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Influence of Photoperiod on Hormones, Behavior, and Immune Function

James C. Walton[*], **Zachary M. Weil**, and **Randy J. Nelson**
Department of Neuroscience, The Ohio State University Medical Center, Columbus, OH 43210 USA

Abstract

Photoperiodism is the ability of plants and animals to measure environmental day length to ascertain time of year. Central to the evolution of photoperiodism in animals is the adaptive distribution of energetically challenging activities across the year to optimize reproductive fitness while balancing the energetic tradeoffs necessary for seasonally- appropriate survival strategies. The ability to accurately predict future events requires endogenous mechanisms to permit physiological anticipation of annual conditions. Day length provides a virtually noise free environmental signal to monitor and accurately predict time of the year. In mammals, melatonin provides the hormonal signal transducing day length. Duration of pineal melatonin is inversely related to day length and its secretion drives enduring changes in many physiological systems, including the HPA, HPG, and brain-gut axes, the autonomic nervous system, and the immune system. Thus, melatonin is the fulcrum mediating redistribution of energetic investment among physiological processes to maximize fitness and survival.

Keywords

Photoperiod; melatonin; immune; plasticity; seasonality; annual cycles; tradeoffs; life history strategy

1. Introduction

In order to be successful, individuals must grow, survive, and reproduce. Fitness is determined by how many offspring survive and ultimately produce offspring that themselves survive and reproduce. Investing in survival mechanisms depletes resources necessary for reproduction. Conversely, reproduction requires significant resources that may compromise survival. Thus, fitness reflects successful trade-offs between investments in the mechanisms underlying survival and reproduction that reflect life history strategies [291]. Natural selection has produced exquisite adaptations that have allowed individuals to successfully survive and reproduce in remarkably specific niches. Outside of the tropics, individuals have been selected to adapt to temporal niches, as well as spatial niches, because the yearly orbit of the Earth around the Sun drives seasonal variation in several environmental factors that affect temperature, weather, and food availability.

[*]To whom correspondence should be addressed. walton.315@osu.edu.

Habitats may vary substantially from winter to summer and in some cases distinctive sets of adaptations have evolved to cope with the often unique demands of winter and summer on survival and reproduction. For example, the winter set of adaptations may include a shift of energy allocations from non-essential functions such as growth and reproduction to those functions that are critical for immediate survival [82]. When the odds of successful reproduction are low, resources are shunted from reproduction and growth into survival mechanisms such as immune function, thermoregulation, or cellular maintenance. Consequently, over evolutionary time, seasonal patterns in the expression of adaptations have emerged that allow redistribution of energy resources to mediate trade-offs between traits such as immune function and reproductive effort [219]. During the fall and winter, the dual challenges of limited food availability with the need for additional energy to support thermogenesis make reproductive efforts unlikely to be successful, especially among small vertebrate animals; thus, these animals often reduce the size and function of their reproductive system [220]. In addition to reproduction, small nontropical vertebrates also display seasonal adjustments in body mass, adiposity, foraging, gut efficiency, pelage, sleep, growth, immune function, as well as cognitive and affective responses (reviewed in [253]). Because these seasonal adaptations often require significant time to develop, individuals rely upon an environmental signal to alter gene expression in order to produce the suite of season-specific adaptations.

Photoperiodism is the ability of plants and animals to measure environmental day length (photoperiod), a process that underlies the so-called biological calendar [225]. The biological ability to measure day length permits organisms to ascertain the time of year and engage in seasonally appropriate adaptations. Although the specific mechanisms that underlie the ability to measure day length differ among taxa, individuals that respond to day length can precisely, and reliably, ascertain the time of year with just two bits of data: (1) the length of the daily photoperiod, and (2) whether day lengths are increasing or decreasing. For individuals of many species, the annual cycle of changing photoperiod provides the environmental switch between seasonal phenotypes. Changes in day length, while probably of little direct importance to most animals, provide the most error-free indication of time of year, and thus enable individuals to anticipate seasonal conditions. Because the same photoperiod occurs twice a year (e.g., 21 March and 21 September), animals must be able to discriminate between these two dates; many photoperiodic vertebrates have solved this problem by developing an annual alteration between two physiological states (reviewed in [253]). Obviously, the environmental switch that controls the phenotypic trajectory is important in teasing out the interaction between environment and genes which drives phenotype.

The goal of this review is to focus on the influence of photoperiod on phenotype, the distribution of energetically expensive processes across the year to maximize survival and fitness, and the enduring effects of early life photoperiod on adult phenotype. Phenotype is the result of the interactions between genes and environment. In the wild, day length often determines the phenotype of newborn small vertebrates [46,99,129]. In mammals, photoperiodic information can even be passed to developing fetuses *in utero* so that the summer or winter phenotype can begin to develop prior to birth [323]. Thus, photoperiodic rodents born in the spring will grow to adult size, undergo puberty, and become reproductive in 6-8 weeks, whereas a sibling born in the autumn will not grow or undergo puberty for 4-5 months [108,144]. Day length can be used in the laboratory as a precise environmental factor to probe gene expression during phenotypic development.

2. The pineal gland, melatonin, and photoperiod

To understand photoperiodism, it is important to understand how animals keep time physiologically. The pineal gland, and its hormone melatonin, mediates photoperiodic time measurement in mammals [136,195]. Pinealectomy blocks responsiveness to photoperiod in every mammalian species studied [138]. Information about environmental light arrives to the brain via the lateral eyes in mammals [228]. A nonvisual neuronal pathway, the retinohypothalamic tract, carries light information from melanopsin expressing retinal ganglion cells directly to the suprachiasmatic nuclei (SCN) of the hypothalamus [55,187,284]. The SCN are the primary mammalian biological clocks [275]. From the SCN, the main pathway for photoperiod information to the pineal gland is relayed through the paraventricular nucleus of the hypothalamus, leaving the brain through the intermediolateral cells of the upper spinal cord, and then through the superior cervical ganglion. Postganglionic noradrenergic fibers project back into the brain and innervate the pineal gland, where neural information is transduced into a hormonal message [60,100]. Melatonin, an indole amine hormone secreted rhythmically by the pineal [9], can induce photoperiodic responses when exogenously administered in a number of ways [20,116,284] (Figure 1). Particular aspects of the responses observed following constant release implants, daily injections, or daily infusions of melatonin led to some early controversy regarding the significance of various temporal characteristics of melatonin secretion. Melatonin is normally secreted in a circadian fashion, with an extended peak occurring at night, and basal secretion during the day [9]. The duration of this nocturnal ‘peak’ varies inversely with day length in several species, including humans. Results obtained in sheep and in Siberian hamsters strongly favor the overriding importance of the duration of the melatonin peak to transduce photoperiodic information. When pinealectomized hamsters or sheep were infused with melatonin on a daily basis, the types of responses elicited depended on the duration, but not on the phase, of the daily infusion [20,38,56]. Data obtained from similar studies in several other mammalian species support the conclusions that the duration of melatonin is the critical physiological parameter providing photoperiod information [13,266,272].

With the use of 2-[^{125}I]iodomelatonin, melatonin binding sites have been discovered throughout the periphery and nervous system in vertebrates [93]. Among mammals, high melatonin binding is commonly observed in the pars tuberalis (PT) of the pituitary, the suprachiasmatic nuclei (SCN) and dorsalmedial nucleus of the hypothalamus, preoptic area, and area postrema [154,210,318,348]. Lesions or pharmacological blockade of 2-[^{125}I]iodomelatonin-binding sites in the mediobasal hypothalamus blocks the inhibitory effects of endogenous and infused melatonin on gonadotropin secretion [15,199,242]. Low densities of 2-[^{125}I]iodomelatonin binding have been reported elsewhere throughout the central nervous system (CNS) and periphery [93], and are reported to have a wide range of functions (reviewed in [94], including modulation of visual function in the retina [10,91], immunomodulation [131], and cerebrovascular physiology (reviewed in [74]).

Two mammalian G protein-coupled melatonin receptors, MT_1 and MT_2, have been identified based on their affinity for 2-[^{125}I]iodomelatonin and classified via molecular cloning techniques [92,262]. Several other receptors in this family have been characterized (Mel_{1c} [97], GPR50 [263]), as well as other proteins that bind melatonin (MT_3 [231], RZR/ROR [25]). MT_1 is the dominantly expressed subtype of melatonin receptor, and targeted deletion of the MT_1 gene in *Mus* disrupts prolactin release from the PT by altering clock gene expression, implicating it in neuroendocrine regulation of reproduction (reviewed in [318]). Further evidence for MT_1 being the putative receptor for neuroendocrine photoperiodic responses comes from two photoperiodic species which do not express MT_2 receptors: Siberian hamsters [324] and sheep [238]. Thus, all photoperiodic responses in these species are mediated via the MT_1 receptor [238,242]. MT_1 activation primarily inhibits

adenylate cyclase and enhances phosholipase C activation [114], but also has other effects through various signal transduction pathways, depending on tissue (reviewed in [196,261,318]).

At the intracellular level, melatonin, via activation of cell surface G protein-coupled receptors, interacts with circadian clock genes in target tissues to transmit the circadian light signal [138,155,212,281]. Mammalian cellular circadian clocks are tightly regulated by a suite of clock genes that generate a self sustaining cycle via transcriptional feedback loops with approximately a 24 hr period. Cellular circadian rhythms are generated by a molecular pacemaker involving dimerized CLOCK-BMAL transcription factors that promote expression of period (PER) and cryptochrome (CRY) proteins, which in turn feedback to inhibit CLOCK and BMAL activity [164,295]. Melatonin influences the rhythmic expression of several clock genes [155,184], except in the SCN, where compensatory mechanisms may mask melatonin receptor signaling [281]. Onset of darkness and onset of light differentially modulate clock gene expression patterns in the PT: increasing levels of melatonin induce *Cry* expression, while decreasing levels induce *Per1* expression [184,205]; thus, the molecular circadian clock in extra-SCN tissues can entrain to the light phase of the external environment using a hormonal signal. These effects are indeed melatonin dependent, as pinealectomy or deletion of the MT_1 receptor abolishes these rhythms in the PT [204,317].

3. Photoperiod and energy balance

As noted above, individuals of several photoperiodic species undergo a suite of adaptive responses when exposed to short day lengths, putatively to allocate energy resources among energetically expensive processes to survive the harsh days of winter and to maximize fitness. Because many of these adaptations require significant time to develop, anticipating the appropriate adaptive response using photoperiodic information to alter physiology and reproductive state is critical to maximize survival (and ultimately, fitness) across seasons.

3.1. Somatic responses to photoperiod

The majority of research on somatic responses to photoperiod in mammals has been conducted in small rodents, which use different strategies in their responses to short day exposure. Although many temperate rodents regress their gonads in response to short days (see discussion below on reproductive responses to photoperiod [217]), they differ in their body mass response. Two alternate strategies are used to survive the energetic bottleneck of winter: 1) gain body mass via increased adiposity [22,54,170,214], or 2) decrease body mass via decreased adiposity and regression of other tissues [41,68,70,142,226,292,319]. Increased adiposity equates to elevated endogenous energy stores for use during times of reduced energy intake, and decreased body mass would equate to reduced energy requirement to support total body mass; both are energy conserving strategies [69].

3.1.2. Neuroendocrine mechanisms—One of the hallmarks of photoperiodic responses to short days in rodents is the reduction in circulating gonadal steroids due to the involution of the gonads (see discussion of photoperiodic effects on the HPG axis below). Although gonadectomy can recapitulate the appropriate short day responses in body mass and adiposity in many rodents that use both adaptive strategies (reviewed in [225]), further reductions in mass occur when gonadectomized animals are exposed to short days [319]. Additionally, gonadectomized animals maintained in short days will become photorefractory and return to long day body mass in the absence of gonadal steroids [143]. Thus, gonadal steroids alone are not the only factor contributing to photoperiodic mass regulation.

In many species circulating leptin, which is synthesized in white adipose tissue, correlates strongly with body fat content, suggesting that it is the signal for monitoring adiposity. Leptin binds to receptors (Ob-Rb) in the arcuate nucleus (ARC), which in turn sends projections of orexigenic peptides (neuropeptide Y (NPY), agouti-related protein (AGRP), anorexigenic peptides (pro-opiomelanocortin (POMC), and cocaine- and amphetamine-related peptide (CART) to various nuclei in the hypothalamus to control feeding behaviors potentially based on a seasonal adiposity "set-point" (reviewed in [141,211,312]). Although there are seasonal changes in leptin sensitivity [171,306], individuals are not in negative energy balance during photoperiod-mediated weight loss [1]. Precisely how the hypothalamic set point is established for satiety is unknown [21]. However, establishing the set point may involve converging input on the gut-brain axis of photoperiodic information (pineal melatonin), leptin signaling from the ARC, and ascending short-term satiety information from brainstem nuclei [140].

Within the mediobasal hypothalamus, triiodothyronine (T_3) has been implicated in regulation of food intake [166]. One of the primary loci of photoperiodic signaling of pineal melatonin to the neuroendocrine axis is in the mediobasal hypothalamus (see above). Indeed, melatonin-dependent photoperiodic variation in deiodinase expression regulates T_3 levels in the mediabasal hypothalamus [18,264,343]. Hypothalamic T_3 levels are controlled by expression levels of deiodinase II (DIO2), which converts thyroxine (T_4) into the active form of T_3, and deiodinase III (DIO3), which leads to the conversion of T_3 and T_4 into inactive forms [136]. DIO3 is upregulated in short days, whereas DIO2 is upregulated in long days, resulting in elevated hypothalamic levels of active T3 during long days (see below). The majority of research on the contribution of thyroid hormones to photoperiodism has been in regulation of reproduction (see below); thus, the role of thyroid hormones in photoperiodic regulation of body mass has not been fully investigated.

In addition to hormonal and behavioral regulation of body mass, central control over energy homeostasis and lipid mobilization is regulated by autonomic outflow. The autonomic nervous system (ANS) innervates both white adipose tissue and brown adipose tissue [19,48,139,177]. Both branches of the ANS are dynamically regulated by photoperiod [329], and the sympathetic branch of the ANS plays an important role in lipid regulation and lipid mobilization. Melatonin receptors (MT_1) are expressed in many distributed forebrain nuclei involved in sympathetic outflow, and timed infusion of melatonin into these nuclei, mimicking short day levels for 5 weeks, can elicit short day body mass responses in Siberian hamsters [177].

3.1.4. Enteric mechanisms—Photoperiodic changes in gut morphology have been observed in diverse rodent species such as prairie voles (*Microtus ochrogaster*) [126], cavies (*Microcavia australis*) [271], alpine marmots (*Marmota marmota*) [148], and deer mice (*Peromyscus maniculatus*) [122]. Short photoperiod-mediated increases of intestinal mass and surface area help maximize energy and nutrient absorption during times of low food availability [122,298]. In addition to photoperiod-mediated morphological changes to the gut, there is a growing body of evidence demonstrating coevolution of commensal gut microbiota and host (reviewed in [182]), and variations in gut microbiota composition can regulate host adiposity independent of changes in food intake [11-12,181,308]. Gut bacteria can sense, respond to, and participate in neurotransmission and neuroendocrine signaling [63,147,189-191,233]; thus it is possible that gut microbiota may interact with the neuroendocrine system to contribute to the regulation of photoperiodic body mass changes.

In Siberian hamsters, photoperiod alters gut bacteria composition independent of changes in food intake [17]. Exposure to short days decreases relative abundance of Proteobacteria, which are most efficient at harvesting energy from high fat foods [17]. In a laboratory

setting, exposure to long days increases high fat diet preference in Siberian hamsters [102], which raises the possibility that the gut microbiota may interact with photoperiod to drive seasonally specific feeding behaviors; however, synergy among behavioral, enteric, and neuroendocrine systems with photoperiod remains largely unexplored.

3.1.5 Photoperiod and central energy conservation—The CNS is composed of the most energetically demanding cells in the body [3]. Minimizing CNS metabolic demands during times of restricted energy availability (*viz.*, short days), without impairing CNS function to the point of impacting long term reproductive fitness and survival, presumably provides adaptive advantages [150]. Seasonal brain plasticity has been reported for all vertebrate taxa [303], and photoperiodic brain plasticity has been studied in birds, primarily in two circuits; the song control system and the hippocampus. In support of this hypothesis of short-day energy conservation, upon exposure to long days, brain volume and soma size increases in several nuclei of the song system (reviewed in [150,201]). In white-footed mice (*Peromyscus leucopus*), exposure to short days decreases hippocampal volume, with concurrent impairment in hippocampal function (see *learning and memory* below, [259,337]). Short day reductions in brain mass have also been reported in meadow voles (*Microtus pennsylvanicus*) [67,111], bank voles (*Myodes glareolus*) [342], and shrews (*Sorex araneus L.*) [72,341]. However, short day increases in hippocampal volume occur in several species of wild food-caching birds [280]. Total brain volume also increases among long-day squirrels (*Sciurus carolinensis*) [173]. Energetic investment in increased brain volume in short days, in these cases, may impart an adaptive advantage by increasing spatial memory needed to locate food caches, which outweighs the increased energetic demands of supporting the increased neuronal volume. Alternatively, these volume increases could simply be a result of increased hippocampal usage during caching behavior (see [173,280]). However, the direct contribution of varying seasonal demands in energy homeostasis to the evolution of these adaptations remains unspecified.

3.2. Photoperiod and immune function

Photoperiodic plasticity in the reproductive system is mirrored by alterations in various aspects of immunological physiology. Short day lengths generally enhance many types of immune responses in the laboratory, although others specific immune defenses are inhibited [220,222]. The working theory in our laboratory has been that enhanced immunological defenses in short day lengths serve to oppose the stressful effects of winter conditions including reduced food availability and increased thermoregulatory demands [224] (Figure 2 A, B, D). This phenomenon of seasonal plasticity in the immune system is highly conserved and has been observed across vertebrate taxa. Most aspects of cell mediated immune responses including lymphocyte proliferation to mitogens, delayed-type hypersensitivity responses, and overall numbers of circulating immune cells are increased by exposure to short day lengths [32,44,83-84] (Figure 2 C). Additionally, both natural antibodies and antigen stimulated antibody responses are boosted by long term housing in short day lengths [83,85] (Figure 2D). In contrast, most aspects of the innate arm of the immune system including cytokine responses to inflammogens are inhibited by winter-like day lengths [33,247].

Seasonal plasticity in the immune system raises an important conceptual question. Why should immune responses be seasonally variable at all? Given the ubiquity of parasites and other pathogens why are immune defenses not maintained at maximal levels all year round? The answer may relate to the energetic cost of maintaining and activating immune function. Maximally investing in the immune system is not possible in the face of other energetically demanding processes [45,79,161]. During the spring and early summer small mammals invest heavily in the behavioral and physiological costs associated with breeding and most

immune defenses are reduced [222]. However, during winter when successful breeding is typically impossible energetic investments are biased towards the immune system [225].

3.2.1 Mechanisms—Photoperiodic adjustments in immune defenses are mediated almost entirely by the pineal melatonin rhythm. Melatonin is generally anti-inflammatory and immunoenhancing in most laboratory animal species [128,193]. However, melatonin largely recapitulates the short day effect among photoperiodic mammals rather than being universally immunoenhancing [34]. However, the way in which melatonin alters immune responses appears to be related both to direct actions of melatonin on immune cells, as well as via prolonged systemic adjustments that are associated with longer-term exposure to short day lengths. Pinealectomy prevents short-day induced changes in immune responses and exogenous melatonin can induce the short day phenotype in animals housed in long days [34,84,346]. Short day patterns of most immune responses require extended time in short photoperiods or long term exposure to short day patterns of melatonin. In contrast to the effects of long term melatonin treatment, short term (2 weeks) lengthening of the endogenous melatonin rhythm is not sufficient to alter either febrile or antibody responses in Siberian hamsters [34,84]. There is one notable exception: melatonin added to lymphocyte cultures can directly modulate proliferative responses and do so in a photoperiod-dependent manner [251-252]. In sum, most of the immune changes associated with short days require extended periods to develop.

Although melatonin signaling is necessary for photoperiodic adjustments in immune responses, it is difficult to parse the differential direct effects of melatonin on immune cells from indirect modulatory actions on other neuroendocrine axes including the systems that control gonadal and adrenal steroids. However, the hypothesis that melatonin acts on immune function via downstream hormonal effects has not been born out, as gonadectomy and steroid replacement has minimal effect on photoperiodic plasticity in the immune system [86,245]. Further, although androgens tend to be immunosuppressive estrogens often have the opposite effect [162]. Therefore, the short day induced gonadal regression would likely induce opposite effects in males and females if sex steroids were directly responsible for photoperiodic adjustments in immune responses. In general, both males and females respond similarly to changes in day length [35]. Gonadal steroids probably serve to modulate the larger melatonin-mediated effects of day length rather than directly driving photoperiodic changes [243].

Glucocorticoid hormones are also unlikely to be the primary drivers of photoperiodic changes, as circulating glucocorticoids are not systematically related to photoperiodic changes in immune responses across species [260,328,331]. Basal glucocorticoids are not the only relevant parameter associated with HPA axis function and some studies have reported photoperiodic adjustments in glucocorticoid receptors and feedback parameters [257,267]. Additionally, acute stress-induced glucocorticoids are greatly enhanced in short day Siberian hamsters and elevated glucocorticoids appear to drive enhanced delayed type hypersensitivity responses in this species [32]. As sex steroids, glucocorticoids appear to act as modulators rather than driving forces behind photoperiodic adjustments in immune responses.

Immune function, as stated above, is energetically costly; thus, individuals, especially individuals of small vertebrate species, attend to their energetic status when mounting immune responses. That is, when energy is readily available more resources can be devoted to host defense, whereas when energy is more limited, resources will be more tightly controlled [77]. One hormone that is both immunomodulatory and responsive to changes in energy balance is leptin. Leptin, a peptide produced almost exclusively in adipose tissues, closely tracks body fat in mammals that undergo seasonal changes in body mass (see above

[269,273,336]). For instance, Siberian hamsters, which lose body mass and adiposity in short day lengths, reduce circulating leptin, as well as leptin and leptin receptor gene expression in short days [146,202,268]. Siberian hamsters housed in short day lengths reduce antibody responses to the protein keyhole limpet hemocyanin [130,244]. Exogenous leptin blocks the short day-mediated reduction in immune responses but only when food is available *ad libitum* [90]. When leptin-induced increases in food intake were prevented by food restriction, leptin no longer blocked the short day decrement in immune responses [90]. Similarly, reductions in body fat reduce humoral immune responses, but this effect can be blocked with the administration of exogenous leptin [82,88]. Interestingly, leptin induced enhancement of antibody production requires intact innervation of the spleen suggesting that autonomic inputs are involved (see below, [76]) and leptin only alters immune responses *in vivo*, but not *in vitro*, suggesting that the effects are not mediated directly on the leukocytes [75]. Leptin likely provides important information about adiposity and thus can modulate photoperiodic adjustments in immune responses.

The autonomic nervous system is also a potential intermediate mechanism for photoperiodic modulation of the immune system. The sympathetic nervous system contributes directly (and presumably indirectly via changes in adiposity) to photoperiod changes in immune responses. For instance, surgical extirpation of the adrenal medulla, the principal source of blood-borne catecholamines, inhibits antibody production, but only in long days. On the other hand, denervation of the sympathetic inputs to the spleen significantly attenuates antibody production, but only in short days [81]. Splenic norepinephrine content is increased by short day lengths in Siberian hamsters and this phenomenon appears to be at least partially responsible for the short-day induced reduction in lymphocyte proliferation in this species. Adding norepinephrine to lymphocyte cultures attenuates proliferation responses, but only in short day lengths [78]. Although not yet functionally studied, photoperiod also increases activity of the parasympathetic branch of the autonomic nervous system, which may also have immunomodulatory actions [329].

3.3. Photoperiod and reproduction

Maintenance and support of reproductive function in mammals is dependent upon activation of the hypothalamic-pituitary-gonadal (HPG) axis. Pulsatile gonadotropin releasing hormone (GnRH) secretion from the hypothalamus into the hypophyseal portal system stimulates releases of gonadotropins (luteinizing hormone – LH, follicle-stimulating hormone – FSH) from the anterior pituitary, which in turn supports development and maintenance of mature gonads [42,179]. The HPG axis can be modified at multiple levels to regulate reproductive function, some of which are influenced by photoperiod and the influence of photoperiod can vary depending on previous photoperiod exposure.

3.3.1 Short-day breeders—Sheep (*Ovis aries*), in common with other ungulates and most large seasonally-breeding mammals, are so-called ‘short-day breeders’. Ewes have relatively long periods of gestation; mating typically occurs in the autumn and lambs are born and nursed in the spring when food and other conditions are most conducive for survival. As day lengths decrease in late summer, the rate of GnRH secretion increases, which eventually stimulates increased gonadotropin secretion that initiates reproductive function [340]. In Suffolk ewes, seasonal reproductive transitions appear to reflect changes in the responsiveness of the GnRH neurosecretory system to the negative feedback of estradiol. In common with other mammals, GnRH neurons in sheep do not express estrogen receptor alpha (ER) [340]. Although ~50% of GnRH neurons in sheep express estrogen receptor beta (ER) [287], the role of these receptors in estrogen feedback regulation of GnRH signaling remains unidentified. However, ER may be the putative estrogen receptor for feedback regulation of GnRH secretion as targeted disruption of ER in female mice does

not impair reproduction [169,186]. The ultrastructure and synaptic inputs of GnRH neurons in the preoptic area of ewes during the breeding season receive more than twice the mean number of synaptic inputs per unit of plasma membrane than GnRH neurons in anestrous animals [340], thus the influence of estradiol on GnRH neurosecretory activity may be conveyed via converging afferents on GnRH neurons from: A) estradiol sensitive glutamatergic cells in the hypothalamus, BNST, and brainstem [241], B) BNST neurons receiving input from estradiol sensitive noradrenergic cells in the brainstem [239], and C) dopaminergic input from the A15 nucleus [58]. These seasonal alterations in synaptic input are independent of seasonal fluctuations of steroid concentrations as both intact and ovariectomized ewes bearing estradiol implants show changes in synaptic inputs onto GnRH neurons [340], but how photoperiodic information is relayed through these pathways remains unspecified. After mating season, sheep become photorefractory; i.e., short days lose their stimulatory effects and mating behavior wanes. Exposure to the long day lengths of summer is not necessary to re-establish responsiveness to short days, suggesting the presence of an underlying circannual cycle of photosensitivity [265].

3.3.2 Long-day breeders—Syrian, or golden, hamsters (*Mesocricetus auratus*), and Siberian hamsters (*Phodopus sungorus*), represent the most common mammalian models used in laboratory investigations of photoperiodism. Hamsters, in common with most small mammals, are so-called ‘long-day breeders’. Gestation is relatively brief in these animals; mating, pregnancy, and lactation occur during the long days of late spring and early summer. The minimum day length that supports reproduction is called the ‘critical day length’. Critical day length is not a fixed variable, but differs among populations of animals living at different altitudes and latitudes [49]. Adult male Syrian hamsters undergo gonadal regression when day lengths fall below 12.5 hours of light [98]. However, Siberian hamsters, which live at higher latitudes than Syrian hamsters, display a critical day length for reproductive function of 16 hours of light/day [96]. In addition to latitudinal variation in critical day length, manipulation of photoperiod history in the lab can also influence critical day length. Siberian hamsters held in long or short day lengths will show correct photoperiodic reproductive responses to opposite photoperiods if placed in intermediate photoperiods that differ by >1.5 hr from the initial photoperiod [246,250]. It should be noted here that most laboratory studies of photoperiodism involve abrupt transfer to different day lengths, which does not reflect naturalistic conditions. Using simulated natural photoperiod (SNP) exposure, to mimic gradual incremental changes in day length, in Siberian hamsters has demonstrated that photoperiod history is critical for determining critical day length. Critical day length can be shifted up to 6 hours by manipulating the simulated natural photoperiod history [121]. Thus, early observations that latitude determines critical day length, while correct, should be interpreted as photoperiod history, which changes with latitude, is responsible for determining critical day length.

When Syrian hamsters are maintained in day lengths < 12.5 hours of light, blood concentrations of gonadotropins and sex steroid hormones decrease, accessory organ mass diminishes to about 10% of the original size, and reproductive behaviors stop (reviewed in [253]). Male hamsters remain reproductively quiescent for approximately 16-20 weeks, a period of time that roughly corresponds to the duration of short days experienced in the wild during autumn and winter. Hamsters are photorefractory during the recrudescent phase; i.e., gonadal condition becomes unlinked from photoperiodic inhibition. Photorefractoriness permits attainment of fully functional gonads in the spring before environmental photoperiods attain 12.5 hours, the day length necessary for gonadal maintenance in the autumn. This is an important adaptation that allows burrowing animals (that live in constant dark conditions) to anticipate spring conditions with the development of fully functional reproductive systems without long-day exposure. Once animals become photorefractory

exposure to increasing day lengths initiates reestablishment of photoresponsiveness, but the process takes ~10 – 15 weeks to complete after initiation [51,159].

One of the mechanisms by which the nightly duration of melatonin secretion affects the reproductive system is by altering the steroid negative-feedback mechanisms in the hypothalamus and pituitary gland (reviewed in [117]). In long-day and short-day breeders, reduced secretion of pituitary LH and FSH during the non-breeding season results from increased sensitivity of the hypothalamic-pituitary axis to the negative feedback effects of gonadal steroid hormones [176,296,307]. Low concentrations of blood androgens are more effective at inhibiting post-castration elevations in pituitary gonadotropin secretion in hamsters and rams, when males are housed in short or long days, respectively. A return to the lower level of sensitivity returns the animals to a state of reproductive activity via increased pituitary hormone secretion. A similar phenomenon has been implicated in puberty, during which a prepubertal decrease in sensitivity to steroid negative feedback leads to increased secretion of LH and FSH and activation of the reproductive system [286].

In addition to changes in the sensitivity of the gonadotropin secretion system to gonadal steroid hormones, several steroid-independent mechanisms have also been implicated in the regulation of seasonal changes in the rate of gonadotropin secretion. In long days, female hamsters display ~8-10-fold increase in baseline serum LH concentrations following ovariectomy, and LH concentrations can be returned to baseline by administration of estrogens. After several weeks of short-day exposure, female hamsters become anovulatory and serum LH concentrations are very low during most of the 24 h cycle; however, the anovulatory females display daily LH surges during the afternoon. This pattern of LH secretion is steroid-independent, as it continues following ovariectomy or adrenalectomy [40]. A steroid-independent, but melatonin-dependent, photoperiodic LH secretion pattern difference is also found in ewes. In ovariectomized ewes, LH pulse frequency is suppressed in long days and recovers to normal breeding season rate in short days. This difference is abolished by pinealectomy, but recovered with melatonin infusions mimicking short- and long-day photoperiods [39]. Although it is currently unknown whether steroid-dependent or -independent mechanisms are more common in photoperiodic mammals, seasonal variation in circulating and pituitary concentrations of gonadotropins has been reported for several mammalian species [36,39,158,203].

Recent research in birds has identified two members of the RFamide family of peptides that regulate the HPG axis, kisspeptin and gonadotropin inhibitory hormone (GnIH), which may have similar roles in mammals (reviewed in [124,304]). These peptides act in an antagonistic fashion on GnRH neurons; kisspeptin stimulates GnRH release [288] and GnIH inhibits GnRH release [305]. Although the role of these peptides in photoperiodic control of the HPG axis has not been completely specified, both cell types are responsive to melatonin. In cultured mammalian hypothalamic neurons, expression of kisspeptin is decreased and RFamide-related peptide (RFRP, the mammalian homologue of GnIH) expression is increased by melatonin [113]. Exogenous and endogenous melatonin drives GnIH release in birds [62,310], and short photoperiod increases RFRP expression in hamsters [197,237]. Consistent with the effects of melatonin on kisspeptin in rats [113], kisspeptin immunoreactivity in the anteroventral periventricular nucleus of the thalamus of Siberian and Syrian hamsters is reduced in short days [123,283]. However, in the arcuate nucleus, kisspeptin immunoreactivity is elevated in short-day Siberian hamsters [125,198], but no effect of photoperiod was reported on gene expression [237].

As noted above, thyroid hormones have also been implicated in photoperiodic regulation of the HPG axis in both mammals and birds [107,216,347]. Hypothalamic T_3 levels are higher in long days and hypothalamic implants of T_3 can block short day photoperiodic responses

in Siberian hamsters [18]. Exposure to long days increases thyroid stimulating hormone (TSH) release from the PT, and the increased TSH release from the PT acts in a paracrine manner to induce DIO2 expression in the tanycytes lining the third ventricle in the mediobasal hypothalamus, resulting in elevated T_3 availability [134,345]. Reciprocal expression of DIO2 and DIO3 in the mediobasal hypothalamus thereby regulates thyroid hormone activity in the hypothalamus, and expression of these genes is regulated by melatonin (see discussion above [232,264,322,344-345]). Conservation of this mechanism suggests that it may represent an ancestral mechanism of seasonal timing driven by photoperiod [136-137].

4. Photoperiod, affect, and non-reproductive behaviors

Although many seasonal behaviors in photoperiodic mammals are specifically associated with reproduction (see above), there are several behavioral traits, such as affective responses and aggression, that are modulated by photoperiod independent of gonadal steroids. Immunological, hormonal, and neural factors, all of which are modulated by photoperiod, converge to modify behavioral output. Affective disorders are generally considered maladaptive; however, photoperiodic changes in affect may represent an adaptive strategy to conserve energy during the energetic bottlenecks encountered during the short days of winter (e.g., [229-230,326]). Additionally, conservation of energy during the short days of winter may also be the putative mechanism driving photoperiodic modulation of aggression (see below). Not only are these traits influenced by photoperiod in mammals that respond reproductively to photoperiod, behavioral responses to photoperiod are also observed in mammals that do not respond reproductively to photoperiod, which has implications for developing animal models of human pathologies with a seasonal component, such as seasonal affective disorders and depression [338].

4.1. Affective responses

Observable and abnormal emotional states, such as excessive elation or sadness, define affective disorders [270]. Behavioral responses which comprise human affective disorders, such as altered food intake and reduced motivation (depressive-like), and increased anxiety and fearfulness (anxiety-like), can also be observed in rodents in a laboratory setting. Until recently, there was little evidence that photoperiod itself could alter affective behaviors, even though it has been known for decades that there is a correlation between season and affective disorders in humans [106,180,234]. Recent research has now identified several rodent species that display changes in affective behaviors that are induced by changes in photoperiod.

In reproductively photoperiodic rodents, exposure to short days induces changes in affective behaviors that are independent of changes in reproductive hormones. Exposure to short days increases anxiety-like and depressive-like responses in collared lemmings [327] and Siberian hamsters [249,258]. These photoperiodic behavioral changes develop early during short day exposure [249], and can persist after maximal gonadal regression [258,327], supporting the idea that the influence of photoperiod on affect can be independent of circulating gonadal steroids. Further support of this idea comes from a growing body of evidence showing that animals that do not respond reproductively to photoperiod also display photoperiodic responses [218,293]. Short-day exacerbation of depressive-like and anxiety-like behaviors have been reported in both nocturnal rodents (rats [29,207,248]), and diurnal rodents (e.g., Nile grass rats [6], and sand rats [7-8]). These affective responses to short days are unambiguously linked directly to pineal melatonin secretion duration [8], which may model the extended duration of melatonin secretion observed in humans with seasonal affective disorder [326].

4.2 Non-reproductive social behaviors

It is presumably adaptive for organisms to differentially display complex social behaviors such as aggression and non-reproductive affiliation at different times of the year. Aggressive behaviors occur because of competition for limited resources, whereas affiliative behaviors occur when long term survival probability is increased by sharing resources with conspecifics to liberate physiological resources for other processes. Both aggression and affiliation display seasonal variation, influenced by photoperiod, in reproductive and non-reproductive contexts.

Rodents, such as wood rats (*Neotoma fuscipes*) [52], rat-like hamsters (*Cricetus triton*) [349], Siberian hamsters [87,151,276], California mice (*Peromyscus californicus*) [282], and Syrian hamsters [14,103,112,152], increase aggression in short days. Elevated aggression in short days may be adaptive to protect limited resources or territories during the winter non-breeding season [87,274,297]. In males, testosterone concentrations are positively correlated with aggression during the breeding season [172,221,334]. Elevated aggression in short days, however, is typically independent of testosterone [52,87,112,151-152,349]. Although male aggression has been studied extensively, female aggression has received far less scientific scrutiny [227]. Nonetheless, elevated non-reproductive aggression in females also varies in response to photoperiod in rat-like hamsters [349], Siberian hamsters [276], California mice [282], and Syrian hamsters [103].

The precise mechanisms underlying short-day increases in aggression in both sexes remain unidentified; however, recent studies have identified some potential factors. Nitric oxide, a gaseous neurotransmitter, has been implicated in male aggression [223]. Short photoperiod reduces nNOS expression, the enzyme producing nitric oxide in neurons, in the amygdala of male Siberian hamsters, and nNOS expression is negatively correlated with aggression in short days [332]. Melatonin, a physiological signal of photoperiod, may directly modulate aggression. Laboratory house mice (*Mus musculus*) display increased territorial aggression when given a short day like regimen of melatonin [236]. Short-day alterations in aggression have been directly linked to pineal melatonin in Syrian hamsters [14,103], Siberian hamsters [277], and fat sand rats [8]. Although testosterone concentrations are at their nadir in short days (see above), it is possible that testosterone synthesized and converted to estrogen *de novo* in the brain can influence short-day aggression [289]. Photoperiod and estrogen receptor distribution also interact to modulate short-day aggressive behaviors [301-302], but how activation of this pathway occurs in short days remains unspecified. Melatonin can also interact with the HPA axis, which has been implicated in the modulation of aggression [132]. Exposure to short days alters HPA axis reactivity [257] and the HPA axis interacts with melatonin to modulate aggression [87,236].

In contrast to increased aggression, some rodent species display reduced aggression in short days [4,8,26]. To reduce thermoregulatory demands during the harsh days of winter, several rodent species form communal nests [4-5,192,335]. Conspecific tolerance in these communal nests necessarily requires reduced territorial aggression and increased affiliative behavior. The oxytocin (OT) and vasopressin (AVP) family of neuropeptides has been implicated in the control of diverse social behaviors, including affiliation and aggression (reviewed in [119,315]). Generally in mammals, increased oxytocin binding is associated with increased affiliative behavior [175] and increased vasopressin binding is associated with aggressive behavior [31,101]; thus, this system is poised to be a target for photoperiodic modulation of these behaviors. Indeed, pineal melatonin can modulate neurohypophysial AVP and OT neuronal activity (reviewed in [156]). Photoperiodic differences in oxytocin receptor distribution underlie increases in affiliation in short-day female meadow voles [28,235], but the role of vasopressin in mediating photoperiodic changes in aggression are less clear (see [2,37,53]). Thus, although photoperiod and pineal

melatonin modulate non-reproductive behaviors, the systems are distributed and the effects are species-specific.

4.3 Learning and memory

In addition to the social and affective behavioral changes described above, photoperiod can modulate learning and memory, potentially a functional result of altered hippocampal morphology (see above). In rodents, seasonal variation in spatial learning and memory has been reported in fox squirrels (*Sciurus niger*) [320], deer mice (*P. maniculatus*) [109-110], and white-footed mice [257,259,337]. In a naturalistic setting, seasonal variation in hippocampal and brain volume is positively correlated with seasonal spatial navigation and spatial memory requirements [173,342]. Indeed, in deer mice, seasonal territory maintenance life history positively correlates with photoperiodic variation in spatial learning and memory, leading to sex and population based differences in spatial learning and memory performance across seasons [109-110]. When male white footed mice, which have seasonal variation in territory size, are brought into the lab where there are no territories to maintain, a similar decrease of hippocampal volume observed during winter in the wild is observed in laboratory short days [259], indicating an underlying photoperiodic mechanism in brain morphological plasticity. Supporting this conjecture, exposure to short days alone impairs spatial learning and memory, alters dendritic morphology of hippocampal neurons [259], and impairs long term potentiation [321], the putative mechanism for memory formation in the brain [43].

5. Enduring effects of photoperiod

5.1. Early life photoperiods organize adult phenotype

In addition to the seasonally variable phenotypic changes discussed above, photoperiod history can also affect adult phenotype. Many adult diseases and disorders are influenced by the season of birth. For example, season of birth in humans has been correlated with a number of disorders and pathologies, including increased risk of several types of cancer [23,194], susceptibility to pulmonary fibrosis [133], metabolic disorders [127,174,311], and susceptibility to cardiovascular disease [47,174]. Late gestation and birth in short days, in both northern and southern hemispheres, is associated with increased prevalence of schizoaffective disorder, autism, and major depression in the adult population [135,299]. Season of birth may also differentially affect subtypes of affective disorders, as long day births are associated with an increase in the deficit subtype of schizophrenia [160] and risk of completed suicide [89]. Some of these disorders can be modeled by early life differences in photoperiod.

5.1.1. Somatic and reproductive effects of early life photoperiod—As described, the endogenous developmental programming effects of birth season can be investigated by manipulating an environmental factor (day length) that individuals of many animal species use to predict challenging conditions. Although much research on seasonality in small mammals has focused on photoperiod manipulations in adults, early-life photoperiod is also an important source of seasonal information and can establish individuals' developmental trajectory by regulating somatic and reproductive development [50]. Because the adaptations associated with investing in reproduction or survival mechanisms are generally mutually exclusive, it is useful for small animals to follow the appropriate seasonal developmental trajectory soon after birth. Siberian hamsters born late in the breeding season delay puberty until the following spring, whereas hamsters born early in the breeding season undergo rapid reproductive development, presumably to have the opportunity to mate prior to autumn [120]. Photoperiod information is communicated *in utero* to Siberian hamster pups [145] via the maternal melatonin rhythm. In addition to regulation of developmental processes, early

life photoperiod also affects reproductive [145] and affective responses to day lengths later in life (discussed below). Intermediate day lengths (e.g., 14 h/day in Siberia) occur at both the beginning and the end of the breeding season; thus, the same day lengths forecast very different environmental conditions. Photoperiodic rodents solve this problem by comparing ambient day length to a reference day length that is encoded prenatally via a mechanism termed photoperiodic history [145,246,250,279]. This mechanism appears to be mediated by melatonin rhythmicity. Pups born to pinealectomized dams are reproductively suppressed even when housed in long days presumably because the duration of the daily melatonin rhythm is increasing [309]. That is, pinealectomy of the dams blocks reception of any rhythmic melatonin signals in hamster fetuses and neonates. When the pups' circadian system matures such that the neuroendocrine system starts producing melatonin, despite encoding long days, this melatonin signal is interpreted as a decreasing photoperiod resulting in gonadal inhibition [309].

Photoperiodic rodents represent an ideal animal model for studying the programming, or organizational, effects of early life environmental conditions on adult phenotype. The effects of being born at different times of the year can be simulated in the lab by manipulating the perinatal and then postweaning photoperiod. As noted above, young animals are exceptionally responsive to day length information and early life photoperiod is sufficient to organize many physiological systems and establish a developmental trajectory. Male and female hamsters born in short days will delay reproductive maturation, but will rapidly undergo reproductive development if exposed to long days at weaning; the inverse case is also true [330]. In female hamsters, rearing in short days alters ovarian physiology through adult life, resulting in increased fecundity and fertility in old age, presumably due to the preservation of more primordial follicles [157]. Male Syrian hamsters that experience gestational short day exposure reduce peak testicular size compared to males gestated in long days [27].

Enduring effects of early life photoperiod are not limited to the reproductive system, however. Male meadow voles reared in short days have reduced brain mass as adults compared to long day reared counterparts [67]. Early removal of the pineal gland impairs antibody-dependent cellular cytotoxicity and alters thymic development in rodents [66,316] and melatonin supplementation *in ovo* enhances cellular and humoral immune responses in domestic fowl [208]

5.1.2. Behavioral effects of early life photoperiod—Perinatal photoperiod conditions can organize adult affective behaviors and can interact with postweaning photoperiod conditions to regulate the expression of affective behaviors in adults. Hamsters exposed to short days early in life have increased anxiety- and depressive-like responses as adults [258]. Exposure to short days increase anxiety- and depressive-like behaviors in hamsters born in long days [249] and exposure to short days perinatally potentiates those differences in adulthood [258]. Additionally, postnatal pinealectomy, interpreted by the animal as a shift from short days to long days via decrease in melatonin duration (see above, [309]), leads to altered anxiety-like behaviors in adult Siberian hamsters [339].

As noted, enduring behavioral effects of early life photoperiod experience are not limited to rodents. Season of birth effects in humans may reflect endocrine changes in HPA axis responsivity. Within a patient population suffering from unipolar major depressive disorder, failure to suppress Cortisol production in the dexamethasone suppression test was significantly increased in patients born in winter [105]. In elderly outpatients in the southern hemisphere, being born during flu season in both hemispheres was correlated with increased depressive and suicidal symptoms [240]. Thus, factors other than the endocrine system (the immune system) may contribute to the enduring effects of photoperiod.

5.1.3. Immune effects of early life photoperiod—Immunologically, animals born at different times of the year permanently alter their immunological priorities to best meet the demands of the environment they are likely to experience. Male and female Siberian hamsters, maintained prenatally and until weaning (21 days) in either short days (8 h light/day; 8L:16D[SD]) or long days (16 h light/day; 16L:8D [LD]), were weaned into either the opposite photoperiod or maintained in their natal photoperiod, forming four groups (LD-LD, LD-SD, SD-LD and SD-SD). After 8 weeks in their respective postweaning conditions, cell-mediated immune activity was compared among groups. Enhanced delayed-type hypersensitivity (DTH) responses were observed in hamsters housed in short days both perinatally and postweaning relative to all other groups. Additionally, splenic masses were enhanced by perinatal and not postweaning exposure to short days. Thus, there are long-lasting organizational effects of perinatal photoperiod on the rodent immune system, but does this model the human state?

5.1.3.1. Season of birth effects on the immune system in humans: Across the globe, resource availability and environmental conditions vary in a predictable fashion over the course of a year. Pathogens, food availability, and ambient temperatures all vary seasonally. Therefore, organisms developing at different times of the year are likely to experience dissimilar environmental conditions. Studies examining season-of-birth effects on immune function have been relatively few, but best documented in humans. By examining epidemiological data for seasonal changes in immune-related disease states, it is possible to make inferences about the immune system. For example, in industrialized countries, the environment during early life has a profound effect on health outcome. Season of birth effects have been reported for cytokine responses [115] and numerous health conditions including asthma [118,163], allergy [178,314], inflammatory bowel disease [16,206,313], and multiple sclerosis [24,200,290,300]. Although the directionality and strength of these relationships varies among the specific immunological component and disease state investigated, these season of birth differences are still apparent.

These seasonal patterns exist despite that most modern societies are buffered from much of the environmental variation that was presumably experienced by our ancestors [104]. In developing countries, the effects of early life experiences and environmental conditions are readily apparent. For example, in rural villages in the West African country of Gambia profound seasonality in humans remains extant. Despite being only 13° north of the equator, there are seasonal rhythms in rainfall that control the timing of the harvest. By the time the rains return in July, the previous year's stores of food have been exhausted. Therefore, there is a distinct season of restricted caloric intake that roughly coincides with the annual onset of the rains, termed the ‘hungry season’ [254]. Pregnant women reduce weight gain during that period [254]; in addition, the incidence of maternal and infant disease, mostly malaria and diarrhea, peak during this time [57]. Because there is a pronounced annual rhythm to these conditions, season of birth can be used as a proxy for early life experience of these factors. This seasonal phenomenon may have effects on immunological development. Children born during the hungry season have attenuated thymic development and are more likely to contract infections later as juveniles [64]. Perhaps the strongest evidence for a role of seasonality in the regulation of developmental processes and adult phenotype is that individuals born during the hungry season are significantly more likely to die prematurely than are those born when food is more plentiful [209]. Moreover, a disproportionate number of these early deaths are associated with infections [209]. It remains unclear whether the effects on phenotype in this population are due to direct actions of malnutrition and early life infection, or indirect endogenous changes in developmental trajectory in response to these conditions.

6. Epigenetic control of gene expression and photoperiodism

Mechanistically, it is unknown how early life photoperiod imparts its enduring effects on adult phenotype. It is possible that photoperiod-based epigenetic modifications occur in the germline cells, *in utero*, or in early life, that endure in the absence of the original causative signal. Although the broad use of the term “epigenetics” in recent literature to describe changes in gene regulation [256] strays from its classical definition as “a stably heritable phenotype resulting from changes in a chromosome without alternations in the DNA sequence” [30], we will use this term in the context of lasting changes in gene expression in the absence of the original causative signal [95]. Epigenetic chromatin modifications have become a focus of research as a putative mechanism for the long-term regulation of gene expression to evoke phenotype. Although detailed description of the mechanisms and molecular pathways involved in epigenetic regulation of gene transcription is beyond the scope of this review (for reviews see [61,153,255]), modifications of histone proteins lead to chromatin remodeling which either permits or prohibits RNA polymerase access to the DNA for transcription, leading to altered gene expression (phenotype) in the absence of genotypic change. These epigenetic modifications can occur as a result of response to an environmental factor, a behavioral factor, or via transmission through the germline.

6.1. Genomic imprinting

Genomic imprinting results from germline epigenetic modifications leading to monoallelic expression of genes from either the maternal or paternal line [95,333]. Whereas over 100 imprinted genes have been identified in rodents and humans [95], the presence of over 600 autosomal imprinted genes, comprising 2.5% of the genome, was predicted for *Mus musculus* [188]. Among imprinted genes already identified are a number of genes directly impacting endocrine function, as well as neuropeptides in behavioral circuits such as the monaminergic system, GABAergic system, and the AVP/OT system (reviewed in [71]). Additionally, recent studies have identified changes in methylation patterns in immune pathways which have been linked to altered immune function and increased risk for asthma in humans [183,185].

6.2. Environmental epigenetic modifications

Epigenetic modifications, independent of imprinted genes, can be induced throughout life via interaction with the environment. One of the most well studied examples of epigenetic modifications induced by social environment is the effect of pre-weaning social environment on adult brain and behavior. Post-natal licking and grooming behavior in rats induces epigenetic changes in the glucocorticoid receptor promoter in the hippocampus and in estrogen receptor alpha in the medial preoptic area of the hypothalamus of the offspring that alters HPA axis reactivity which persists into adulthood [59,294,325].

The immune system is also amenable to epigenetic modification by environmental factors. Bacterial infection in the bovine udder will inhibit lactation, independent of circulating prolactin levels, via an epigenetic mechanism [285]. Stimulation of human $CD4^+$ T cells induces *IL2* expression and epigenetic modifications of the IL2 promoter enhancer which leads to a more rapid and stronger response after a second stimulation, which the authors argue represents an “epigenetic memory” of the regulatory event [213].

6.3. Photoperiodic effects on the epigenome

Although research on the epigenetics of photoperiodism is scant, environmental interactions with the epigenome have been implicated in many of the same social behaviors, such as depression, anxiety, and aggression (reviewed in [65]), that are altered by photoperiod (see previous discussion). More direct evidence of photoperiodic effects on the epigenome come

from plants where photoperiodic variations in methylation patterns of genes involved in flowering in Arabidopsis have been identified [73,278]. Direct evidence for the role of DNA methylation in the control of the photoperiodic flowering response has been reported using *Perilla frutescens* and *Silene armeria*, two species of plants with a photoperiod-stable flowering state. The photoperiodic inhibition of flowering in these two species can be reversed using 5-azacytidine, a DNA demethylating agent [165].

Although no direct evidence of photoperiodic effects on the epigenome has been identified in mammals, it has been hypothesized that melatonin, or its metabolites, can function as inhibitors of DNA methyltransferases due to structural similarity with known methyltransferase inhibitors, and thus may be involved in epigenetic regulation [167]. Recent work identifying the specific role of melatonin in epigenetic regulation of several types of cancer has begun to support this theory [168,215]. Indeed, melatonin plays an important role in cell differentiation during development via interaction with nuclear melatonin receptors, which has been hypothesized to potentially contribute to epigenetic modifications of oocytes to explain adaptive geographic variations in humans [149]. How epigenetic modifications of other genes may be regulated by melatonin, and the potential role in photoperiodism of these genes, remains to be explored.

7. Conclusions

The putative mechanism central to the evolution of photoperiodism in animals is the distribution of energetically challenging activities across the year to optimize reproductive fitness while balancing the energetic tradeoffs necessary for seasonally-appropriate survival strategies (Figure 3). For long-day breeding mammals, the costs of territorial behavior, pregnancy, and lactation constrain reproduction to coincide with the onset of long days when environmental conditions are most conducive to survival. For short-day breeding mammals, lactation appears to be the major energetic cost associated with reproduction; thus, breeding has evolved to occur in fall. Gestation continues throughout the winter and birth and lactation occur in the lengthening days of spring, when food and weather conditions are most conducive to survival. Thus, for both long- and short-day breeders, the energetic costs of supporting reproduction and lactation outweigh the benefits of the investment during times of low reproductive success (*viz.*, winter). Being able to accurately predict future events to allocate energy among competing physiological systems to maximize fitness and survival necessarily requires endogenous mechanisms to permit physiological anticipation of annual conditions. Day length provides the most noise free environmental signal for organisms to monitor and accurately predict time of the year.

Day length is an unambiguous environmental signal. This signal can be used in the lab to explore the mechanisms by which the environment and genes interact to impart phenotype. Photoperiod manipulation is advantageous over other accepted methods of studying gene – environment interactions, where differential responses to “environment” (which entail an unlimited number of variables) are identified, and then comparative genomic methods are used to identify underlying genetic susceptibility factors (see http://www.niehs.nih.gov/). This unique approach allows isolation of a single environmental factor (duration of light) that can be controlled in a laboratory setting, and investigation of how this one factor interacts with the genome to affect multiple behavioral, cognitive, and physiological processes across diverse species. Using non-traditional animal models to investigate how photoperiodic modulation of physiological and behavioral systems interacts to impart phenotype may contribute to our understanding of clinical disorders and other pathologies in a translational setting.

In mammals, melatonin is the hormonal signal of day length. Although acute administration of melatonin can directly impact aspects of physiology and immune function, altering the duration of pineal melatonin secretion drives enduring changes in many physiological systems, including the HPA axis, the HPG axis, the brain-gut axis, the autonomic nervous system, and the immune system. This plastic and complex interplay among these systems is intimately regulated at all levels by melatonin. Thus, melatonin is the fulcrum mediating redistribution of energetic investment among physiological processes to maximize fitness and survival. Whereas many advances have been made in the past several decades, identification of the diversity of systems and multimodal sites of action of melatonin in photoperiodic animals is an ongoing process. Much of the progress in biology during this time has focused on molecular biology, it is now important to use modern molecular approaches and precise environmental factors to study the development of phenotype. Thus, continued research in the mechanisms of how light interacts with genes via melatonin hormonal signaling can provide novel and important insights into conserved molecular mechanistic themes underlying the relationship between phenotype and genotype.

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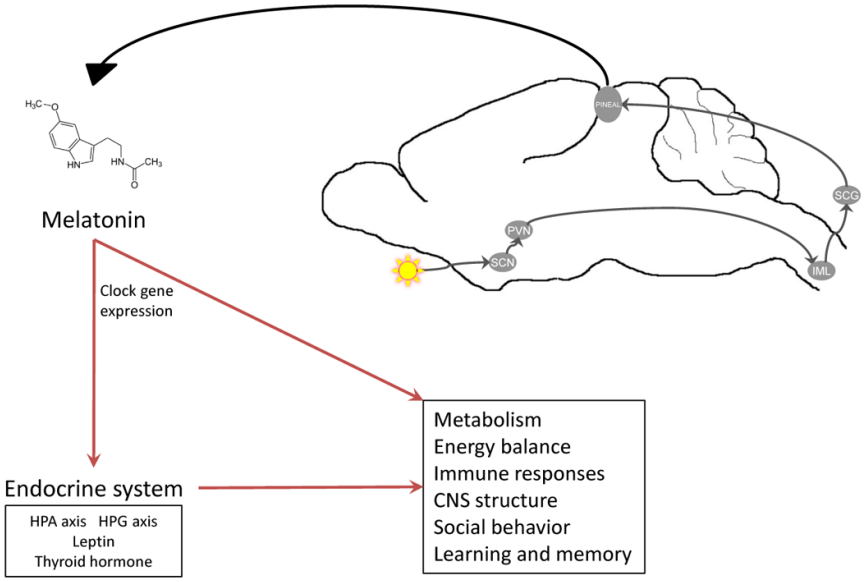

Figure 1.

Photic input is transduced by melanopsin-expressing retinal ganglion cells via the retinohypothalamic tract (RHT) to the suprachiasmatic nuclei (SCN). Output from the SCN is relayed through the paraventricular nucleus of the hypothalamus (PVN), to the intermediolateral cells of the upper spinal cord (IML), then to the superior cervical ganglion (SCG), and postganglionic innervation of the pineal gland regulates melatonin synthesis. Pineal melatonin carries photoperiodic information to distributed systems throughout the body, where it acts both directly and indirectly to regulate endocrine, neuronal, immunological, and behavioral processes.

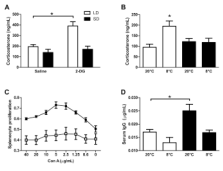

Figure 2.

The interaction of energetic stressors and photoperiod on immune function in deer mice (*Peromyscus maniculatus*). Short day exposure buffers stress responses to 2-deoxy-D-glucose induced metabolic stress (A) and to thermoregulatory stress (B). Short day exposure also enhances splenocyte proliferation in metabolically stressed mice in response to an immune challenge with the mitogen concanavalin A (C), and enhances basal serum IgG levels when mice are held in warm (20°C) ambient temperatures (D). Endogenous bolstering of immune function, coupled with blunted corticosterone responsiveness to stressors, represent short day adaptations that underlie energetic tradeoffs across the year mediated by photoperiod. The short day blunting of corticosterone responses serves to preserve immune function in the presence of stressors, and by applying and environmentally relevant stressor in the lab, such as cold temperature, immune parameters do not differ from long day mice (D). (Figures modified with permission from: [80](A,C); [83](B,D))

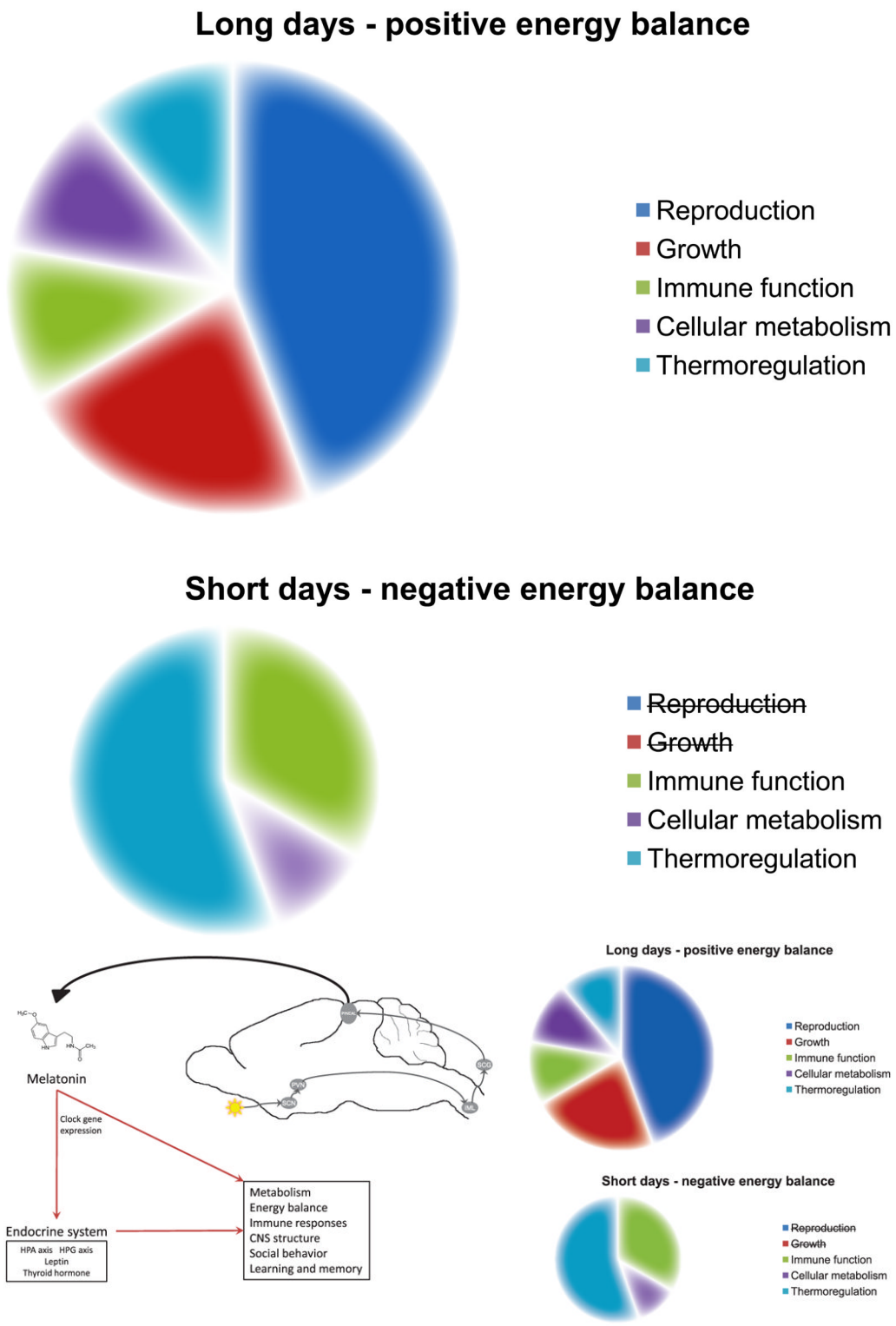

Figure 3.

Hypothetical illustration of photoperiodic differences in allocation of energy among competing processes. During the long days of summer, animals are in positive energy balance due to increased availability of resources (food). Thus, energy is available to support

somatic growth and reproduction. During the short days of winter, energy balance tips to negative. Reproduction and somatic growth processes are curtailed, and available energy is allocated differentially among the immune system, thermoregulation, and cellular metabolism. As stressors mount immune function is eventually compromised. Often animals in the field display compromised immunity and health during the winter. Presumably, compromised immune function would be worse in the absence of short-day bolstering [224]. Elevated energetic constraints and thermoregulatory demands in the short days of winter have led to the evolution of torpor and hibernation to promote survival by further reduction in the energetic demands of the remaining active processes.