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Neuroendocrine control of photoperiodic changes in immune function

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Abstract

Seasonal variation in immune function putatively maximizes survival and reproductive success. Day length (photoperiod) is the most potent signal for time of year. Animals typically organize breeding, growth, and behavior to adapt to spatial and temporal niches. Outside the tropics individuals monitor photoperiod to support adaptations favoring survival and reproductive success. Changes in day length allow anticipation of seasonal changes in temperature and food availability that are critical for reproductive success. Immune function is typically bolstered during winter, whereas reproduction and growth are favored during summer. We provide an overview of how photoperiod influences neuronal function and melatonin secretion, how melatonin acts directly and indirectly to govern seasonal changes in immune function, and the manner by which other neuroendocrine effectors such as glucocorticoids, prolactin, thyroid, and sex steroid hormones modulate seasonal variations in immune function. Potential future research avenues include commensal gut microbiota and light pollution influences on photoperiodic responses.

1. Introduction

Although most neuroendocrinologists consider Darwinian fitness in terms of reproductive success, the concept of fitness comprises both survival and reproductive functions. Production of successful offspring (i.e., production of grand offspring) is certainly the primary measure of fitness; however, outliving competitors also increases fitness because, all things being equal, individuals that survive longer have more opportunities to produce additional offspring. However, with some notable exceptions such as salmon (*Oncorhynchus nerka*) or brown marsupial mice (*Antechinus stuartii*) and laboratory animals, most extant animals do not continuously reproduce from reproductive maturity until they die. Individuals grow and develop and generally limit reproduction to specific times of year. Importantly, producing offspring can use energy necessary for other physiological priorities.

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Thus, adaptations have evolved to allow individuals to maintain a careful balance among reproduction and other survival priorities. Adaptations are often considered in the context of spatial niches, however, animals have also adapted to temporal niches (Nelson, 1987). Environmental conditions can change substantially across the day and across the seasons, especially in temperate or boreal habitats. In response, individuals of many species display separate adaptations to cope with the fluctuating seasonal conditions that favor investing in reproduction at one time of year, and investing more heavily in survival mechanisms at other times of year. Seasonal changes in neuroendocrine function often serve as the physiological switch in mediating many of these seasonal adaptations.

One important proxy for survival is optimal immune function. Maintaining full energetic investment in both the immune and reproductive systems is energetically costly (Demas *et al*., 1997; Hanssen *et al*., 2005; Martin *et al*., 2003; Speakman, 2008); indeed, for many post-pubertal small mammals and birds maximal investment in immune and reproductive functions are energetically incompatible. Energetically demanding processes associated with successful reproduction including the defense of territory, competing for access to mates, pregnancy, and lactation may preclude investment in optimal immune defenses. However, when environmental conditions reduce the possibility of successful breeding, investment in survival (i.e., immune function) may be favored. Thus, natural selection has not favored simultaneous and maximal investment in both the reproductive and immune systems, but rather appears to favor investment in these systems during specific seasonal niches (Nelson & Demas, 1997). This phenotypic plasticity likely evolved to promote survival despite significant, yet predictable, seasonal variation in temperature, weather, predation pressure, and food availability. Importantly, to orchestrate seasonal investments in competing physiological priorities, the neuroendocrine system is required to both transduce seasonal cues and coordinate the activity of target tissues. In this review, we will describe how neuroendocrine function coordinates photoperiodic changes in immune defenses.

Photoperiodism is the biological ability to measure day length. The annual cycle of day lengths (photoperiod) provides one of the most reliable environmental cues for time of year. Animals can gauge time of year with just two pieces of information: (1) the photoperiod, and (2) whether day lengths are increasing or decreasing (Goldman, 2001). Changes in pelage, sleep, body mass, adiposity, reproduction, and immune function are gated by photoperiodic information ensuring their optimization within the relevant adaptive time frame (Prendergast *et al*., 2009). These physiological changes require substantial time to initiate and terminate; thus, anticipatory cues encoded by the annual cycle of changing photoperiods remain an important mechanism to ensure proper timing of development of seasonal adaptations.

Because many seasonal physiological adaptations require substantial time to develop, (e.g., changes in adiposity, reproductive regression, alterations in immune function) neuroendocrine adjustments often predate other physiological changes (e.g., reduced gonadotropin pulse frequency and amplitude lead to gonadal regression) (Wingfield, 2008). Seasonal variation in environmental conditions are generally predictable, but they are neither consistent in timing nor magnitude. Thus, the environmental conditions themselves (i.e., rainfall, temperature, barometric pressure, food availability) are of little predictive

value. Natural selection has favored a strategy of monitoring a relatively neutral geophysical cue, day length, to predict changes in conditions that are more directly relevant to reproduction and survival.

To maintain a sustainable energetic budget, investments in competing physiological priorities are adjusted on a seasonal basis. For most small mammals that breed during long days investments in growth, reproductive physiology and behavior appear to be favored in the long days of spring and summer when resources are abundant and optimal for rearing offspring (Nelson & Demas, 1996). In contrast, during the short days of late autumn and winter when the odds of survival for new offspring are low many species invest more heavily in immunological defenses presumably to increase the probability of surviving to the next breeding season (Nelson *et al*., 2010). Laboratory – based studies have mostly reported that immune defenses are increased during short winter-like day lengths when all other conditions are held constant (Bilbo *et al*., 2002a; Navara *et al*., 2007). Increased immune investments may represent an attempt to buffer individuals from the immune suppression associated with the energetic bottlenecks of the winter when increased thermoregulatory requirements coincide with reduced nutrient availability (Martin *et al*., 2006; Martin *et al*., 2008).

1.1. Immune System

The vertebrate immune system broadly comprises two categories: innate and adaptive (Parham, 2009). The innate immune system is responsible for the immediate response to pathogen infiltration and will ultimately induce inflammation. Inflammatory processes are initiated by pathogen recognition, complement activation, release of antimicrobial peptides, and recruitment of various types of effector cells, including macrophages, granulocytes, and natural killer cells. Toll-like receptors (TLRs) expressed on various cell types throughout the body mediate signaling in response to microbial products (Janeway *et al*., 2001). Macrophage TLR4 activation induces gene expression and release of inflammatory cytokines. Innate immune system activation is often assessed by treatment with the endotoxin, lipopolysaccharide (LPS), a component of gram-negative bacteria cell walls which acts as a ligand of TLR4. Secretion of cytokines, from infection or LPS treatment, coincident with various physiological and behavioral responses, forms a coordinated adaptive recovery reaction (Ashley & Wingfield, 2012; Hart, 1988). Mounting an innate immune response is relatively nonspecific, energetically costly (Bonneaud *et al*., 2003), and generally compromised during the winter (Navara *et al*., 2007).

The adaptive immune system is a focused response to a specific pathogen only recruited if the innate immune response fails to eliminate pathogen infiltration (Parham, 2009). An adaptive immune response requires recruitment of lymphocytes. Pathogen specificity is encoded in the variety of antigen receptors expressed by lymphocytes. T lymphocytes are responsible for specific antigen recognition to defend against both intracellular (cytotoxic T cell) and extracellular (helper T cell) infection. B-lymphocytes mediate pathogen recognition and endocytosis, as well as release of appropriate antibodies. B and T cells create ‘memory’ cells that ensure future infections with the same pathogen will elicit a faster and more powerful response from the immune system. Although more specific, an initial

adaptive immune response requires several days to generate sufficient antigen-specific B and T cells, and is also energetically costly to mount and develop although there is some debate about the relative costs of the different arms of the immune system (Bonneaud *et al*., 2003; Hanssen *et al*., 2004; Klasing, 2004).

The immune system does not exist in isolation; recent studies have outlined functional bidirectional interactions among the immune, endocrine and nervous systems (Haddad *et al*., 2002). Peripheral cytokine release, as a signal of infection, can be relayed to the brain directly by crossing the blood brain barrier at circumventricular organs or indirectly through vagal afferents (Haddad, 2008). Cytokine signaling to the CNS can affect neuronal excitability, pituitary development, and hormone release from the anterior pituitary (Bumiller *et al*., 1999; Haddad *et al*., 2002). Likewise, central cytokine release can affect peripheral immunity through the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis activation (Woiciechowsky *et al*., 1999). As one of the largest circumventricular organs and the primary site of synthesis and secretion of melatonin, the hormone largely responsible for transduction of day length, the pineal gland stands at the interface among the circadian, immune, and endocrine systems. In the next sections we outline the influence of photoperiod on seasonal changes of neuroendocrine systems and overall immune function.

2. Pineal Gland, Melatonin, and Other Hormones

2.1 Transduction of Day Length Information

The pineal gland acts as the key structure responsible for conveying photoperiodic information to peripheral tissues via nocturnal secretion of the indoleamine, melatonin (N-acetyl-5-methoxytryptamine), directly into blood and cerebrospinal fluid. An endogenous signal of darkness (Tan *et al*., 2010), melatonin is secreted from the pineal gland during the night in both diurnal and nocturnal vertebrates (Challet, 2007). Therefore, changes in day length throughout the year coincide with changes in the duration of nightly melatonin. It communicates both circadian and photoperiodic information to peripheral tissues to regulate responses at multiple temporal levels; melatonin rhythms can be considered to serve as both a ‘clock and a calendar’ to individuals (Hazlerigg, 2012; Reiter, 1993a; Zawilska *et al*., 2009).

Pinealectomy blocks all photoperiod-induced phenotypic changes in most mammalian species studied thus far (Hazlerigg & Wagner, 2006). Furthermore, pinealectomized animals treated with exogenous melatonin either tonically or via timed daily injections display phenotypes similar to pineal-intact animals maintained in short photoperiods (Bartness *et al*., 1993; Goldman, 2001; Hiebert *et al*., 2006; Walton *et al*., 2013), suggesting that melatonin alone is sufficient to elicit a photoperiodic response. However, melatonin may not be necessary for this response (Hiebert *et al*., 2000; Lincoln *et al*., 1989; Monecke *et al*., 2013), and a pineal independent photoperiodic pathway may exist. Importantly, avian reproductive photoperiodism is largely independent of melatonin signaling (Bentley, 2001).

In mammals, photic information reaches the pineal gland through a polysynaptic pathway beginning with a diverse population of melanopsin expressing intrinsically photosensitive

retinal ganglion cells (ipRGCs) located in the retina (Berson, 2003; Schmidt *et al*., 2011a). These cells play a primary role in circadian entrainment and only a marginal role in low-acuity vision (Schmidt *et al*., 2011b). Their axons travel along the non-visual retinohypothalamic tract and provide glutamatergic input to cells in the suprachiasmatic nuclei (SCN) of the hypothalamus (Baver *et al*., 2008). Collateral axons also innervate the intergeniculate leaflet (IGL) and olivary pretectal nucleus (OPN) to encode ambient light levels, and mediate the pupillary light reflex (Chen *et al*., 2011b). The SCN, composed of mainly GABAergic cells within the anterior hypothalamus, act as the primary circadian pacemakers for peripheral tissues in mammals (Bass & Takahashi, 2010; Moore, 1983). SCN cells display autonomous rhythmicity *in vitro* (Welsh *et al*., 2010) and lesions of the SCN abolish circadian rhythms in physiology and behavior (Stephan & Zucker, 1972). Transplantation of donor SCN tissue into the 3rd ventricle restores these rhythms (Ralph *et al*., 1990). The SCN modulate ipRGC input and project to the nearby paraventricular nucleus, to the interomediolateral cell column of the cervical spinal cord, and then onto the superior cervical ganglion. From there, sympathetic post-ganglionic noradrenergic projections innervate the pineal gland to modulate melatonin secretion (Teclemariam-Mesbah *et al*., 1999).

2.2 Melatonin

Melatonin is widely distributed in plants, unicellular organisms, algae, bacteria, invertebrates, and vertebrates (Hardeland & Poeggeler, 2003; Iriti *et al*., 2010; Stehle *et al*., 2011). This wide distribution reflects its pleiotropic functions, acting through several signaling pathways (Celinski *et al*., 2011; Gomez-Moreno *et al*., 2010; Jung-Hynes *et al*., 2010; Paradies *et al*., 2010; Reiter, 1991; Tan *et al*., 2010).

Photoperiod-responsive melatonin production is primarily reserved to the pineal gland in mammals, but extra-pineal melatonin is produced in the retina, skin, gut, and immune competent cells (Chen *et al*., 2011a; Huang *et al*., 2013; Kleszczynski & Fischer, 2012; Maldonado *et al*., 2010). Melatonin is synthesized in a two-step process from its precursor serotonin via N-acetyltransferase (AANAT) and then hydroxyindole-O-methyltransferase (HIOMT). Its production is driven by noradrenergic input from the superior cervical ganglion, with adrenergic receptor signaling-induced cAMP formation leading to downstream expression of AANAT (Carpentieri *et al*., 2012; Konturek *et al*., 2007). In many non-mammalian vertebrates, AANAT expression in the pineal is under the direct control of circadian clock genes (Hardeland & Poeggeler, 2003).

By using a radioiodinated ligand, 2-[^{125}I]iodomelatonin, melatonin binding sites were discovered throughout the mammalian central nervous system (Dubocovich & Markowska, 2005) and periphery (Slominski *et al*., 2012). Melatonin signals via multiple membrane bound G-protein linked receptors (MT1 and MT2) and a receptor independent pathway via quinone reductase II enzyme binding (previously identified as MT3). MT1 and MT2 can homo-or heterodimerize, but the role these receptor dimer species play in melatonin signaling outside the retina are unclear (Ayoub *et al*., 2002; Ayoub *et al*., 2004; Baba *et al*., 2013). A feedback loop mediating the mid-night peak and pre-dawn decline in melatonin secretion is thought to be governed by MT1 but not MT2 (Bedrosian *et al*., 2013b). More

controversially, melatonin has also been shown to be synthesized directly by T lymphocytes and act as a ligand of the retinoic acid-related orphan receptor alpha (ROR-α) and other nuclear receptors ((Carrillo-Vico *et al*., 2004; Lardone *et al*., 2011; Slominski *et al*., 2012). Intracellularly, the melatonin signal is largely transduced to influence downstream gene transcription via G_i and G_q activation, which leads to a reduction in cAMP via adenylyl cyclase inhibition (G_i) and in some cells increases Ca2+ via phospholipase-C activation (G_q) (Carrillo-Vico *et al*., 2004; Lardone *et al*., 2011; Slominski *et al*., 2012). MT1 is the receptor subtype primarily responsible for the transduction of photoperiodic information by melatonin (Pelletier *et al*., 2000; Prendergast, 2010; Walton *et al*., 2011; Weaver *et al*., 1996; Yasuo *et al*., 2009), and several photoperiodic species do not express MT2 (e.g., Siberian hamsters ("nature's knockout") and sheep).

Immune function varies seasonally in many mammalian species, including humans, and this variation is likely coordinated and modulated by melatonin signaling (Nelson, 2004). The immunomodulatory role of melatonin was first recognized ∼four decades ago when researchers observed reduced immune capacity following pinealectomy in rats (Csaba & Barath, 1975). The direct action of melatonin on immune function was then tested and described by Maestroni and colleagues (Maestroni *et al*., 1986), where immunosuppression by propranolol (a beta adrenergic antagonist) and p-chlorophenylalanine (a tryptophan hydroxylase inhibitor) was reversed via melatonin treatment (Maestroni *et al*., 1986). Since then, MT1 and MT2 receptors have been localized to major immune tissues involved in both innate and adaptive immune responses like the thymus and spleen, and specifically to CD4+ and CD8+ lymphocytes, as well as B cells (Carrillo-Vico *et al*., 2005). A bidirectional pathway between the immune system and pineal gland exists, with cytokine signaling affecting pinealocytes to transiently inhibit melatonin synthesis and shift melatonin production to circulating macrophages (da Silveira Cruz-Machado *et al*., 2010; Fernandes *et al*., 2006; Markus *et al*., 2013; Markus & Ferreira, 2011). Macrophage derived melatonin acts in a paracrine/autocrine fashion to inhibit nuclear factor κ-light chain enhancer of activated B cells (NF-κB) action to attenuate inflammation. In this way, short-day melatonin levels may facilitate the recovery from immune challenges by buffering the innate inflammatory response. Indeed, short photoperiods attenuate fever, hypothalamic cytokine expression, and 'sickness behavior' induced by lipopolysaccharide (LPS) administration in male and female Siberian hamsters (*Phodopus sungorus*) (Pyter *et al*., 2005; Wen & Prendergast, 2007). The effect is not limited to a gram-negative bacterial endotoxin (LPS), and short days attenuate responses to gram-positive (muramyl dipeptide) and viral (polyinosinic polycytidylic acid) immune challenges (Baillie & Prendergast, 2008). In male Wistar rats, which do not undergo reproductive responses to changes in photoperiod, short days augment T lymphocyte numbers and attenuate behavioral and cytokine responses to LPS (Prendergast *et al*., 2007). Therefore, photoperiodic modulation of the immune system can be accomplished independently of seasonal changes in reproductive capacity. Importantly, short day attenuation of sickness responses and cytokine signaling in Siberian hamsters is only accomplished via chronic (but not short term) lengthening of the melatonin signal (Bilbo *et al*., 2002b; Bilbo & Nelson, 2002).

Broadly, melatonin is immuno-enhancing (Carrillo-Vico *et al*., 2005), and increased duration of nightly melatonin corresponding with reduced day length is accompanied by increased splenocyte proliferation and IgG production (Demas *et al*., 1996). However, the actions of melatonin on immune system function depend on the species and 'arm' of the immune system analyzed (Martin *et al*., 2008). For example, short day lengths or chronic melatonin administration via Silastic capsules increases lymphocyte proliferation in deer mice (*Peromyscus leucopus*), but decreases this measure and antibody production in Siberian hamsters (Bilbo & Nelson, 2002; Drazen *et al*., 2002; Pawlak *et al*., 2009; Yellon *et al*., 1999). Melatonin implants also act on the SCN to reduce sickness behavior in Siberian hamsters (Freeman *et al*., 2007). In Syrian hamsters (*Mesocricetus auratus*), melatonin augments humoral and cell-mediated immune responses following dexamethasone-induced stress (Vishwas *et al*., 2013) and short photoperiods increase IgG responses to ovalbumin in piglets (Lessard *et al*., 2012). Photoperiodic modulation of immune function may be accomplished not only through alterations in melatonin secretion, but sensitivity to the melatonin signal via changes in receptor expression. For example, MT1 expression in the spleen is decreased by extended light exposure in several species, and is directly related to amount of light and circulating melatonin concentrations (Lahiri *et al*., 2009; Maestroni, 1993; Shiu *et al*., 2000; Yadav & Haldar, 2013).

Not all photoperiodic modulation of immune function can be ascribed directly to the actions of melatonin. For instance, short days prevent dimethylbenzathracene (DMBA) induced tumorigenesis (which may be initially suppressed by the immune system (Pardoll, 2003) in deer mice (*Peromyscus leucopus*); however, treatment of long day animals with exogenous melatonin does not recapitulate the protective effect of short days on tumor growth (Nelson & Blom, 1994). This effect seems to be mediated by photoperiodic changes in prolactin concentrations (see below). Therefore, other neuroendocrine factors that vary seasonally and modulate immune function warrant additional discussion.

2.3 Sex Steroid Hormones

Increased hypothalamic-pituitary-gonadal (HPG) axis activity during puberty initiates adult reproductive physiology and behaviors. Synthesis and secretion of gonadotropin releasing hormone (GnRH) from the hypothalamic preoptic area into the portal blood supply stimulates the anterior lobe of the pituitary to secrete gonadotropins (luteinizing hormone, LH; and follicle stimulating hormone, FSH). In turn, LH and FSH drive increased synthesis and secretion of gonadal steroid hormones. These hormones are regulated by negative feedback mechanisms at the hypothalamic and hypophyseal levels (Bliss *et al*., 2010; Levine, 2003). In many photoperiodic species, HPG activity and reproductive behaviors will cease during the non-breeding season. Consequently, gonad size (Prendergast *et al*., 2003) and circulating sex steroid concentrations will vary in different photoperiods (testosterone in Siberian hamsters (Bedrosian *et al*., 2012) and rams (Casao *et al*., 2010) and temperate and boreal birds (Dawson *et al*., 2001); progesterone in sheep (Birch *et al*., 2003); estradiol in Siberian hamsters: (Salverson *et al*., 2008)) . In addition to their well-described roles in reproduction, sex steroids also modulate metabolism (Grossmann, 2014; Michalakis *et al*., 2013) and immune function (Grossman, 1984; Olsen & Kovacs, 1996).

As mentioned, pineal melatonin acts as both a 'clock and calendar' to communicate photoperiodic information to the immune system (Reiter, 1993b). Significant interactions among circulating sex steroids, gonadotropins, and melatonin signaling occur to modulate photoperiodic changes in immune function (e.g., (Bentley *et al*., 1998; Demas *et al*., 1996)). However, sex steroid hormones exert a largely secondary effect (compared to other humoral mediators) in response to changes in photoperiod, and the extent to which they contribute to immune changes is largely species dependent (Demas & Nelson, 1998a; Drazen *et al*., 2000).

Investigators initially hypothesized that short days enhance immune responses in part by reducing circulating androgens. However, this hypothesis failed to gain substantial experimental support due to the different immunological effects of estrogens and androgens. Broadly, females have more robust immune responses than males and this phenomenon has been partially attributed to the immune-enhancing functions of estrogens and the immunosuppressant effects of androgens (Casimir *et al*., 2013; Klein, 2012). Photoperiod-induced gonadal regression should have sex-dependent (i.e., opposite) effects on immune system function. However, several studies have now demonstrated that immunological adaptations in males and females respond similarly to photoperiod with a higher adjustment response in males (Demas & Nelson, 1998a; Weil *et al*., 2006; Weil *et al*., 2007).

An alternative hypothesis is that sex steroids alter the response of the immune system to photoperiod. Castration increases the number of lymphocytes, and attenuates weight loss and anorectic response to LPS in male Siberian hamsters housed in both long and short days (Prendergast *et al*., 2008). Estrogens and androgens enhance lymphocyte proliferation in both sexes housed in long days (Bilbo & Nelson, 2001). However, hormone replacement in gonadectomized deer mice of both sexes does not influence the increase in lymphocyte production in response to short days (Demas & Nelson, 1998a; Demas & Nelson, 1998b). Similarly, no differences in delayed type hypersensitivity (a measure of cell-mediated immunity) occur in castrated Siberian hamsters treated with testosterone (Prendergast *et al*., 2005). However, in white crowned sparrows, exogenous testosterone supplementation attenuates LPS-induced sickness behavior , whereas castration has no effect (Ashley *et al*., 2009).

Independent of photoperiod, sex steroids modulate the immune system. In general, females display more pronounced innate and adaptive immune responses than males, allowing for faster clearance of pathogens, but leading to higher vulnerability to inflammatory and autoimmune diseases (Klein, 2012).

Folstad and Karter (1992) highlighted the role of testosterone in increasing the immunocompetence handicap, but also underlined the lack of full understanding of this hypothesis that remains controversial. On the one hand, castration of mature male rodents decreases testosterone production and elevates immunoglobulin levels, thymic weight, and humoral and cell-mediated immune function (Alexander & Stimson, 1988). On the other hand, other studies have documented no relationship between endogenous testosterone concentrations and immune response against parasitic infection (Ganley & Rajan, 2001; Klein *et al*., 1999). A more recent study suggests that infection increases circulating cortisol

and decreases circulating testosterone in rodents. This can be interpreted as physiological response aimed at redistribution of resources under immunological challenge (Lutermann *et al*., 2012).

Sex steroids exert differential effects on immune function. For example, the first response of the innate immune system is via the recruitment and mobilization of neutrophils and their over-abundance can have adverse effects on healthy tissues. Estrogens can reduce recruitment of neutrophils in humans and experimental animals (Pacifici, 2008; Sheh *et al*., 2011; Shih *et al*., 2011). Testosterone inhibits the secretion of interferon-γ (IFN-γ) from natural killer cells increasing pathogen proliferation (Lotter *et al*., 2013). Estrogen deficiency promotes the production of tumor necrosis factor-α (TNF-α) production from T cells (Pacifici, 2008). In addition to androgens and estrogens, progesterone plays an anti-inflammatory role by suppressing macrophage activity and enhancing T cell activity (Mao *et al*., 2010; Savita & Rai, 1998).

Sex steroid hormones do not directly affect the relationship between photoperiod and immune system, but play a subtle facilitating role. Apart from photoperiod, the sex steroid hormones are prominent players in the modulation of immune system.

2.4 Other Hormones

Among seasonally breeding rodents (e.g., Siberian hamsters), thyroid hormone signaling plays a central role in reorganization of reproductive physiology in response to short days (Yasuo *et al*., 2009). Under long day conditions, the conversion of the prohormone, thyroxin (T4), to its receptor-active metabolite triiodothyronine (T3) is accomplished via the increased expression of iodothyronine deiodinase 2 (DIO2). T3 then enhances gonadotropin-releasing hormone (GnRH) signaling to the pituitary from the median eminence of the hypothalamus to mediate reproductive physiology (Nakao *et al*., 2008; Ono *et al*., 2008; Prendergast *et al*., 2013). Short day exposure increases DIO3 expression, which leads to the conversion of T4 to a biologically inactive enantiomer, rT3; and T3 into T2. This effectively eliminates GnRH signaling to inhibit reproductive development (Nakao *et al*., 2008).

Thyroid hormones play a central role in seasonal variation in reproduction and have immunomodulatory actions (Dorshkind & Horseman, 2000). Thyroid hormone receptors are expressed in many lymphoid tissues (De Vito *et al*., 2011; Foster *et al*., 1999; Segal & Ingbar, 1982), and T3 modulates lymphoid cell development and function (Mascanfroni *et al*., 2008; Mascanfroni *et al*., 2010). Recently, day length-induced epigenetic modification of the dio3 promoter has been demonstrated to be a mechanism by which short photoperiods alter lymphoid T3-signaling to enhance adaptive immune function (Stevenson *et al*., 2014). Epigenetic silencing of DIO3 signaling in short day lymphocytes results in the opposite pattern observed to reproductive physiology (Nakao *et al*., 2008) or in response to exogenous melatonin (Prendergast *et al*., 2013). Therefore, a reciprocal relationship between dio3 methylation within the hypothalamus and in lymphocytes seems to facilitate seasonal plasticity in reproduction and immune function (Stevenson & Prendergast, 2013). In short days, increases in hypothalamic DIO3 results in reproductive suppression, and epigenetic silencing of *dio3* in peripheral lymphocytes leads to simultaneous immune augmentation.

Glucocorticoids play a pivotal role in immune system modulation via hypothalamic-pituitary-adrenal (HPA) axis activation in response to environmental stressors. HPA-axis physiology is modulated by photoperiod as reflected in altered mineralocorticoid receptor (MR), glucocorticoid receptor (GR) gene expression, circulating glucocorticoid concentrations, negative feedback mechanisms, and behavioral response to glucocorticoid administration (Breuner & Wingfield, 2000; Pyter *et al*., 2007; Ronchi *et al*., 1998; Walton *et al*., 2013). MR (high affinity, low capacity) and GR (low affinity, high capacity) are present on most immune cell types, and their complementary signaling properties allows for anti-inflammatory actions in response to both phasic and tonic glucocorticoid elevations, respectively (Armanini *et al*., 1988; McEwen *et al*., 1997; Munck *et al*., 1984). HPA axis responsiveness varies in response to changes in photoperiod in several avian and mammalian species (Astheimer *et al*., 1995; Breuner & Wingfield, 2000; Reeder & Kramer, 2005; Ronchi *et al*., 1998; Sapolsky *et al*., 2000).

The HPA axis plays a prominent negative feedback role in response to immune challenge. Upon HPA activation by inflammatory cytokines (e.g., IL-1β, TNF), glucocorticoids are released and negatively regulate further cytokine production, thereby attenuating and preventing ‘runaway inflammation’. However, upon chronic HPA axis activation, sustained glucocorticoid elevation can lead to a maladaptive suppression of immune responses (McEwen *et al*., 1997; Sapolsky *et al*., 2000).

Glucocorticoids can act in a reciprocal fashion to melatonin signals to modulate T-cell mediated immune responses under physiologically stressful conditions (Gupta & Haldar, 2013). The interaction between melatonin and glucocorticoids may underlie differential photoperiodic responses to environmental stress in a tissue specific manner. Several species increase circulating glucocorticoids and alter GR expression in short days (Bilbo *et al*., 2002a; Pyter *et al*., 2005; Weil *et al*., 2006). Indeed, GR expression in the spleen (but not skin) varies seasonally in house sparrows *(Passer domesticus)*, and is increased in the hippocampus of Siberian hamsters following short day exposure (Lattin *et al*., 2013; Walton *et al*., 2012). Similar seasonal variation likely exists in other species, and contributes to seasonal plasticity in immune function.

Prolactin, a protein hormone released by the anterior pituitary, has pleiotropic actions on several organ systems, (Goffin *et al*., 1999) and varies in response to photoperiod in many species (Goldman & Nelson, 1993). Hypophysectomized animals have impaired adaptive and innate immune functions, and either prolactin and/or growth hormone supplementation can restore these functions (Gala, 1991). The large number of functions attributed to prolactin has led to the suggestion that it be re-named “versatilin” or “omnipotin” (Bern & Nicoll, 1968; Weigent, 1996). Specifically, leukocytes express prolactin receptors, and administration of bromocriptine, a drug that blocks prolactin release, impairs immune responses (Gala, 1991). Furthermore, lymphoid cells express prolactin, in an autocrine fashion, to affect proliferation, cytokine secretion and function (Lopez-Rincon *et al*., 2013).

Short-days typically induce reductions in circulating prolactin concentrations (Auchtung & Dahl, 2004; Goldman & Nelson, 1993). Prolactin is unique in that it is broadly immunoenhancing and consistently increased in long day conditions, and exogenous

prolactin administration can promote a long day immune phenotype (Auchtung & Dahl, 2004).

3. Role of Perinatal Photoperiods in Programming Adult Immune Function

In addition to regulating adult phenotypic plasticity, photoperiodic experiences during early life can establish a developmental trajectory with important implications for immune defenses. As noted, small mammals are typically born during the long days of spring and summer (Bronson, 1985; Goldman & Nelson, 1993). However, if these animals are born early in the spring, then they are likely to undergo rapid reproductive development and attempt to mate before the end of their first summer (Gorman, 2001). In contrast, animals born late in the summer are unlikely to have the time necessary to grow, undergo reproductive development, and breed before the onset of winter (Horton, 1984). Late season animals typically maintain a prepubertal phenotype and delay growth and reproductive development until the following spring. These rapid and significant shifts in physiological priorities are mirrored by adjustments in immune physiology (Weil *et al*., 2006).

The reproductive system appears to measure seasonal time by comparing the ambient photoperiod to the photoperiod that preceded it (Hoffmann *et al*., 1986). Siberian hamsters and other photoperiodic rodents use a system, termed ‘photoperiod memory’, wherein they compare the ambient photoperiod to one encoded prenatally (Elliott & Goldman, 1989; Stetson *et al*., 1986). Thus, a reduction in day length will result in gonadal regression to intermediate photoperiods. For instance, hamsters born in long days (15L), then transferred to an intermediate day lengths (13.5L), retard reproductive development (Prendergast *et al*., 2000). However, hamsters born in short days (12L), then transferred to the same intermediate day length (13.5L) will undergo rapid reproductive development (Prendergast *et al*., 2000).

The immune system of Siberian hamsters, in contrast, appears to be influenced by the absolute photoperiod, rather than the directionality of change. Hamsters born in long day lengths, then transferred to intermediate day lengths failed to enhance circulating lymphocytes, monocytes, or delayed-type hypersensitivity responses as did hamsters housed in unambiguously short day lengths (Prendergast *et al*., 2004). Similarly, hamsters housed perinatally in long days, then transferred into short days at weaning, markedly regressed their reproductive system, but failed to undergo the typical short day pattern of delayed-type hypersensitivity responses (Weil *et al*., 2006).

3.2 The Evolution of Photoperiodic Reproductive-Immune Relationships

The results of studies of perinatal and intermediate photoperiods that immunological and reproductive adjustments to day length could be dissociated have two important implications. First, hamsters can show the short day pattern of gonadal responses simultaneously with long day typical immune responses (Weil *et al*., 2006; Weil *et al*., 2007). If enhanced immune responses, in short day lengths, were a byproduct of passive shunting of energy from the reproductive system to the immune system, then this pattern of responses should not occur. Rather, it seems that the investment in immune defenses in short day lengths is an active process that is dissociable from changes in the HPG axis.

Importantly, to our knowledge, there are no published examples of animals simultaneously displaying enhanced short day pattern of immune responses and large functional gonads. Whether these two conditions are physiologically impossible to maintain together remains unspecified. One possible experiment would involve housing animals in very short day lengths (6L) and then transferring them to 12L. Theoretically this manipulation should stimulate the gonads to grow but maintain a sufficiently short day length to enhance immune function (Rivkees *et al*., 1988).

A second, but equally important, conclusion to draw from the dissociation of immune and reproductive responses to day length is that it is possible that the immunological adjustments associated with changing day lengths evolved independently from photoperiodic reproductive regulation. Free-living animals experience day lengths that are constantly, but gradually, changing and the laboratory conditions that are necessary to dissociate the reproductive and immune responses are unlikely to occur (Prendergast *et al*., 2004). Therefore, in the vast majority of situations the environmental cues responsible for alterations in the reproductive and immunological systems would overlap. However, they have very different formal properties such that the reproductive system attends primarily to the directionality of change in day length where the immune system attends to the absolute day length (Bronson, 1985; Prendergast *et al*., 2004; Weil *et al*., 2006).

It seems likely that melatonin regulation of photoperiod-mediated seasonal reproductive function first evolved and that over evolutionary time the immune system evolved to "eavesdrop" on the signals controlling reproduction. An analogy can be drawn to the relationship among sex steroid hormones, gonadal activity, and mating behaviors. Presumably the HPG axis evolved to regulate gonadal function, but over evolutionary time the nervous system co-opted the endocrine signals to synchronize sexual behavior with maximal fertility (Adkins-Regan, 2005; Lange *et al*., 2002). In the photoperiodism--melatonin circuitry it is possible that a similar process occurred, although this remains conjecture. In any case, the overlapping, but distinct, melatonin signals to which the immune and reproductive systems respond suggest such an arrangement. Finally, although birds are much less dependent on melatonin signaling for control of reproduction the thyroid axis seems to regulate both immune and reproductive physiology and may be another example of the co-opting of one system for the control of another.

4. Future Directions

4. 1 The Gut Microbiota

Increasingly, the role of commensal microbes inhabiting the gut has been revealed to modulate metabolism, inflammation, immune defenses, as well as learning and memory and affective responses (Backhed *et al*., 2004; Cryan & Dinan, 2012; Round & Mazmanian, 2009). Microorganisms outnumber the number of host cells by nearly two orders of magnitude and chronically colonize mammals (Gordon, 2012; Xu & Gordon, 2003). This symbiotic relationship is critically important to the host as the microbial population can assist in extracting nutrients from otherwise indigestible dietary components (Sonnenburg *et al*., 2005). Additionally, the microbial population contributes to the defense against pathogenic microbes by sequestration of nutrients, production of antimicrobial compounds,

physical fortification of epithelial barriers, and stimulation of host production of secretory IgA (Round & Mazmanian, 2009).

The neuroendocrine system has bidirectional interactions with the gut microbiome. The gut resident microbes can synthesize or alter the production of metabolically (and immunologically) relevant peptides including glucagon such as peptide-1, protein YY, ghrelin, leptin, and several other signaling molecules (Ellis *et al*., 2008). The interactions among the neuroendocrine system, photoperiodic modulation of physiology, and the gut microbiome warrant discussion here. Siberian hamsters weigh significantly less because of reduced body fat in short compared to long days (Weil *et al*., 2011). This response likely reflects resistance to leptin signaling in the hypothalamus in long days (Ellis *et al*., 2008). Leptin knockout mice display significant shifts in gut microbiome constituents (Ley *et al*., 2005). Because food quality and availability are reduced during the winter at high latitudes, the relative abundance of microbes of the phylum Firmicutes was predicted to increase under short day lengths to aid in extracting increased energy from plant-based diets (Bailey *et al*., 2010). Previous studies demonstrated that an increase in Firmicutes prevalence is associated with obesity in both humans and nonhuman animals (Ley *et al*., 2005; Turnbaugh *et al*., 2006). Bacterial tag-encoded FLX amplicon pyrosequencing of hamsters housed in short or long day lengths indicated that the composition of the Siberian hamster microbiota shifted in response to changing photoperiods. However, the relative abundance of the Firmicutes did not change; rather, hamsters housed in short day lengths reduced numbers of organisms within the phylum Proteobacteria and had fewer organisms from the genus Citrobacter without altering the total numbers of microbes or the overall microbial diversity (Bailey *et al*., 2010).

One potential explanation for the photoperiodic changes in gut proteobacteria may reflect seasonal variation in diet. In the spring and summer, Siberian hamsters eat a larger proportion of seeds, which are rich in both fats and proteins (Fine & Bartness, 1996). In the laboratory, hamsters increased preference for high fat diets in long day lengths (Fine & Bartness, 1996). High fat feeding increases Proteobacteria and may help in maximizing nutrient extraction from these types of foods (Hildebrandt *et al*., 2009). Thus, a long day increase in Proteobacteria may reflect a preparatory response to changing diets.

Additionally, it remains possible that changes in the gut microbiota bidirectionally interact with changes in immune defenses across the year; that is the changing priorities in immune defenses may make the gut differentially hospitable to different classes of microbes while the possibility also exists that changes in the gut microbiota drive alterations in immune physiology. Conversely, Citrobacter spp, which are from the Enterobacteriaceae family, are related to intestinal inflammation (Lupp *et al*., 2007). During experimental intestinal infection, the levels of pathogenic Campylobacter and Salmonella are positively associated with Enterobacteriaceae prevalence; these components of the microbiota provide a conducive environment for pathogenic bacteria (Stecher *et al*., 2007). Further, Proteobacteria are both pro-inflammatory and increase in response to inflammation suggesting that the short day hamsters limit the proliferation of these microbes in order to reduce the potential for pathological infection and inflammation during the energetically challenging days of winter (Pedron & Sansonetti, 2008).

Conversely, the gut microbiota regulates adult immune defenses in part by regulating mucosal immunity, dendritic cell activation and differentiation and expansion of regulatory T cells and in particular the TH17 population (Round & Mazmanian, 2009). Immune defenses are intimately regulated by these cell types (Martin *et al*., 2008; Pedron & Sansonetti, 2008). Future studies need to investigate the neuroendocrine signals responsible for changes in gut microbiota and potential immune responses, as well as assess the role of the microbiota in the previously observed photoperiodic changes in immune defenses. Finally, a study of hamsters raised in sterile conditions or otherwise depleted of gut microbiota and then inoculated with the intestinal contents of either long or short day hamsters will provide information regarding the role of these microbes in metabolic and immune changes induced by photoperiod.

4.2. Climate Change and Light Pollution

As temperatures rise worldwide and climate differs from the predictable annual patterns of weather, the relationship between photoperiod and optimal timing of food availability and reproduction are becoming mismatched. Furthermore, photoperiodic neuroendocrine modulation of the immune system evolved over a vast period of time when light was largely restricted to the day (with the exception of moon light and other natural sources at night). However, during the past ∼120 years urbanization and the development of powerful artificial lighting sources have led to pervasive light pollution. For instance, a full moon produces around 0.1–0.3 lux, an overcast night sky is illuminated only at around 0.00003–0.000001 lux whereas street lights produce 5–60 lux depending on the distance and type of light which are sufficient to block nighttime melatonin production (Rich & Longcore, 2006). In urban environments, where multiple light sources are present night time lighting levels may be even higher (Gaston *et al*., 2012). European blackbirds exposed to light at night at intensities typical for urban environments display significant annual advancements in breeding and molting (Dominoni *et al*., 2013). Further, photoperiodic bird species typically require prolonged exposure to short photoperiods to reset their annual cycle of breeding (Dawson *et al*., 2001). In the absence of dark nights a birds did not exhibit annual cycles of testicular development or breeding behavior. Therefore, the consistent and largely noise-free signal that was once available from attending to the daily light-dark cycle is no longer reliable for many free living animals, especially those living in close association with humans.

Immunological responses are altered by light at night. For instance, housing Japanese quail (*Coturnix coturnix japonica*) in constant light attenuated swelling responses to phytohemagglutinin and reduced antibody responses to sheep red blood cells (Moore & Siopes, 2000). Nocturnal light exposure reduces natural killer cell responses in rats (Oishi *et al*., 2006) and reduces both basal and stress-modulated delayed type hypersensitivity responses in Siberian hamsters (Bedrosian *et al*., 2013a). Additionally, even dim light at night can interfere with the photoperiodic modulation of the immune system such that the generally immune enhancing effects of short days are lost, presumably by inhibiting nighttime melatonin secretion. Siberian hamsters housed in short day lengths increase delayed type hypersensitivity responses relative to long day conspecifics. However, if the dark nights of these photoperiod conditions are replaced with low levels of ambient light

(dim light at night, 5-lux), then both the reproductive and immunological adjustments associated with short days are abolished (Aubrecht *et al*., 2014; Ikeno *et al*., 2014). Further, whereas acute stress prior to antigenic challenge typically enhances delayed type hypersensitivity responses in both long and short day lengths, exposure to dim light at night abolishes that stress response in hamsters (Aubrecht *et al*., 2014; Dhabhar & McEwen, 1997; Dhabhar & McEwen, 1999). Therefore, the consequences of nocturnal light pollution are significant for photoperiodic animals because it can prevent the acquisition of the short day phenotype and also directly suppress immune responses. The extent that light pollution is contributing to species extinction requires substantial additional research.

5. Conclusion

Photoperiodic adjustments in immune function are among the most pronounced and important adaptations to the changing seasons that have been observed in free living and laboratory studies. The work of many groups has demonstrated the overarching role of pineal melatonin and many other components of the neuroendocrine system as master regulators of physiological adjustments to the changing seasons. New components in these systems are constantly being discovered and include previously neglected organisms like the gut microbiome. In the modern era, the relationship between the neuroendocrine and immune systems is being obscured by light pollution and climate change. Our challenge now is to understand the way in which animals adapt to changing environmental conditions so that we can begin to understand the physiological and fitness consequences of these new environmental changes. The seasonal and photoperiodic adjustments in the relationship between the neuroendocrine and immune systems is a useful model system for understanding the way organisms adjust to changing conditions, prioritize among competing physiological systems, and increase immune defenses without immunological pathology.

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- Animals face different challenges at different times of the year.
- Many species use day length and melatonin to monitor the changing seasons.
- Melatonin drives seasonal changes in the neuroendocrine system.
- Melatonin alters immune function both directly and indirectly via neuroendocrine signaling.

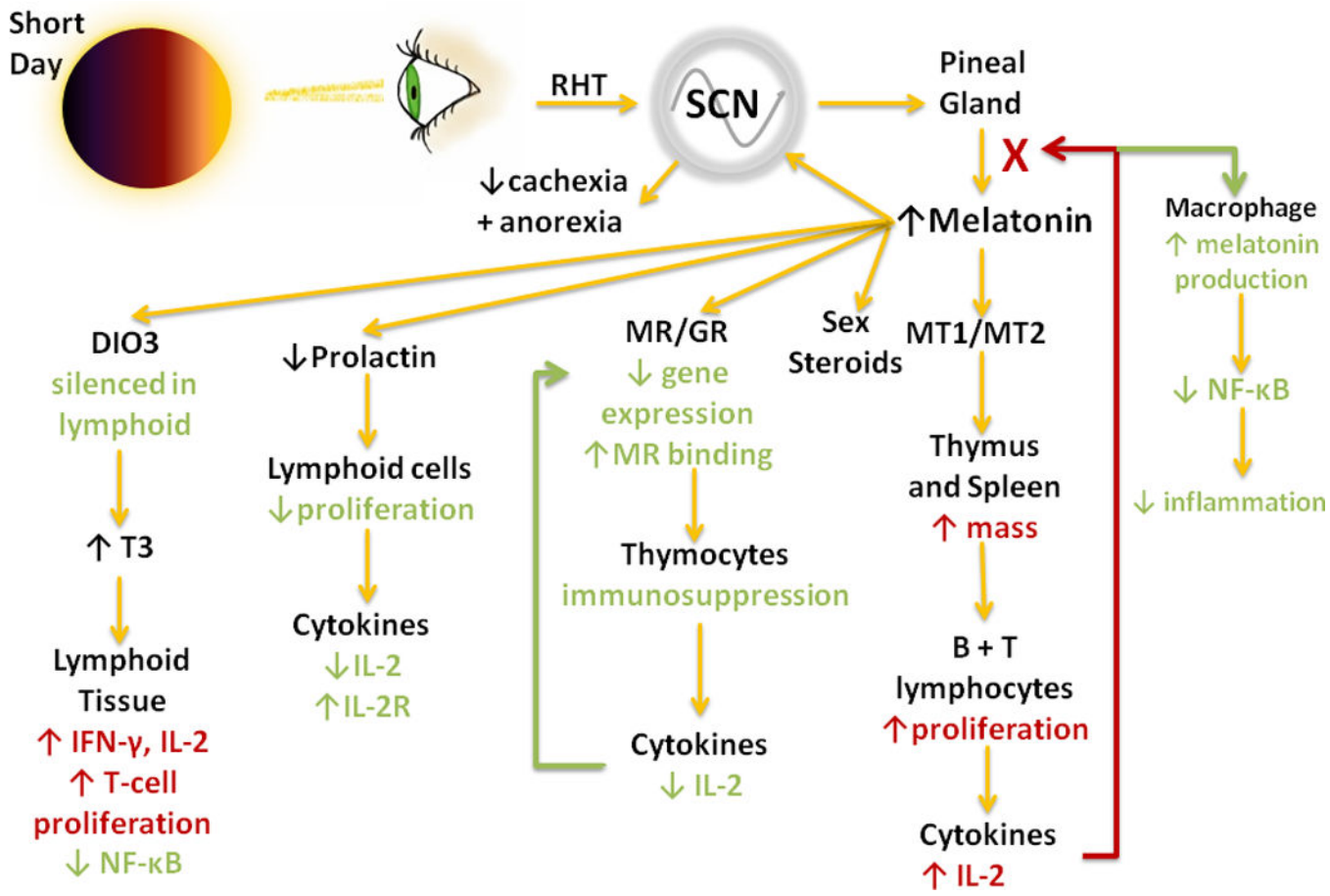

Figure.

Photic information is transmitted along the retinohypothalamic tract (RHT) by intrinsically photosensitive retinal ganglion cells (iPRGCs) to the suprachiasmatic nucleus (SCN). Photoperiod is transduced from an environmental cue into a neuroendocrine one via the nighttime secretion of pineal melatonin. Short day lengths are represented physiologically by increased duration of melatonin secretion. Melatonin in turn, regulates immune physiology both directly, through MT1/2 receptors on immune tissues, and indirectly via modulation of several neuroendocrine systems. The combined effect results in a system primed for immediate response to immune threats and stunted long term sickness behavior. RHT, retinohypothalamic tract; SCN: suprachiasmatic nucleus; MT1/2, melatonin receptors 1 and 2; MR, mineralocorticoid receptor; GR, glucocorticoid receptor; DIO3, deiodinase iodothyronine type III; T3, triiodothyronine.