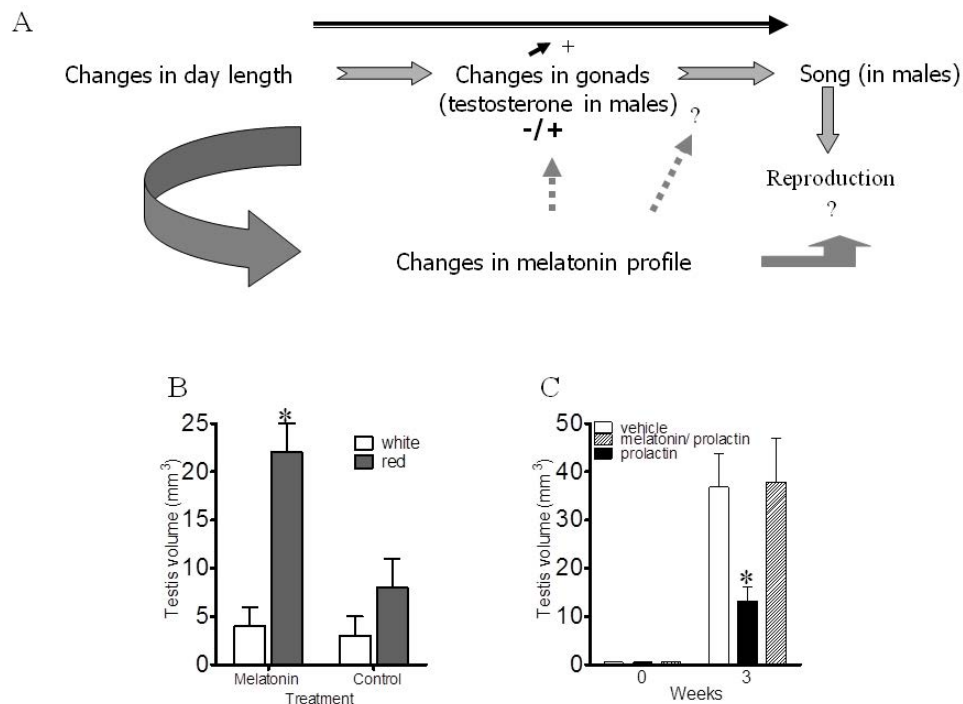

Figure 3. **(a)** Hypothetical scheme of the possible involvement of melatonin in photoperiodically regulated seasonal events in birds. Melatonin can influence seasonality at one or multiple levels. As conventional, plus sign is for stimulation and minus sign is for inhibition of the photoperiodic effects. Sign of question mark indicates controversial reports. **(b)** Melatonin implanted subcutaneously in silastic capsules influences the stimulatory effects of red light on photostimulation of testicular response in the black-headed bunting exposed to 11.75 h light per day (adapted from[32]). **(c)** Pretreatment with melatonin blocks the suppressive effects of prolactin on testicular growth in the redheaded bunting exposed to long day lengths (adapted from[62]).

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