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Abstract

Seasonality has profoundly shaped the evolution of virtually all long-lived organisms on earth. Over most of the planet environmental conditions are not constant, but instead vary in dramatic albeit predictable ways. Food availability, ambient temperatures, rainfall, and a variety of other conditions vary with the changing seasons. As such, behavioral and physiological adaptations to the changing seasons are common among long-lived species across taxa. This chapter will cover some of the key seasonal rhythms in behavior and the neuroendocrine mechanisms that mediate seasonal timing.

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Abbreviations

cAMP	Cyclic adenosine monophosphate
DHEA	Dehydroepiandrosterone DHT Dihydrotestosterone
DIO3	Iodothyronine deiodinase type 3
GnIH	Gonadotrophin inhibitory hormone
GnRH	Gonadotrophin releasing hormone
IML	Intermediolateral cell column
MT1	Melatonin receptor type 1
MT2	Melatonin receptor type 2
nAT	<i>N</i> -Acetyl transferase
NRe	Reuniens nucleus
PVN	Periventricular nucleus of the hypothalamus
PVT	Periventricular thalamus
SCG	Superior cervical ganglion
SCN	Suprachiasmatic nucleus
T3	Triiodothyronine

Brief History

Seasonality has profoundly shaped the evolution of virtually all long-lived organisms on earth (Bronson 1985; Goldman 2001; Nelson et al. 2010; Prendergast et al. 2009). Over most of the planet environmental conditions are not constant, but instead vary in dramatic albeit predictable ways. Food availability, ambient temperatures, rainfall, and a variety of other conditions vary with the changing seasons. As such, behavioral and physiological adaptations to the changing seasons are common among long-lived species across taxa. This chapter will cover some of the key seasonal rhythms in behavior and the neuroendocrine mechanisms that mediate seasonal timing.

The earth is tilted approximately 23.5° relative to its orbital plane. As a consequence, at any given point during the summer or winter, one hemisphere is more directly exposed to the sun's rays than the other hemisphere. The changes in temperature between winter and summer are therefore mediated by three factors. First, when the sun's rays are spread over a greater distance (by the shallower angle at which they strike the earth), they are less effective at warming the planet. Second, the shallower angle means that more of the light is dissipated or reflected by the

atmosphere. Finally, the duration of daily illumination is reduced in the winter, meaning that the more diffuse rays of the sun are also present for a shorter percentage of the day. This change in day length serves as the key proximate cue that animals utilize to monitor seasonal time.

A further determinant of seasonal changes in temperature is mediated by the shape of the earth's orbit around the sun. The orbit of the earth is not round, but rather elliptical. The earth is at the closest point to the sun (the perihelion) in December and the furthest point (aphelion) in July. This effect tends to counteract the larger effects of orbital tilt and slightly buffers the winters in both the northern and southern hemispheres.

Introduction

The Evolution of Seasonal Rhythms

The changes in temperature and associated changes in rainfall produce seasonal rhythms in plant growth that significantly modulates food availability for herbivores that in turn limits the prey availability for carnivores. This set of seasonal changes in environmental conditions has profoundly shaped the evolution of long-lived organisms on the planet. For instance, small animals living at the higher latitudes experience a severe energetic bottleneck during the winter months. During this period, increased thermoregulatory costs coincide with reduced food availability and, in many cases, increased predation pressure by other foraging animals. Even large animals that are able to store significant amounts of energy in the form of fat face significant challenges in maintaining a positive energy balance.

Although the winter months represent serious challenges, these challenges are highly predictable; that is, over evolutionary time, the mild conditions of the summer and early fall have always been followed by harsh winter months. Therefore, many animals living in highly seasonal environments have evolved a series of adaptations that aid in successful overwinter survival and serve to increase the chances for successful reproduction. Key among these adaptations is seasonal breeding. Reproduction is among the most energetically expensive processes in the lives of wild animals. For instance, many male mammals compete for access to reproductively mature females which requires the maintenance of fully functioning reproductive systems and sexually attractive traits and, in some species, the acquisition and defense of a territory. For females, pregnancy and especially lactation are enormously expensive activities that consume large amounts of energy. Further, young animals are much less likely to survive when born during the winter when the energetic budget of their parents (on whom most mammalian young are completely reliant) is already strained. These two factors, the energetic requirements of breeding and the reduced odds of survival of those offspring born during the winter, has strongly favored animals that time breeding to the times of the year when it is most likely to be successful.

In general, animals with short gestation periods such as small mammals breed during the early spring and summer so that their young will be born to coincide with the mild summer conditions. In contrast, many large, long-lived animals with extended gestational periods breed during the fall and gestate over the winter, and the young are born in the spring. As a general rule, natural selection has favored timing the birth and hatching of young, rather than mating per se, to the spring and early summer. The other components of breeding, including courtship, copulation, parental care, and territorial defense, are also timed to the appropriate part of the year. This is possibly the reason why strong seasonality has not evolved in humans; gestation and lactation in most human societies span multiple years, and, as such, there is not a specific time of year when it is universally advantageous for all human populations to breed. However, that does not preclude the existence of some seasonality to human breeding within specific groups.

Photoperiodism: Type I

The seasonal transitions from summer to winter phenotype involve the coordination of multiple physiological systems. Many animals undergo time-consuming changes including molt to winter coats, fat deposition, cessation of reproduction, and adjustments in immune defenses. Therefore, predicting the onset of winter-like conditions before they occur is advantageous. There are two general types of seasonal rhythms. The first type of rhythm requires an environmental cue to synchronize physiological processes with the changing seasons. Animals could respond directly to changing environmental conditions such as falling temperatures by shifting into the winter phenotype. However, this strategy has not been favored by natural selection because environmental factors such as temperature are highly variable across the year and, as such, are of limited usefulness as predictive cues. Additionally, if animals waited to respond directly to changes in temperature, then there might not be sufficient time to undergo all seasonal adaptations before the harshest part of the winter. As such, natural selection has favored monitoring of an environmental factor that satisfies the requirements that other environmental variables do not. That factor is day length (photoperiod), the number of hours of light per day. This signal is virtually noise free, and with just two pieces of information, the current day length and whether the photoperiod is currently increasing or decreasing, animals are able to precisely determine the date (see Fig. 1 for day lengths across latitudes in the northern hemisphere).

Photoperiodism in Small Mammals. Much of the understanding of photoperiodic mechanisms comes from studies of hamsters, which are prototypical long day breeders. As such, a relatively thorough description of the seasonal patterns of these animals is warranted. These animals undergo marked phenotypic shifts across the year. In the winter, these animals molt to a thick winter coat (that in some cases changes colors at different times of the year), regress their reproductive tracts, and either add body mass and fat or become markedly leaner, depending on the species. Importantly, virtually all of these adaptations can be induced in a laboratory setting simply by manipulating day length. In the laboratory, reducing day length to less

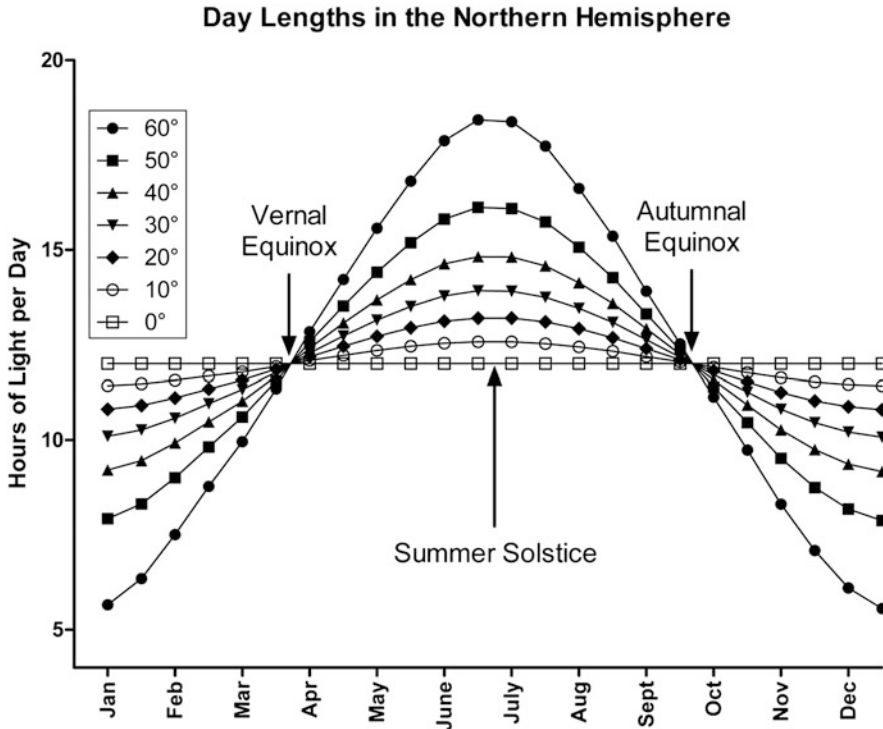


Fig. 1 Day lengths in the northern hemisphere across the year. Day lengths vary systematically across the year, and the magnitude of annual changes increases with increasing latitude

than approximately 12.5 h of light per day (short days) is sufficient to induce the winter phenotype (although this value varies across species and the latitude of origin of the population in question). The winter phenotype cannot be maintained indefinitely; however, after approximately 20–30 weeks of exposure to short day lengths, hamsters will become refractory to the inhibitory effects of short day lengths and spontaneously reactivate their reproductive systems. Even if hamsters are kept in constant darkness for the rest of their lives, they will not regress their gonads again. Prolonged exposure to long day lengths is necessary to break photorefractoriness and render animals responsive to the inhibitory effects of short day lengths again. Falling day lengths at the end of the summer induce gonadal regression but also engage an endogenous timing mechanism that reactivates the summer phenotype in the absence of photic cues. This mechanism is presumably adaptive because it allows animals to predict the next breeding season even if living underground and away from daily photic cues. Conversely, hamsters and other small mammals that depend upon this type of seasonal rhythm will maintain reproductive competence indefinitely if housed in long summer-like day lengths.

There are several complicating factors to this system. First, day length changes gradually across the year and so hamsters, like other creatures, respond to the

changing direction of the day length more than the absolute number of hours per day. This is critically important because each day length occurs twice per year, e.g., 12 h of light and 12 h of dark occur at both solstices while 14 h of light and 10 h of dark occur at both the beginning and end of the breeding season in temperate latitudes. After the summer solstice, day lengths begin to decrease. So 14 h of light per day, a photoperiod that was reproductively stimulatory in the spring, is now interpreted as inhibitory because day lengths are decreasing.

In virtually all photoperiodic populations, some percentage of individuals will fail to regress their gonads in response to short day lengths. Individuals that exhibit this strategy are termed photoperiodic nonresponders. This strategy presumably evolved in order to allow for nonresponsive individuals to breed in a mild winter. However, this strategy is presumably costly during more severe winters, thus maintaining this population as a relatively small percentage of individuals. The proportion of a population that exhibits a nonresponsive phenotype increases in lower latitudes.

The mechanisms that underlie photoperiodic nonresponsiveness differ across species but typically involve either a failure to entrain to inhibitory day lengths or insensitivity to pineal melatonin rhythms. This phenotype appears to be subject to selection pressure as photoperiod nonresponsiveness can be artificially selected in the laboratory. Within four generations, a line of Siberian hamsters selected for nonresponsiveness consisted of more than 90% of individuals that failed to respond to short day lengths.

Photoperiodism in Birds. The mechanisms of photic entrainment of seasonal rhythms in birds are very similar to mammals with one important difference. Like small mammals, temperate zone birds breed in the spring and early summer. However, one prominent difference is that although long day lengths are necessary for breeding, birds maintained in long days will become photorefractory and regress their reproductive system. Prolonged exposure to short day lengths is necessary to restore sensitivity to the stimulatory effects of long day lengths. Just as in small photoperiodic mammals, this type of rhythm is a combination of an exogenous rhythm that interacts with an endogenous interval timer that controls photorefractoriness.

Photoperiodism in Amphibians and Reptiles. The taxa that contain reptiles and amphibians contain thousands of different species that exhibit differential photoperiodic regulation of reproduction and other physiological systems. Although many of the seasonal mechanisms are similar to other vertebrates, many reptiles and amphibians are differentially reliant on other nonphotoperiodic cues compared to other vertebrates. In particular, for many species, day length is only one of the cues that also include temperature and rainfall that control the timing of reproduction. Importantly, photoperiod information interacts with environmental conditions to determine the timing of various physiological processes rather than either type of cue being dominant at all times of the year.

One fascinating type of seasonal rhythm that is fairly rare across vertebrate taxa is a so-called dissociated reproductive pattern. Animals that exhibit this type of rhythm use day length cues to time spermatogenesis, steroidogenesis, and mating behavior. However, these events do not occur at the same time! Rather, the production of androgens and sperm occurs approximately 6 months before mating, and the sperm

are stored in specialized organs until the breeding season. Red-sided garter snakes (*Thamnophis sirtalis*) turn on their reproductive systems following the breeding season and do not mate until the following summer. The mating behavior at that point is independent of circulating androgens. Importantly, both photoperiodic time measurement and pineal melatonin appear to be involved in coordinating reproductive behavior and the subsequent spermatogenesis.

Photoperiodism in Short Day Breeders. The photoperiodic responses of short day breeders such as sheep have been extensively studied because of the important agricultural contributions of these animals. Short day breeders are reproductively stimulated by falling day lengths and regress their gonads in response to increasing or static long photoperiods. However, at least ewes (female sheep) become refractory to both the stimulatory effects of short days and the inhibitory effects of long days and require the opposite photoperiod to restore sensitivity. Other short day breeders simply require exposure to short day lengths to break photorefractoriness to the inhibitory effects of long days.

Circannual Rhythms: Type II

The second general class of seasonal rhythms is circannual rhythms. Circannual rhythms are endogenous clocks that have a period of approximately 365 days and can persist in the absence of environmental signals. However, photoperiodic information can entrain circannual rhythms to exactly 365 days. For instance, golden-mantled ground squirrels exhibit circannual rhythms in body mass even when housed in a constant unchanging photoperiod although the period is shorter than 12 months. However, if housed in a simulated natural photoperiod (laboratory lighting that tracks day-to-day changes in photoperiod at a given latitude), the period of body mass rhythms is close to 365 days.

Neuroendocrine Transduction of Seasonal Time

Photoperiodic mammals transduce day length from an environmental signal into a physiological one by secreting the hormone melatonin from the pineal gland during the dark. In this manner, central and peripheral tissues can attend to day length (by physiologically monitoring night length) by monitoring the duration of the daily elevation in melatonin. Increased duration of melatonin secretion in short day lengths is found in virtually all vertebrates studied. Lengthened melatonin rhythms occur in both long and short day breeders, nocturnal and diurnal animals, and animals that breed opportunistically (i.e., not on a strictly seasonal basis).

The production of melatonin is under the control of circadian rhythms produced by the primary circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus. As this rhythm is controlled endogenously, it will persist under conditions of constant darkness. This clock is entrained by photic information sent along a multi-synaptic pathway originating in noncone/nonrod photoreceptors in the retina. These

photoreceptors contain the photopigment melanopsin and give rise to the retinohypothalamic tract that sends direct projections to the SCN. From the SCN, this photic information is relayed synaptically to the periventricular nucleus of the hypothalamus, down to the intermediolateral cell column in the spinal cord, and then innervates the pineal gland via a sympathetic synapse in the superior cervical ganglion. Alpha and beta adrenergic receptors in the pineal gland activate the production and release of the indoleamine hormone melatonin. Melatonin is produced in a two-step enzymatic process from the neurotransmitter serotonin (see Fig. 2).

Virtually all of the seasonal adaptations associated with day length are mediated by melatonin. This was first suspected in the mid-1960s when it was reported that removal of the pineal gland blocked the induction of the short day phenotype. Later, when melatonin was isolated and synthesized, it was demonstrated that administration of exogenous melatonin (see below for details) is sufficient to induce gonadal regression in long days.

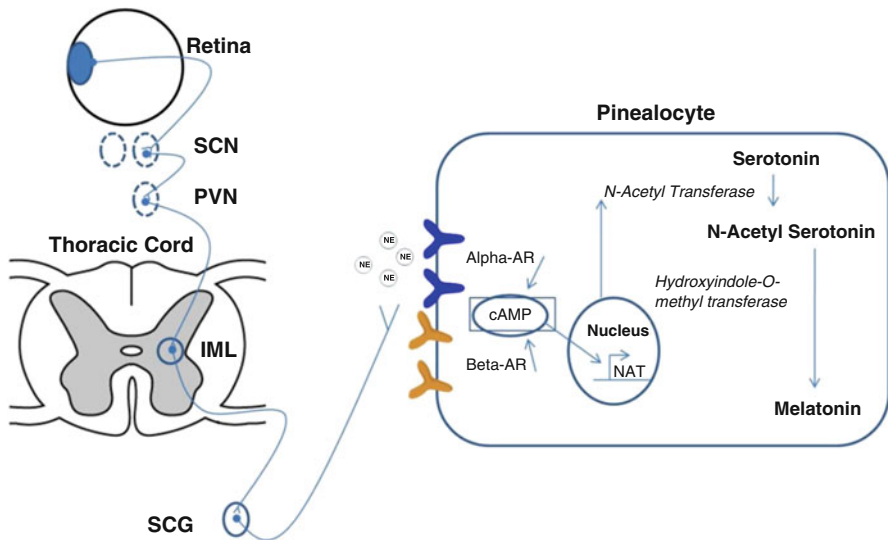


Fig. 2 Anatomical pathway responsible for transducing light into a biochemical signal. Light interacts with nonrod, noncone (melanopsin-containing retinal ganglion cells) photoreceptors in the eye. These cells give rise to the retinohypothalamic tract that sends projections to the master biological clock in the suprachiasmatic nucleus (SCN); the SCN sends projections to the periventricular nucleus of the hypothalamus (PVN) which, in turn, innervates cells in the intermediolateral cell column of the spinal cord (IML). These sympathetic neurons in the spinal cord send cholinergic projections to the superior cervical ganglion (SCG) in the autonomic chain which, in turn, send adrenergic projections to the pineal gland. Alpha and beta adrenergic receptor activation causes increases in cyclic adenosine monophosphate (cAMP) that in turn increases gene expression of the *N*-acetyl transferase enzyme (NAT). NAT activity is the rate limiting step responsible for the conversion of serotonin into melatonin. This entire system is inhibited by light and becomes active in the dark. In this manner, melatonin secretion serves as a systemic proxy for darkness

The key component of most (but certainly not all) neuroendocrine signal transduction systems is the concentration of the hormone that reaches target tissues.

Within a certain physiological range, a greater amount of insulin secreted by the pancreas or testosterone from the testes will lower blood sugar and promote muscle growth respectively. Melatonin is different because it is not the amplitude of melatonin concentrations in the blood that is the key feature of the biological signal, but rather the duration during which melatonin concentration in the blood is elevated that provides the key information to target tissues. Long-duration melatonin signals induce gonadal regression in rodents and other long day breeders. In pineal intact long day breeding animals housed in long day lengths, an infusion of melatonin approximately 4 h before lights out will induce gonadal regression. The melatonin target tissues interpret this signal as a long duration melatonin signal because the initial elevation (from the infusion) occurs early in the day and then the pineal begins producing its own melatonin as the lights go out. These signals summate into a long duration signal. Although there is some controversy about this issue, the general consensus is that a long duration of melatonin elevation regardless of the time of day at which it is introduced will induce the short day phenotype.

Again, specific day lengths can be either stimulatory or inhibitory to the reproductive system, depending on whether the duration of day length is increasing or decreasing. There is a similar phenomenon reflected in the duration of the melatonin rhythm that is required to induce gonadal regression. Seven-hour long melatonin infusions cause gonadal growth in hamsters that were housed in short day lengths, but cause gonadal regression in hamsters that were previously housed in long days. There is also some evidence that duration of the endogenous melatonin rhythm is altered by previous photoperiod exposure.

As described earlier, after prolonged exposure to a specific day length, individuals of some species will become refractory to further light treatments and revert to the opposite reproductive state. Hamsters exposed to short day lengths eventually regrow their testes and will not respond to an additional short day signal until exposed to long days for an extended period. Photorefractoriness is paralleled by refractoriness to the inhibitory effects of melatonin, and further, pineal melatonin rhythms do not change markedly in photorefractory animals. Instead most target tissues become unresponsive to melatonin signaling. If hamsters, housed in long days, are injected daily with melatonin in a pattern that mimics short day lengths, then they will first regress their gonads and eventually redevelop them without any change in the melatonin signal. Additionally, some aspects of immune function that are typically enhanced by melatonin are no longer affected by exogenous melatonin in photorefractory animals.

Melatonin signals via two (or three in some species) high-affinity G-protein-coupled receptors termed MT1 and MT2. MT1 is sufficient to mediate all of the photoperiodic responses to melatonin in hamsters, and the specific role of MT2 in photoperiodic signal transduction remains unclear. The site of action of melatonin in the brain has been mapped out using I^{125} -melatonin autoradiography. The nuclei that bind melatonin vary markedly across species but include the SCN, periventricular thalamus (PVT), and reuniens nucleus (NRe) of the thalamus. All species studied

thus far exhibit I¹²⁵-melatonin binding in the pars tuberalis of the pituitary gland, and this probably contributes to photoperiodic control of prolactin secretion.

Melatonin appears to affect a distributed neuronal system to control different aspects of the seasonal phenotype. Importantly, the effects of melatonin on reproduction appear to be mediated by the nervous system as there is little evidence for direct melatonin action on the gonads, and, in some cases, implanting melatonin directly into the brain (and therefore presumably not able to reach the gonads) is sufficient to induce gonadal regression. In some, but not all rodent species, lesions of the mediobasal hypothalamus and SCN block the inhibitory effects of long-duration melatonin on gonadal regression.

Local melatonin implants into the SCN, NRe, and PVT induce gonadal regression in hamsters and other photoperiodic animals. Long-term administration of melatonin induced refractoriness, but only in the specific brain nuclei that were infused. The other nuclei retained responsiveness to melatonin, indicating the refractoriness occurs independently at multiple brain sites. This phenomenon can be used to determine the role of individual brain nuclei in the regulation of seasonal phenotypes. Hamsters can be exposed to short day lengths and then implanted with melatonin into a specific nucleus. Hamsters can then be exposed to long days, but the nucleus retaining melatonin implants would remain refractory. Obscuring melatonin signaling in the NRe interfered with long day-induced gonadal regrowth, whereas implants into the SCN and NRe blocked the ability of the photoperiodic signal to determine the direction of change in day length.

Regulation of Reproductive Systems

Short photoperiods markedly suppressed function of the hypothalamic-pituitary-gonadal axis, resulting in marked regression of reproductive tissues in both sexes. In long days, the negative feedback system maintains circulating androgens at concentrations sufficient to maintain spermatogenesis, function of the accessory reproductive organs, and sex behavior. However, in short days, negative feedback regulation of hypothalamic gonadotrophin releasing hormone (GnRH) and pituitary gonadotropin secretion by steroid hormones is markedly enhanced. Following castration, gonadotropins are freed from negative feedback by gonadal steroids and rapidly rise; administration of low doses of testosterone inhibits gonadotropin, and this occurs to a greater extent in short day lengths.

Recently, two new peptides have been identified that are capable of directly modulating the activity of GnRH neurons. Kisspeptin is a peptide that is expressed in the arcuate and anteroventral periventricular nuclei (AVPV) of the hypothalamus and is a potent activator of GnRH production and release. Siberian hamsters housed in short day lengths have reduced immunoreactive kisspeptin neurons in the AVPV. This effect is both androgen dependent and independent as the reduction in kisspeptin neurons could be induced by both castration and exposure to short day lengths. Testosterone replacement in short day lengths only partially restored kisspeptin cell numbers to the long day levels. Kisspeptin activated GnRH neurons

(as measured indirectly by assessing pituitary gonadotrophin release) even in short day hamsters. It is not clear at this time whether kisspeptin neurons are directly responsive to melatonin signaling or some other downstream signal. It seems plausible that photoperiod and melatonin regulate GnRH by modulating the activity of kisspeptin neurons.

An additional related peptide called gonadotropin inhibitory hormone (GnIH) has also been identified. This peptide is located in the dorsomedial hypothalamus in mammals and projects to GnRH neurons in the preoptic area. In ewes, there are fewer numbers of GnIH immunoreactive cells and fewer overall GnIH synapses onto GnRH neurons during the breeding season. However, the number of GnIH cells and synapses increases following prolonged exposure to suppressive photoperiods. Curiously, Siberian hamsters exposed to short day lengths exhibit *fewer* GnIH-positive neurons and GnIH gene expression. Further research is necessary to determine the role of this peptide in small mammal seasonal breeding.

Another neuroendocrine system that is involved in the regulation of reproduction is the hypothalamic-pituitary-thyroid axis. Thyroid hormones have complicated concentration-dependent interactions with the reproductive system. However, in general, thyroid hormones enhance reproductive function, and removal of thyroid hormone signaling suppresses reproduction. Systemic administration of exogenous T3 (bioactive thyroid hormone) can induce gonadal regrowth in short day animals. Additionally, regulation of thyroid hormone-converting enzymes in the nervous systems appears to be part of the endogenous regulation of reproduction. Exposure to inhibitory photoperiods increases expression of the type 3 iodothyronine deiodinase (DIO3), the primary enzyme responsible for inactivating thyroid hormones, in the mediobasal hypothalamus. At the same time, DIO2 expression is reduced, leading to an overall decrease in bioavailable thyroid hormone in the hypothalamus. These effects are reversed by exposure to a stimulatory photoperiod. Melatonin directly activates DIO3 gene expression while inhibiting DIO2. Additionally, day length regulates the expression of thyrotropin genes in the pituitary pars tuberalis. Finally, thyroid binding hormones are reduced in hamsters refractory to short day lengths, suggesting that increased thyroid hormone signaling is involved in return to reproductive competence.

Additionally, there is no evidence from mammalian systems that short day lengths reduce the sensitivity of the pituitary gland to GnRH. In any case, prolonged exposure to short day lengths causes the circulating concentrations of sex steroid hormones and pituitary gonadotrophins to decline markedly. In fact, in many species, sex steroid hormones are undetectable in short days. The reduction in gonadotrophins and sex steroid hormones leads to the collapse of steroid-dependent tissues in the reproductive tract including the uterine horns in females and the seminal vesicles in males and the cessation of spermatogenesis.

In addition to the collapse of the anatomical components of the reproductive tract, mating behavior also ceases in short days via both steroid-dependent and steroid-independent mechanisms. Castrated male hamsters bearing a testosterone replacement capsule mated less frequently when housed in short day lengths than in long days. Female hamsters gradually become anovulatory after exposure to short day

lengths. Additionally, female hamsters over time fail to exhibit the lordosis reflex (female mating posture that is necessary for copulation), and this effect is very likely to be mediated by a reduction in estrogen production as activation of estrogen receptors is necessary for the expression of lordosis. However, short days inhibit exogenous estrogen-mediated expression of lordosis in response to male stimuli. These data suggest that in addition to reducing steroid hormone concentrations, exposure to short day lengths reduces sensitivity of the neural substrates that mediate mating behavior to the activational effects of steroid hormones.

Photoperiodic Regulation of Metabolism

Changes in metabolic function, adiposity, and food intake are among the most common adaptations to the changing seasons, and particularly so in small animals. There are two general strategies for altering metabolic function across the year. Some animals, such as Syrian hamsters, gain body mass and increase adiposity prior to the winter. This allows for increased stored energy that can be utilized over the winter when food is scarce. Additionally, there are thermoregulatory advantages to this approach as added fat deposition can serve as insulation and produces an overall decrease in surface area:mass ratio that reduces heat loss. Alternatively, other species such as Siberian hamsters take the opposite approach. These animals become markedly leaner in anticipation of the winter, lose adiposity, and decrease food intake and apparently make up the difference energetically by running their metabolic systems at much lower rates.

A significant portion of the changes in body mass can be recapitulated by manipulating gonadal steroids. For instance, species that lose weight in short days including Siberian hamsters, deer mice, and meadow voles also lose weight when gonadectomized. Conversely, gonadectomy increases body mass in species that typically gain weight upon exposure to short day lengths such as Syrian hamsters or collared lemmings. Importantly, following a return to long days or the onset of spontaneous recrudescence, most animals revert to the long day condition.

Although gonadal steroids are important mediators of photoperiodic changes in body mass, they are only part of the story. Insulin is notable in that it is the only hormone that *reduces* blood glucose concentrations and it is a critical hormone both centrally and peripherally that coordinates feeding, metabolic processes, and energy storage. In general, circulating insulin adjustments in photoperiodic rodents track the direction of weight change following exposure to short day lengths. That is, Siberian hamsters that reduce body mass in short day lengths also exhibit reduced circulating insulin concentrations while Syrian hamsters increase both body mass and insulin following transfer to short day lengths. However, Siberian hamsters rendered diabetic (by killing pancreatic beta cells with the drug streptozotocin) still reduced body mass when transferred to short day lengths, suggesting that insulin is not necessary for the short day-induced reduction in body mass.

The adipose tissue-derived hormone leptin, on the other hand, appears to be a central player in photoperiodic body mass adjustments. Leptin was originally

identified as the protein product of the *obese (ob)* gene. This hormone is produced almost exclusively by adipose tissue, and concentrations of leptin are highly correlated with overall body fat. Circulating leptin tracks the body mass dynamics of Siberian hamsters across their seasonal cycles. Additionally, leptin and leptin receptor gene expression are reduced in short day Siberian hamsters coincident with their reduced body mass. These data indicate that hamsters both produce less and are less sensitive to leptin in short day lengths. Importantly, in most species, falling leptin concentrations are associated with increased food intake (i.e., low concentrations of leptin usually signal starvation conditions and therefore promote increased food intake), but in Siberian hamsters, lower leptin signaling is associated with reduced food intake in short day lengths, suggesting that short photoperiod establishes a new lower body mass set point.

In addition to hormonal regulation of body mass, there is evidence that the CNS directly alters adiposity. Adipose tissue is richly innervated by the sympathetic nervous system as well as sensory nerves. Denervating fat tissue blocks short day-induced fat loss in Siberian hamsters. Multisynaptic tract tracing experiments indicate that melatonin receptors are present in the cells that control sympathetic output from the CNS. If a single fat depot is removed from a Siberian hamster, the other remaining depots grow to replace the lost adipose tissue. Additionally, the compensatory growth in fat depots can also be induced by removing the sensory innervation to a specific fat pad, indicating that the brain is actively and directly monitoring adiposity.

Seasonal Rhythms of Behavior

In addition to the physiological adjustments to the changing seasons, there are several behavioral adjustments that also serve to enhance winter survival. Three broad classes of behavior including affective (mood related), aggression/territoriality, and learning and memory are discussed below that are likely to have broad importance for animals living in highly seasonal environments.

Affective Behaviors. The study of affective-like behaviors in seasonal animals has been motivated by two general observations. First, a subset of individuals suffering from depression exhibit worse symptoms during the short days of winter (a condition called seasonal affective disorder). Secondly, many of the features of depression that humans consider aversive could potentially have some survival benefit to animals living in harsh environments during the winter. Prominent among the symptoms of major depressive disorder are lethargy, loss of interest in social interactions, fearfulness, and reduced appetite, all changes that might serve to conserve energy in the winter. Taken together, these observations suggest that depression may have an evolutionary origin and that photoperiodic animals could serve as models of seasonal affective disorder.

Siberian hamsters housed in short day lengths from weaning (approximately 21 days of age) markedly increase in anxiety- and depressive-like responses compared to those housed in long days. Specifically, these hamsters spent less time

exploring the anxiety-provoking open areas of elevated plus maze and open field tasks and exhibited much more immobility in the Porsolt forced swim task, which is generally agreed as representing a depressive behavioral response. Hamsters housed in short day lengths perinatally (before birth and until weaning) increased depressive- and anxiety-like responses even when housed in long days after weaning. Apparently, photoperiod early in life has a persistent effect on affective behaviors even when hamsters are later transferred to the opposite photoperiod. The hippocampus is one region strongly associated with depression, and chronic stressors that induce behavioral indications of depression also cause atrophy of the large neurons in the hippocampus (reduced dendritic branching and fewer dendritic spines). Siberian hamsters housed in short day lengths exhibited a similar atrophy of hippocampal dendrites and a reduction in spine density that correlated strongly with depressive-like behaviors.

Aggressive Behavior. The changing seasons are associated with markedly different social structures in some species, and this is associated with changing behavioral priorities. For instance, a particularly illustrative example is the red deer (*Cervus elaphus*) that live on the Isle of Rum off the coast of Scotland. The males of this species spend most of the year in bachelor herds and are highly tolerant of other males. However, in the late summer (these animals are short day breeders), they grow hard bony antlers and stake out and defend breeding territories into the early fall. The aggressive behavior among the red deer is fierce during this period, and by some estimations, nearly a quarter of the males are seriously injured. The stakes are high, however, as the males that control the best rutting areas are the ones most likely to gain reproductive access to multiple females. After the rutting season ends, the males' horns degenerate (due to withdrawal of the blood supply to the tissue) and they revert to their peaceful coexistence. If the deer are castrated (removing the source of testosterone), then they will quickly lose their social status and their horns! Conversely, implanting testosterone capsules into deer prevents the reduction in aggressive behavior and the loss of their horns after the rutting season. Testosterone-implanted deer therefore exhibited aggressive behavior toward other males at a socially inappropriate time of the year. Importantly, despite bearing testosterone capsules, male deer never attempted to mate with the females at any time of the year except during the normal breeding season, indicating that hormones interact with day length to control behavior and physiology.

The overall impression of seasonal changes in aggressive behavior has been tied up with the idea that androgens increase both sexual and aggressive behaviors during the breeding season. There are certainly examples of this relationship. Many bird species display aggressive behaviors during the breeding seasons that can be prevented by castration. Additionally, many small mammals live in multispecies burrows during the nonbreeding season in order to conserve energy and heat. Presumably, reduced circulating testosterone is necessary to permit this peaceful cohabitation. However, there is simply not a universal relationship between androgens and aggressive behavior. The reality is quite a bit more complex and varies across species and the specific type of aggression under investigation. There are some species, such as wood rats, that exhibit seasonal changes in aggressive

behavior that are apparently androgen independent as castration fails to alter aggressive behavior during or after the breeding season.

Rodents such as hamsters and deer mice display *increased* aggressive behavior when housed in short day lengths when their gonads were regressed and thus produce markedly low circulating androgen concentrations. Elevated short day aggressive behavior has been examined closely in Siberian hamsters and beach mice, and this chapter will cover photoperiodic adjustments in aggressive behaviors in those two species closely.

As mentioned above, short day lengths increase aggressive behavior in Siberian hamsters. This effect on aggression can be recapitulated by short term (10 days) melatonin injections that lengthen the overall rhythm. However, this short period of exogenous melatonin treatment is not sufficient to reduce body mass or circulating testosterone concentrations, indicating that this effect is at least partially testosterone independent. Further evidence for a limited role for androgens in hamster seasonal aggression is that testosterone implants into short day hamsters actually reduced aggressive behavior relative to blank implants. Another possible source of endocrine mediation of the aggressive behavior is the adrenal gland. Bilateral adrenalectomy prevents the melatonin-induced aggressive behavior in Siberian hamsters. Importantly, removal of only the adrenal medulla (source of catecholamines) had no effect on melatonin-induced aggression, meaning that the adrenal cortex (steroidogenic component of the adrenal gland) was necessary for melatonin-induced aggressive behavior. Although the specific steroid that mediates melatonin-induced aggressive behaviors remains to be identified, most of the focus has been on the adrenal androgen DHEA (dehydroepiandrosterone). There is evidence from avian studies that DHEA promotes aggression during the nonbreeding season and exogenous melatonin can increase DHEA production in cultured mouse adrenal glands.

Part of the inconsistency regarding the testosterone-aggression relationship is that testosterone is actually a rather weak androgen but serves largely as a prohormone. Specifically, testosterone is enzymatically converted either into the potent androgen dihydrotestosterone (DHT) and the estrogen 17-beta-estradiol. Therefore, changes in circulating androgens can have distinct effects on two different steroid receptor systems. Aggressive behavior in male California mice housed in long day lengths correlates strongly and negatively with aromatase activity (the enzyme that converts testosterone into estradiol) in the bed nucleus of the stria terminalis. Along similar lines, administration of exogenous estrogen to male beach mice reduces aggressive behavior in long days but increases aggression in short photoperiods. The divergent effects of exogenous estrogens appear to be mediated by different mechanisms. Gene array analysis suggests that more estrogen-responsive genes were upregulated in long day animals relative to those housed in short day lengths, indicating genomic effects of estrogen in long day lengths. On the other hand, exogenous estradiol rapidly (within 15 min) increased aggressive behaviors in short, but not long, day lengths. This rapid time scale is not consistent with a genomic route of signaling as steroid-induced gene expression requires considerably more time to affect behavior. Rather, a rapid nongenomic mechanism seems to mediate the estrogen-induced aggressive behavior in short day lengths.

Photoperiodic Regulation of Neuronal Morphology, Learning, and Memory. The study of seasonal rhythms in brain morphology has been derived largely from two seasonally occurring phenomena, bird song and food caching behavior. Bird song is a rich experimental topic that is beyond the scope of this chapter but will be briefly discussed here. Song birds typically sing prior to and during the breeding season but not at other times of the year. In general, males sing more than females (to attract potential mates and ward off potential competitors), although there are a few species where females also sing. Importantly, the regulation of the seasonality of bird song appears to be regulated by day length and androgens. When birds are reproductively stimulated and their gonads produce androgens, the formerly quiescent vocal circuit in the brain becomes active and birds begin to sing. This activation of song control nuclei involves synaptic plasticity, the birth of new neurons and glia, and noticeable increases in the size of song control nuclei. The volume of two song control nuclei called the higher vocal center and robust nucleus of the archistriatum increase by 99% and 77%, respectively, when canaries are housed in long day lengths.

Similarly, food caching animals (a behavioral pattern common in squirrels and some bird species) hide stores of nuts and other nutrients such that these items can be retrieved during the winter when food is comparatively scarce. The hippocampus is a brain region necessary for spatial learning and memory and thus is certainly involved in seasonal food caching behavior.

Implicit in studies of seasonal regulation of cognitive behavior is that the brain is a disproportionately expensive organ to maintain energetically. In humans, for instance, the brain weighs only around 4% of total body mass but consumes around 25% of the total energetic budget. Therefore, even small reductions in brain size, synaptic connectivity, or cell number could result in marked energetic savings.

Wild-caught mammals including several species of rodents and shrews caught in the winter had smaller overall brain sizes compared to animals caught in the summer. Additionally, the brain did not decrease proportionately, but rather, several regions including the neocortex and hippocampus were smaller both in absolute and relative terms during the winter. Until recently, there has been comparatively little research into seasonal differences in learning and memory performance. White-footed mice housed in short day lengths, in the laboratory, decreased performance in a spatial learning and memory task and reduced overall brain size and reduced hippocampal size. Additionally, short day lengths reduced the complexity of apical dendritic trees in the CA1 region of the hippocampus and increased basilar dendritic spine density in the CA3 region.

Seasonality of Human Reproduction. As mentioned above, humans are not strongly responsive to photoperiod. This probably represents the comparatively long period of gestation and lactation that makes no particular season advantageous for mating. However, in some high-latitude communities in the northern hemisphere, there is a seasonal increase in the number of conceptions around the vernal equinox. Importantly, this pattern is 6 months out of phase in the southern hemisphere. It is very difficult to determine the role of circannual or photoperiodic rhythms in

producing these comparatively tiny patterns of seasonal births, and other societal or environmental conditions may have larger modulatory effects.

Climate Change and Seasonality

Our planet's surface temperature is rising while annual precipitation patterns across Earth are changing. There is broad agreement that anthropogenic activities are driving these climate changes. Climate change has resulted in global variations in the onset of seasons, delaying winter and advancing spring. As noted, production of offspring is timed to coincide with optimal food availability; thus, individuals of many species display annual rhythms of reproductive function driven by photoperiod. Over evolutionary time, there has been precise fine-tuning of critical photoperiod and onset/offset of seasonal adaptations. Climate change has provoked changes in the availability of insects and plants which shifts the timing of optimal reproduction. However, day lengths remain the same and adaptations to the stable photoperiod may be insufficiently plastic to allow a shift in the seasonal timing of bird and mammal breeding. Coupled with the effects of light pollution at night which prevents these species from accurately determining day length, climate change presents extreme evolutionary pressure that can result in severely negative consequences for individual reproduction and survival.

Outlook

There is much known about the physiological mediators *and* consequences of seasonal time measurement. However, most of that research has been conducted on a relatively small number of photoperiodic and seasonally breeding animals. Further, many of the advancements in molecular biology that have revolutionized behavioral biology are not available for use in nontraditional laboratory species such as hamsters and lemmings. There is still much to learn about the molecular details of both circannual and photoperiodic rhythms, and these studies should be conducted across many species if we are to understand how natural selection has shaped these phenomena.

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