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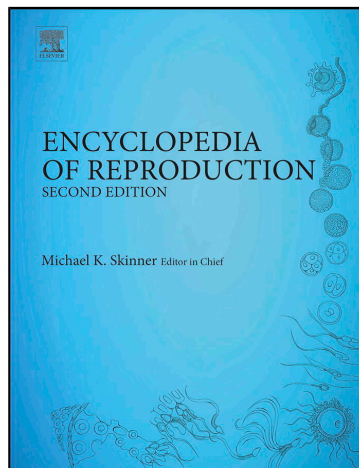
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Circannual Rhythms

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Glossary

Amplitude Difference of maximum or minimum from the mean value of a biological oscillation.

Biological rhythm Repeated cycles of a biological function at relatively stable interval.

Circadian rhythm Endogenous biological rhythm with period length of about 24 h.

Circannual rhythm Endogenous biological rhythm with period length of about 1 year.

Clock gene Gene involved in the transcription-translation feedback loop producing near 24 h time.

Free-running rhythm Endogenous rhythm repeats with its natural period under constant conditions.

Free-running period The time interval between consecutive recurrences of the phase marker (e.g., the time of peak or trough) of a free-running rhythm.

Phase An instantaneous point (particular reference point) within the biological rhythm (e.g., onset, mid point or end of activity).

Period The time interval after which a particular phase recurs during the complete biological rhythm.

Entrainment The process which enables endogenous rhythm to assume the period length of the external (environmental) periodicity, e.g., 24 h light-dark cycle or annual changes in the photoperiod cycle.

Synchronization The state in which endogenous and exogenous (environmental) periodicities assume same period length; i.e., both run with same frequency.

Introduction

Circannual rhythms (Latin: *circa* = about; *annum* = year) are endogenously generated oscillations in biological processes with period length of approximately 1 year (12 months) and time changes in the physiology and behavior within each year in long-lived animals. Corresponding to this are circadian rhythms (Latin: *circa* = about; *diem* = day), which are endogenously generated biological functions with period length of approximately 24 h time changes within each day. Among animals, there are many different examples of circannual rhythms; the most notable ones include the insect pupation rhythms, animal migration patterns, pelage growth, hibernation, reproduction and molt cycles. Hence, circannual rhythms are adaptive, and have been evolved to ensure the success of the long-term biological functions, since mistiming of these with the seasonal world will have serious fitness consequences. For example, organisms reproduce during the period of optimal food availability, which is directly responsible for the offspring survival. The life-span of Siberian chipmunks (*Eutamias sibirium*) is affected by their ability and inability to undergo hibernation: those who undergo hibernation cycles live about 11 years, and those failing to do so, live a reduced life-span of about 3 years (Kondo et al., 2006). Overall, circannual timing mechanisms appear to be universal. As we know now that humans themselves are no exception; we are far more a seasonal species than has previously been assumed (Stevenson et al., 2015). Studies have also revealed that basic mechanisms of the circannual rhythmicity are present in the primate lineage; the ancestral circannual clocks continue to tick in us in still unexplored ways, and significantly affect contemporary human life (Stevenson et al., 2015; Helm and Lincoln, 2017).

Naturalists have long speculated endogenous timing mechanism on yearly time scale in the control of biological events. At the beginning of eighteenth century, Ferdinand J. A. von Perna, a pioneer student of bird behavior, suggested that migratory birds were "driven at the proper time by a hidden drive". Early in nineteenth century, Arnold A. Berthold suggested that the emergence from hibernation in spring was due to the action of endogenous timing factors, and not a simple response to the prevailing environmental stimulus. About a century later, William Rowan argued for the involvement of an internal factor, i.e., a physiological rhythm, in migratory birds that breed in the northern hemisphere, and winter around equator or in the southern hemisphere. In 1960, A. B. Misra suggested, "... the internal rhythm, guided and controlled by genetical factors and fixed by natural selection is the supreme governor of recurrent reproductive physiology of the birds". Both, naturalists and farmers have noted timely return of migratory great knots (*Calidris tenuirostris*) year-after-year, and in few instances this record worked as an agricultural calendar (Foster and Kreitzman, 2009).

Most evidence for the existence of endogenous circannual rhythms, as consolidated by experimental demonstrations in several species, are consistent with the hypothesis that annual timing is based on self-sustained circannual clock(s) which interacts with the environmental photoperiodic zeitgeber (German: *zeit* = time, *geber* = giver; Gwinner, 1986; Numata and Helm, 2014). Few taxonomic groups like insects, birds and hibernating mammals, in particular, captured human interest for detailed scientific investigations over the last about six decades, with seminal and extensive works of Eberhard Gwinner and Eric T. Pongelley on birds and mammals, respectively. An early evidence for circannual rhythm in mammals came from golden-mantled ground squirrel

(*Callospermophilus lateralis*), which displayed circannual cycles in hibernation, food consumption and body mass under constant light and ambient temperature conditions (Pengelley and Fisher, 1963). Strong evidence for avian circannual rhythms came from Ebo Gwinner's studies; the rhythms in migratory restlessness (*Zugunruhe*, demonstrated by intense night activity and wing whirring in night migrants) and molt persisted in captivity for 3 years, suggesting an endogenous regulation of annual migration in willow warblers (*Phylloscopus trochilus*; Gwinner, 1986).

Formal Properties, Stability, and Entrainment

Formal Properties

Circannual rhythms are self-sustained endogenously driven biological oscillations that persist with a regular periodicity of about 12 months in the absence of environmental cycles. Hence, a rhythmic process cannot be designated as 'circannual rhythm' unless it has been experimentally observed to persist in the organism under condition that provides no information about its period. Hence, the constant darkness (DD) or constant dim light (dimLL) can be considered as constant environment condition for circannual rhythm demonstration. Also, 24 h light-dark (LD) cycle (e.g., 12 L:12D) with an unchanging photorefraction contains no information about the year, and so it can be considered as a constant condition for circannual rhythms. Circannual rhythms are temperature compensated: cycle lengths do not vary significantly with change in the constant temperature environment. Overall, circannual rhythms share all fundamental properties with those of the circadian rhythms (Gwinner, 1986; Helm and Lincoln, 2017).

Irving Zucker (2001) reviewed annual rhythms in mammals and distinguished them in three categories, types I, II, and III (Fig. 1). Common among short-lived temperate and boreal species, type I rhythms, although with an endogenous component, do not persist beyond 1 cycle under constant conditions; hence, they are contingent on periodic environmental input. Type II circannual rhythms are found in long-lived species like rodents, carnivores, ungulates, bats and primates. These are endogenous and persist with cycle length of ~12 months under constant conditions; hence, they are not contingent on periodic environmental input. Type III rhythms occur almost with regular periodicity in response to the environmental periodicities; hence, these rhythms do not have an endogenous component, e.g., seasonal allergies in reaction to production of pollens. By-and-large, our present discussion includes types I and II rhythms, which are displayed by different groups, particularly in controlling seasonal reproduction.

Stability and Lability

The period length (Greek: tau, τ) of the free-running circannual rhythm deviates from a year, usually shorter than 12 months. Measured as intervals between two successive peaks in testis growth, circannual testicular rhythm in spotted munia (*Lonchura punctulata*) was found to have $\tau = \sim 11$ months under both constant photoperiod, LL or alternate 24 h of LL/DD at $\sim 20^\circ\text{C}$ temperature (Budki et al., 2012). Circannual reproductive rhythm shows period stability in, as evidenced by similar periods in the circannual testicular cycle in spotted munia under LL at 22- and 90-lx light intensities (cf. Budki et al., 2012, 2014; Fig. 2). Similarly, the average body mass in hibernating ground squirrels (*Citellus lateralis*) cycle with $\tau = 11.3$ and 10.9 months under high ($34 \pm 1^\circ\text{C}$) and low ($5 \pm 1^\circ\text{C}$) temperatures, respectively (Gwinner, 1986). Also, Siberian chipmunks (*Eutamias sibiricus*) maintain precise circannual rhythms of core body temperature for up to a decade both in continuous cold and darkness, although with τ ranging from 5 to 13 months, and hibernation period ranging from 2 to 8 months (Kondo et al., 2006). However, circannual cycles can differ between sexes. Whereas male spotted munia cycle with $\tau = \sim 11$ months (see above), females under same light conditions exhibit circannual cycles with relatively large period variations, $\tau = 10\text{--}13$ months (cf. Budki et al., 2012, 2014). Also, male Siberian chipmunks end their hibernation quite early in the spring when there is still sufficient snow cover, but females emerge from hibernaculum much later in the season when food resources become readily available (Florant and Healy, 2012). Furthermore, individuals can exhibit independent circannual phenotypes, as suggested by differences in the period length, hence frequency, between various circannual functions. For example, molt cycles are more frequent and widely scattered in the year than the gonadal cycles in spotted munia under LL (Budki et al., 2012, 2014; Fig. 3).

Entrainment

Circannual rhythms are synchronized (or "entrained") to local time by appropriate phase shifts, and may involve transients. ($\tau = T$; T is cycle length of an environmental *zeitgeber*, e.g., annual LD cycle). The range of entrainment is broader, and so an entraining LD cycle may vary in T from c. 6–15 months, i.e., $\sim 50\text{--}30\%$ of τ of the endogenous circannual rhythm (Gwinner, 1986). Apart from T , the light intensity can influence the synchronization, particularly the inter-individual synchrony. LL at 90 lx reduced variation and increased synchrony between circannual cycles of gonadal maturation and molt among individuals of a group of spotted munia, as compared to those in LL at 22 lx (cf. Budki et al., 2012, 2014).

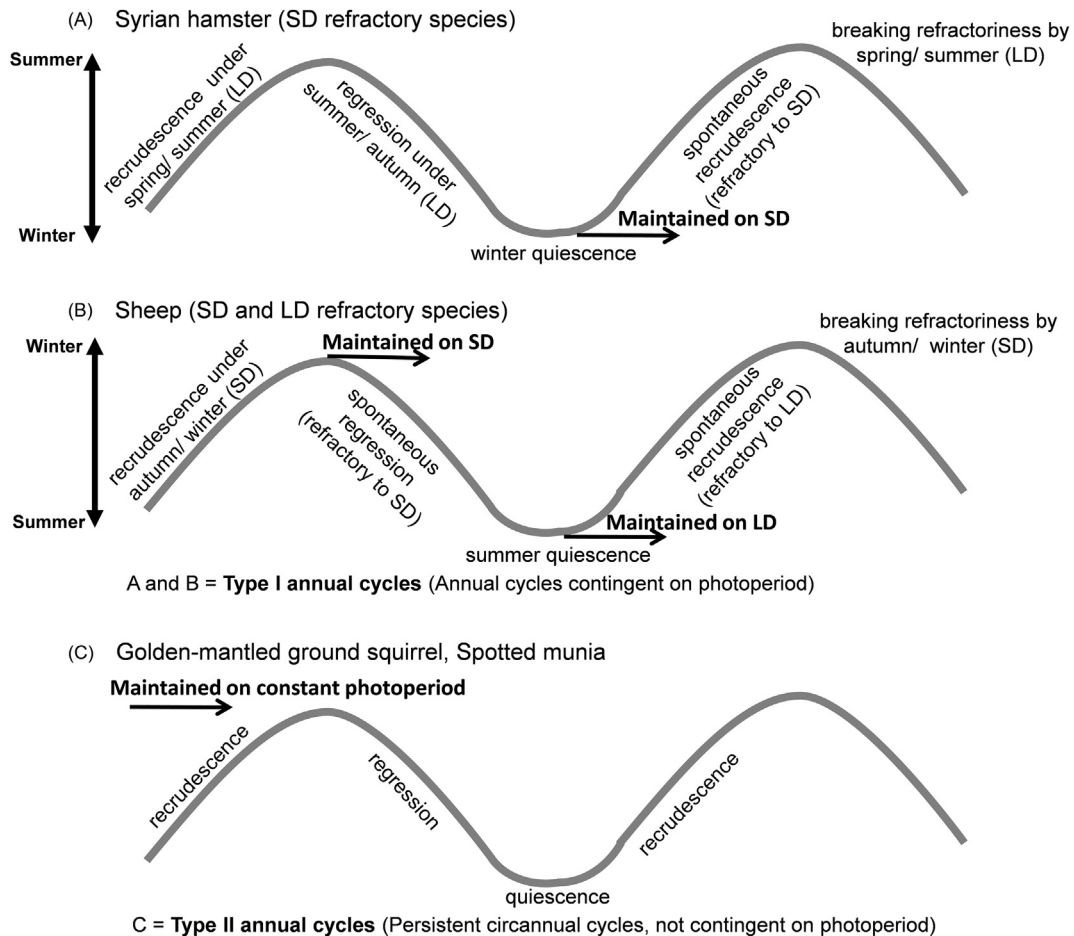


Fig. 1 Schematic representation of the annual reproductive cycle types. Upper 2 panels: Type I rhythms in which environmental photoperiod is the primary zeitgeber in the regulation and synchronization of annual gonadal cycles. (A): Syrian hamsters (*Mesocricetus auratus*) show gonadal recrudescence and regression under long and short days, and spontaneously regrow their testes under prolonged short day exposure; hence they exhibit refractoriness to the inhibitory effects of the short day, SD. (B): Sheep (*Ovis* sp.) shows refractoriness to both, the stimulatory effects of SD as well as inhibitory effects of LD. Hence, there is the recrudescence and spontaneous regression of gonads under SD; converse is true under LD. A photoperiod change is therefore required to break the refractoriness. (C): Type II rhythms are endogenous cycles and persist under constant photoperiod and constant light/darkness. There seems no particular day length requirement to induce the gonadal recrudescence—regression cycle. Drawn based on Zucker (2001).

Circannual Rhythms and Reproduction

Circannual rhythms temporally space out seasonal phenologies in the year such that a species can profitably utilize resources available in its surroundings and survive through the unfavorable conditions, if any. Reproduction, in particular, is timed to occur during the year when feeding resources are optimal and ensure the survival of newborns. This necessitates that physiological processes underlying reproduction (e.g., pair formation, as required; gonadal maturation; mating; incubation/gestation) are initiated, terminated and reinitiated within a specified temporal window in the year, with a great time precision. Hence, species have evolved and are genetically programmed with an endogenous circannual timekeeping system, which in interaction with prevailing environment helps individuals (or population) anticipate the most favorable time in the year. Experimental studies support this. The black caps (*Sylvia atricapilla*) from Cape Verde breed twice and from central Europe breed once a year, and they continue to show two and single circannual cycles in testis maturation, respectively, even when placed under constant artificial 13 h light per day (Helm and Lincoln, 2017). Similar trans-generational persistence of circannual gonadal and molt cycles has been demonstrated in equatorial African stonechats (*Saxicola torquatus axillaris*): both hand-raised and their offspring displayed similar circannual cycles under constant photoperiod conditions (Gwinner, 1996). Thus, circannual rhythm generation and photoperiodism (environmental photoperiod times component events of a seasonal process) may not be mutually exclusive and, in fact, might interact closely, albeit in species-specific manner, as per the adaptive needs.

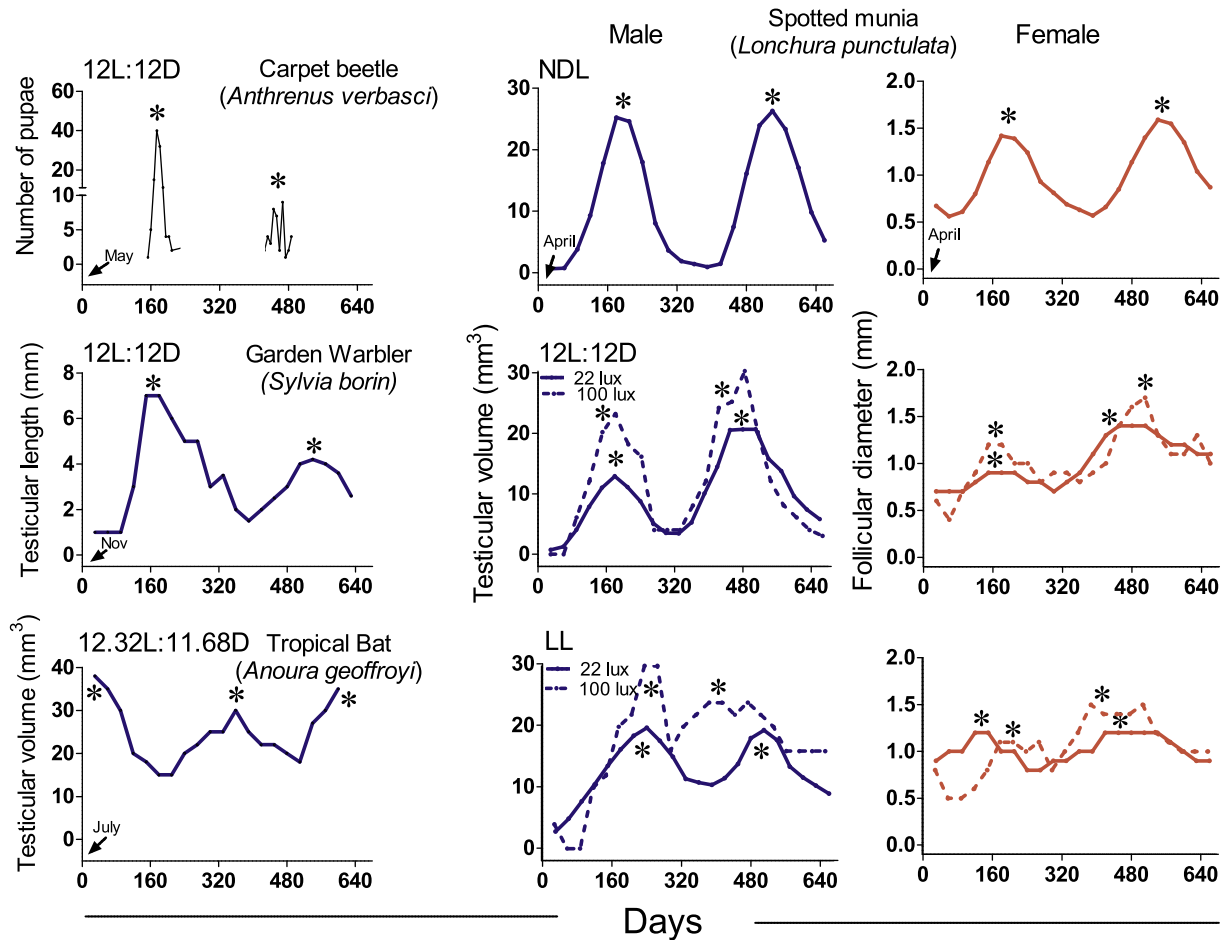


Fig. 2 Circannual reproductive cycles under constant photoperiods. Left panel: circannual cycles in the pupation in Carpet beetles (*Anthrenus verbasci*; 4-stage life cycle holometabolous insect), and in the testicular growth-regression in garden warblers (*Sylvia borin*; an avian migrant) and tropical bat (*Anoura geoffroyi*) under equinox, or near equinox, photoperiod (12L:12D, 12.32L:11.68D). Right panels: circannual gonadal growth-regression cycles in male and female spotted munia (*Lonchura punctulata*) under natural day length (NDL), and under 12L:12D or LL at 22- and 90-lx light intensities. Asterisks indicate the time of peak gonadal growth. Note light intensity dependent modulation of the circannual gonadal cycles in the spotted munia. Drawn based on Gwinner (1986), Heidemann and Bronson (1994), Budki et al. (2012, 2014), and Miyazaki et al. (2014).

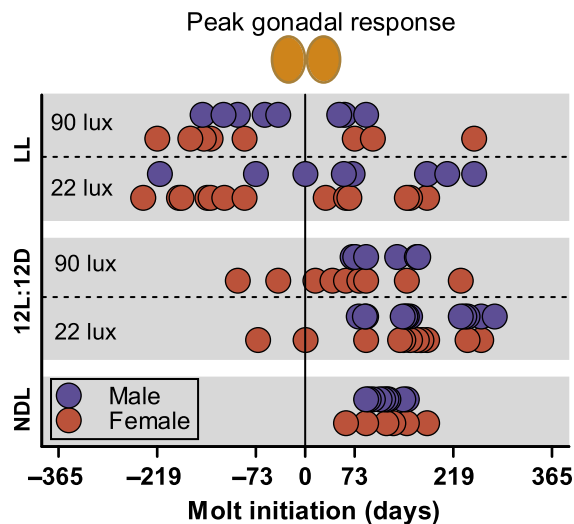


Fig. 3 Relationship of molt with reproductive cycle in spotted munia (*Lonchura punctulata*). The time of initiation of wing primaries molt of in the first circannual cycle plotted in relation to peak gonadal size (indicated by time '0' value on x-axis) under natural day length, and equinox photoperiod (12L:12D) or constant light (LL) at 22- and 90-lx intensities. The time scale on x-axis expands for 365 days on each side of '0', with minus (-) and plus (+) signs indicating the onset of molt prior to, and after the peak gonadal response (time 0), respectively. Blue and red circles represent data for individual male and female birds, respectively. Note light intensity dependent effects under 12L:12D and LL. Drawn based on Budki et al. (2012, 2014)

Insects

Most insect species have life cycle shorter than a year, and thus do not seem to be in need of the circannual timing. But, holometabolous insect like carpet beetles (*Anthrenus verbasci*) with 4-stage life cycle of ≥ 2 years utilize circannual timing for seasonal events. Adult beetles emerge, mate and lay eggs from spring to early summers, depending on the climate and nutritional conditions. Under constant temperature and darkness, the pupation and development of *A. verbasci* exhibits a circannual rhythm with $\tau = \sim 40$ weeks in both British and Japanese populations (Miyazaki et al., 2014). The rhythms were temperature compensated, although larvae pupated earlier at high (25°C) and later at low (15°C) temperatures. Light period also affected the circannual pupation rhythm, as shown by a clear rhythm under 12L:12D and complete arrhythmicity under 15L:9D (Miyazaki et al., 2014). Similarly, circannual cycles persist in oviposition and larvae pupation over 5 years in ants (*Formica aquilina*, *F. polyctena*), although with huge individual differences in the cycle length, to some extent affected by the prevailing photoperiod and temperature (Miyazaki et al., 2014).

Birds

Circannual rhythms have been demonstrated in gonad development and “postnuptial” molt in several birds, with pioneering investigations of Ebo Gwinner (see Gwinner, 1986). The longest record of circannual cycles of gonad development and molt over 15 years is from African stonechats under 12.25L:11.75D (see Gwinner, 1996). In the most constant year-round environment of equatorial rainforest, chestnut-winged babblers (*Stachyris erythroptera*) and little spider hunter (*Arachnothera longirostris*) show circannual cycles in breeding and molt with a period length of about 9 months (see Gwinner, 1986). Similarly, subtropical spotted munia (*Lonchura punctulata*) show recurrent circannual cycles in gonadal maturation and molt under different light conditions, including LD cycles and LL (Figs. 2 and 3; Budki et al., 2014). A circannual cycle in reproduction is not the feature restricted to equatorial or tropical species. Temperate species also show circannual cycles in gonadal maturation. European starlings (*Sturnus vulgaris*) show recurrent testicular cycles under 12L:12D (Gwinner, 1986). Similarly, migratory dark-eyed juncos (*Junco hyemalis*) show circannual cycles in both testes and migratory phenotypes (e.g. spring pre-migratory body fattening, *Zugunruhe*) under dim LL of 1–3 lx (Rani and Kumar, 2013).

Mammals

Circannual rhythms have been shown in short and long day breeding mammals, such as sheep (*Ovis* sp.), sika deer (*Cervus nippon*), bats (*Antrozous pallidus*, *Anoura geoffroyi*, *Phyllostomus hastatus*) and rodents (Syrian hamster, *Mesocricetus auratus*; Siberian hamster, *Phodopus sungorus*; European hamster, *Cricetus cricetus*) (Heidemann and Bronson, 1994; Lincoln and Hazlerigg, 2014; Numata and Helm, 2014; Helm and Lincoln, 2017; Figs. 1 and 2), although with subtle differences in features, as compared to those found in birds (see above). Sheep, a short day breeder, undergoes circannual cycles of reproduction (gonadal maturation, luteinizing hormone and prolactin secretions) and molt under constant conditions. Sika deers display circannual cycles in the testicular growth, antler replacement, and coat color and molt under constant photoperiods. Circannual rhythms persist in gonad development cycle and pelage color in rodents, including squirrels, hamsters and mice. Circannual cycles of body mass and estrous freerun golden-mantled ground squirrels under $T = 23, 24$ or 25 h LD cycles, in which they synchronized circadian activity rhythms (Zucker, 2001). Similarly, small vesper mice (*Calomys laucha*), a south American rodent, show circannual cycles in pelage color (orange and light summer pelage, and gray and dark winter pelage) under 12L:12D at 22°C (Camargo et al., 2006).

Circannual rhythms have also been suggested operating in biological functions of humans including the reproduction-associated measures, albeit with inconsistencies between findings. Human birth pulses can fluctuate seasonally with an amplitude of about 10%, which is substantial for a species that effectively performs physiological functions under conditions of an eternal summer maintained within the body 37°C (the core body temperature). The amplitude of seasonal rhythms indicated by the timing of maxima can vary with the latitude, suggesting an underlying physiological regulatory mechanism. The pattern of birth pulses appears to have a longer-term relevance because birth-month correlates with life-long impacts on health, including the likelihood of general, psychiatric or neurological illnesses (Stevenson et al., 2015). An 8-year study of the semen analysis from human volunteers found a statistically significant high-amplitude seasonal variation in the sperm count (not ejaculate volume or percent motile sperms), with highest values in late winter and early spring, and lowest values in the late summer (Saint Pol et al., 1989). Furthermore, both the presence and absence of circannual cycles in circulating testosterone levels have been reported in humans (Smith et al., 2013).

Inter- and Intra-Specific Differences

Among species that do show circannual rhythms, all individuals may not show them, and the cycle length can also vary considerably from 12 months even among individuals that show them. Circannual cycles of gonadal maturation and pelage growth or molt can also differ between sexes. Unlike males, female European starlings lack a robust circannual response, and exhibit less clear rhythms with larger variations in the period and frequency of cycles in plasma LH and prolactin levels (Dawson, 2007). Also, circannual ovarian cycles, as shown by follicular maturation, were less pronounced and had larger variations than the testes in spotted munia (Budki et al., 2012; Fig. 2). These suggest sex-dependent timing strategies, with females appearing to share a greater role in defining

the reproductive season in relation with the environment. Different circannual rhythms can vary within an individual: cycles of “postnuptial” molt get out of phase with the gonadal cycle in spotted munia under LL (Fig. 3; Rani and Kumar, 2013).

Circannual Rhythms and Photoperiodism

In nature, various environmental factors, most reliably the changes in photoperiod, synchronize the timing of circannual clock-mediated physiological processes to occur at a particular time during the year, which is best-suited for survival and adaptability. Hence, organism-specific experimental strategies are manifested in circannual cycles. Circannual cycles freerun in several birds (e.g., spotted munia, dark-eyed juncos) under constant photoperiod or LL, but these require a photoperiod change at a particular phase of the cycle to express in many mammals (e.g., sheep, sika deer, hamsters; Fig. 1). European starlings held under constant photoperiods exceeding 12.5L:11.5D or < 11.5L:12.5D fail to exhibit circannual cycles. Furthermore, artificial simulations of annual photoperiod variation can entrain circannual cycles to periods as short as 4 months and as long as 2 years. Photoperiodic entrainment can also vary between populations. For example, post juvenile molt in the long distance migrant population of Siberian stonechats (*Saxicola torquata maura*) is earlier and faster than in the short distance migrating European stonechats (*S.t. rubicola*); molt is further slower and late in the nonmigrating east-African stonechats (*S.t. axillaris*).

Circannual Timing: Putative Mechanisms

Va. Endogenous clocks: Several lines of evidence show that circadian pacemaker system (CPS) is not involved in the circannual rhythm generation. The ablation of the suprachiasmatic nuclei (SCN), which contains CPS in mammals, eliminates circadian rhythms in activity, but not the circannual cycles of body mass and reproductive phenotypes in golden-mantled ground squirrels (Zucker, 2001). Sika deers show circannual cycles under LD cycles (4.94 L:4.94D, 6L:6D, 8L:8D and 21L:21D) which fail to induce the circadian entrainment (Helm and Lincoln, 2017). Similarly, spotted munia show free-running circannual rhythms in gonad development and molt under LL which induces circadian rhythm disruption both at the behavioral and circadian gene transcriptional levels (Budki et al., 2014; our unpublished data). Thus, a biological year is not defined by 360-odd circadian days. CPS could still have a modulatory role in the annual timing, as shown by alteration in the long-term timing and structure of circannual hibernation cycle in SCN ablated squirrels (see Zucker, 2001). Daily oscillations of core clock genes (*PERIODS*, *PERs*; *CRYPTOCHROMES*, *CRYs*; *BRAIN AND MUSCLE ARNT LIKE PROTEIN 1*, *BMAL1*; *CIRCADIAN LOCOMOTOR OUTPUT CYCLES KAPUT*, *CLOCK*) also show alterations between short and long days, and between seasonal states in photoperiodic birds (Cassone and Yoshimura, 2015; Singh et al., 2015).

Thyroid Hormone (TH) Responsive Hypothalamic Pathways

Highly conserved TH-responsive molecular mechanism mediates the photostimulation of gonadal growth and development in both short- and long-day species (Cassone and Yoshimura, 2015; Fig. 4). It begins with concurrent activation of the *EYA3* (eye absent 3) and *TSH-beta* (thyroid stimulating hormone-beta) genes in pars tuberalis (PT) thyrotrophs in response to stimulatory photoperiod, as perceived by brain photopigments (e.g., neuropsin) in birds and by CPS-controlled duration of night melatonin secretion in mammals (Fig. 4). TSH (product of *TSH-alpha* and *TSH-beta*) from PT thyrotrophs activates and suppresses transcription of genes coding for type 2 and 3 deiodinases (*DIO2* and *DIO3*), respectively, in tanycytes (ependymal cells lining the third ventricle). *DIO2* and *DIO3* mediate conversion of thyroxin (T4) into biologically active T3 (tri-iodothyronine) and inactive rT3 (reverse T3) forms, respectively. T3 regulates GnRH (gonadotropin releasing hormone) synthesis and/or release from the preoptic area into median eminence, and consequently the pituitary gonadotropins secretion and gonadal response (Fig. 4). TH signaling also plays a role in the seasonal timing of hibernation in golden-mantled ground squirrels. Recently, chromogranin (CHGA, a hormone-packaging molecule) has been identified as the robust marker of short photoperiod in sheep. Wood et al. (2015) report binary switching of PT thyrotrophs: they exist in CHGA+ form under short-day breeding state, TSH-beta/*EYA3*+ form under long-day nonbreeding state, and spontaneously switch from TSH-beta/*EYA3*+ to CHGA+ state under the long-day refractory state (Fig. 4). Thus, apart from TH signaling, PT seems to drive long-term circannual cycles with individual cells undergoing recapitulation of the developmental state. It remains to be tested however if TH-responsive mechanism is key to the circannual rhythm generation in a nonphotoperiodic species; our initial studies on spotted munia fail to this, however.

The Other Hypothalamic Nuclei/Candidate Molecules

Recent researches have implicated various other hypothalamic structures and candidate molecules in the circannual timekeeping. For example, ventromedial and lateral hypothalamus (VMH, LH), arcuate nucleus (ARC), paraventricular nucleus (PVN) and dorsomedial hypothalamus (DMH) play roles in the seasonal regulation of feeding and energy balance. In hibernators, ARC regulates body mass cycles, and mediates the torpor; T3 acts in ARC and PVN as a low energy signal during fasting (Florant and Healy, 2012). In chipmunks, hibernation-specific proteins (HP) complex concentration in blood closely correlates with the circannual hibernation rhythm, with down regulation of HP prior to the onset of hibernation (Kondo et al., 2006). VGF (nonacronymic) is

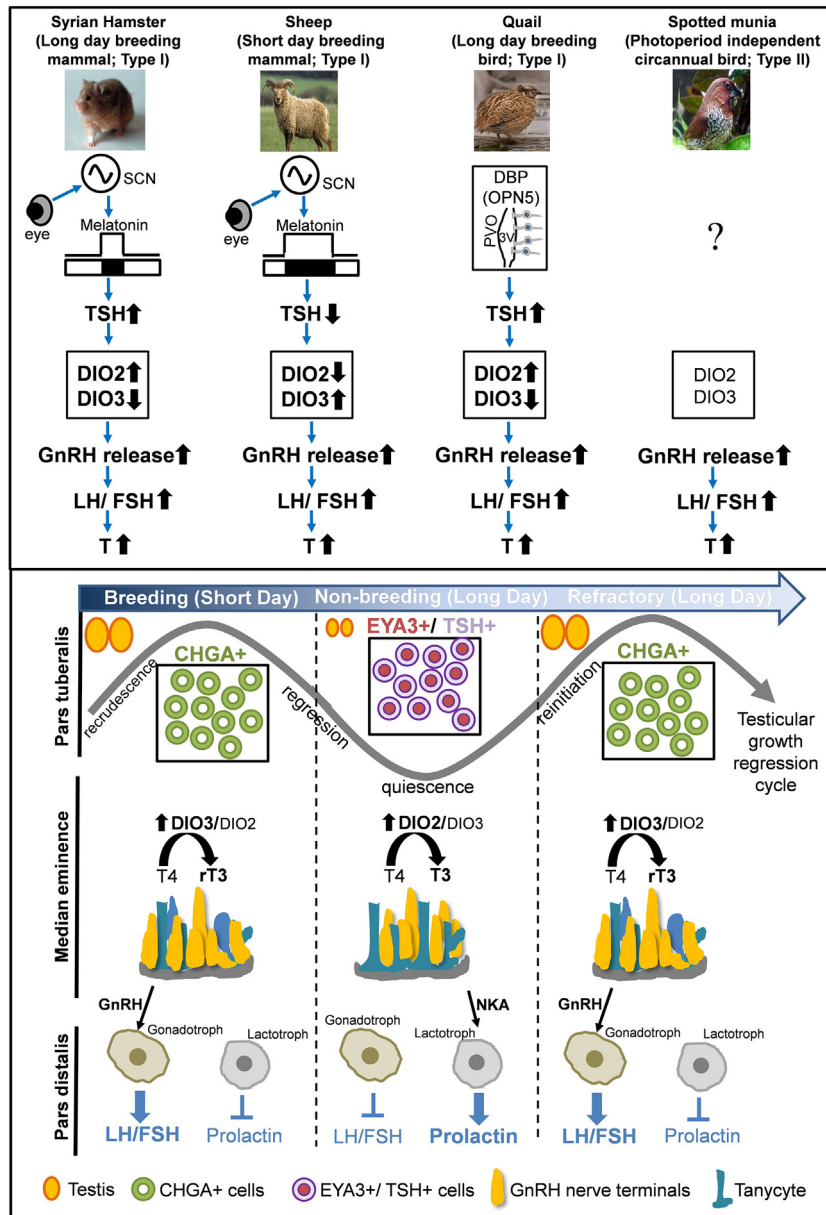


Fig. 4 Mechanisms for seasonal timing of gonad development. Upper half: Changes in the HPG (hypothalamic-pituitary-gonadal) axis involved in the regulation of type I and type II annual reproductive cycles. In type I annual reproductive cycles, the relay of light information in mammals is from the retina via SCN activity-dependent melatonin secretion, while in birds light is perceived through the deep brain photoreceptor photopigments, e.g., neuropsin, OPN5. PT-thyrotroph derived TSH activates DIO2 expression in response to long days in both summer and winter breeders. Although increased synthesis/ release of GnRH (gonadotropins releasing hormone) and pituitary gonadotropins cause gonad development in species that exemplify type II annual reproductive cycles, how is light information decoded and transduced upstream is not well understood, as yet. However, we found no difference in *DIO2* and *DIO3* mRNA expressions in mediobasal hypothalamus of a strong circannual species, the spotted munia (*Lonchura punctulata*; unpubl. Obs.). Up and down arrows in indicate high and low expression levels, respectively. Lower half: A proposed model for circannual timekeeping in sheep. Individual pituitary pars tuberalis (PT) thyrotrophs exist in the binary state. The relative proportion of these binary state cells determines the phase of the circannual cycle (breeding: CHGA+, Chromogranin A positive; non-breeding: EYA3+/TSH+, eye absent 3/thyroid stimulating hormone positive). In SD breeding and LD refractory states (left and right panels), there is an increase in the deiodinase type 3 (*DIO3*) expression in the ependymal cells, the tanycytes lining the 3rd ventricle. *DIO3* mediates the conversion of thyroxine (T4) into its inactive form (triiodothyronine, rT3), and hence reduces local concentration of its active, T3. As a consequence, the tanycyte end feet retract, and eliminate the physical barrier for GnRH secretion. In the nonbreeding LD state (middle panel), PT-thyrotroph derived TSH activates *DIO2* expression and hence enhances T3. As a consequence occur the neuronal remodeling and the encasement of neuronal synapses by tanycyte end feet. These suggest a physical mechanism for the control of GnRH secretion, and downstream gonadotropin release and gonadal response. PT thyrotrophs thus operate as a calendar cell, and generate long-term neuroendocrine rhythms in both the hypothalamus and pituitary gland. Schematically drawn based on Cassone and Yoshimura (2015) and Wood et al. (2015).

another most abundantly expressed molecule in the hypothalamus, and involved in the energy balance and reproduction. *VGF* mRNA is induced in the ARC, in both Syrian and Siberian hamsters transferred from long to short days (Barrett et al., 2005). *VGF* also plays a role in the synaptic plasticity, and seem important for the reduction of synaptic connectivity in the song control system, as required post-breeding in songbirds and during torpor bouts in hibernating mammals (Schwartz and Andrews, 2013). Hypothalamic *VGF* might play a role in the seasonal switch from hyperphagic behavior in summer and early fall to the hypophagic behavior during the hibernation (Schwartz and Andrews, 2013). In hibernators like thirteen-lined ground squirrels (*Spermophilus tridecemlineatus*), brain *VGF* expression is increased in October when there is decreased food consumption and increased white adipose stores, and is the onset of shallow torpor bouts (Schwartz and Andrews, 2013).

Emerging Concepts in Circannual Rhythm Research

At the present time, three concepts seem emerging to explain the annual timing. Recent studies on seasonally breeding sheep suggest pituitary PT as the putative site of the circannual rhythm generation (see above). It remains inconclusive if PT acts as the circannual pacemaker, as does the SCN as the circadian pacemaker; the autonomous switching in PT genes may be governed by still an undefined structure/ mechanism. A second concept revolves around the involvement of circadian timing in seasonal processes, at least in photoperiodic species with a robust self-sustained circadian system. This is supported by recent demonstrations of alteration in the expression level, 24 h expression patterns, and 24 h rhythm waveforms (phase, amplitude) in the hypothalamic mRNA oscillations of core clock genes, and of genes involved in the photoperiodic transduction and neurosteroid dependent processes, in parallel with seasonal changes in the physiology and behavior (e.g., reproduction, migration) in migratory blackheaded buntings (*Emberiza melanocephala*; Singh et al., 2015; Mishra et al., 2017). The third concept underlies that circannual cycles are generated by tissue-autonomous histogenesis, which includes the formation of a complex tissue system from undifferentiated cells, as a result of complex developmental processes such as the cell differentiation, tissue remodeling and feedback signaling between and within tissues (Lincoln and Hazlerigg, 2014). Exclusive demonstration for this is still lacking, however.

Perhaps an answer to the question whether annual timing of temporally spaced seasonal behaviors has a common regulatory site, as is the SCN for the regulation of many daily responses, is key to finding the circannual pacemaker. Else, circannual timing might include independent phase-related seasonal processes? Perhaps, uncovering genes and protein pathways underlying the induction and maintenance, and the termination and reinitiation of seasonal response (e.g., molecular genetics of migratory or seasonally breeding birds) might enable us to understand the mechanism of circannual rhythm generation. Current advances in molecular tools, and its usage in studying the non-model organisms have greatly improved and should enhance our ability to understand where and how are the circannual rhythms generated.

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