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REVIEW

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Seasonality of prolactin in birds and mammals

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Abstract

In most animals, annual rhythms in environmental cues and internal programs regulate seasonal physiology and behavior. Prolactin, an evolutionarily ancient hormone, serves as a molecular correlate of seasonal timing in most species. Prolactin is highly pleiotropic with a wide variety of well-documented physiological effects; in a seasonal context prolactin is known to regulate annual changes in pelage and molt. While short-term homeostatic variation of prolactin secretion is under the control of the hypothalamus, long-term seasonal rhythms of prolactin are programmed by endogenous timers that reside in the pituitary gland. The molecular basis of these rhythms is generally understood to be melatonin dependent in mammals. Prolactin rhythmicity persists for several years in many species, in the absence of hypothalamic signaling. Such evidence in mammals has supported the hypothesis that seasonal rhythms in prolactin derive from an endogenous timer within the pituitary gland that is entrained by external photoperiod. In this review, we describe the conserved nature of prolactin signaling in birds and mammals and highlight its role in regulating multiple diverse physiological systems. The review will cover the current understanding of the molecular control of prolactin seasonality and propose a mechanism by which long-term rhythms may be generated in amniotes.

KEYWORDS
metabolism, neuroendocrinology, prolactin, reproduction, seasonality

1 | INTRODUCTION

Rhythmic seasonal variations in physiology and behavior are present across the animal kingdom, ensuring survival and reproductive success in the face of a changing environment in the temperate and polar zones. This typically presents as restriction of reproductive capacity to a particular time of year (in so-called "seasonal breeders") and altered metabolism and behavior that favor energy conservation in food-scarce winter environments. Seasonal animals typically rely on photoperiod, a reliable environmental cue, to entrain and elicit these anticipatory physiological rhythms. Such rhythms are often associated with marked variation of hormonal signaling pathways, reflecting the suppression or activation of their physiological processes. One such hormone, prolactin, shows seasonality in most animal species that express seasonal biology.

Prolactin was first identified in 1933 by Oscar Riddle and colleagues in pigeons, where it was found to stimulate crop-milk production (Riddle et al., 1933). While it was first identified in birds, a putative, pituitary-derived stimulatory factor driving milk

secretion in mammals had been hypothesized as early as the late 1920s (Riddle et al., 1933)—thus the name prolactin was proposed. Prolactin is an ancient hormone that predates mammalian evolution and is present in all vertebrates (a review of prolactin from an evolutionary perspective is given in Dobolyi et al., 2020). While its critical role in lactation was the first function identified, prolactin is now recognized as a pleiotropic hormone with a growing list of over 300 known functions (Bole-Feysot et al., 1998). Prolactin exerts effects upon a range of tissue types; the diversity of response in various tissues is highlighted in Figure 1. Prolactin has a well-established role in regulating both metabolic and reproductive processes. Given that prolactin levels reflect seasonal status, we are presented with an intriguing possibility that prolactin acts as an integrated hormonal cue that communicates season to a multitude of tissues. The following review will present our current understanding of the basic homeostatic control of prolactin secretion, as well as its roles in regulating metabolic and reproductive physiology and behavior in birds and mammals. We present an overview of seasonal variations of prolactin secretion across a range of model species, as well as our understanding of how seasonal prolactin variability is regulated. Finally, we discuss the effects of melatonin signaling on prolactin seasonal rhythms and postulate how an endogenous timer present in the pituitary gland may drive these rhythms.

2 | THE HYPOTHALAMIC-PROLACTIN AXIS

The mammalian mechanism of prolactin secretion stands apart from nonmammalian species as it is spontaneously released from lactotrophs without requiring hypothalamic input. Early functional studies demonstrated that lesions of the pituitary stalk left female rats capable of lactation (Dempsey & Uotila, 1940). Additionally, prolactin function is rescued in rats where pituitary grafts were implanted following hypophysectomy (Everett, 1954). Such early lesion studies also clearly demonstrated that hypothalamic input is required to maintain of physiological levels of prolactin. Pituitary stalk lesions in female rats induce pseudopregnancy, a physiological indicator of hyperprolactinaemia (Nikitovitch-Winer et al., 1958), and these functional findings were later supported by serum immunoassay studies, demonstrating chronic elevated prolactin (Kanematsu & Sawyer, 1973). It is now well established that the neurotransmitter dopamine (DA) acts as a neurohormone to regulate prolactin secretion. Initially, this was based on observations on the prolactin supressing properties of DA receptor agonists, and subsequent demonstration that DA is present in the hypophyseal portal blood and fluctuates in synchrony with variations in prolactin secretion (Ben-Jonathan et al., 1977; Gibbs & Neill, 1978). Later genetic knockout studies in mice would further elucidate the

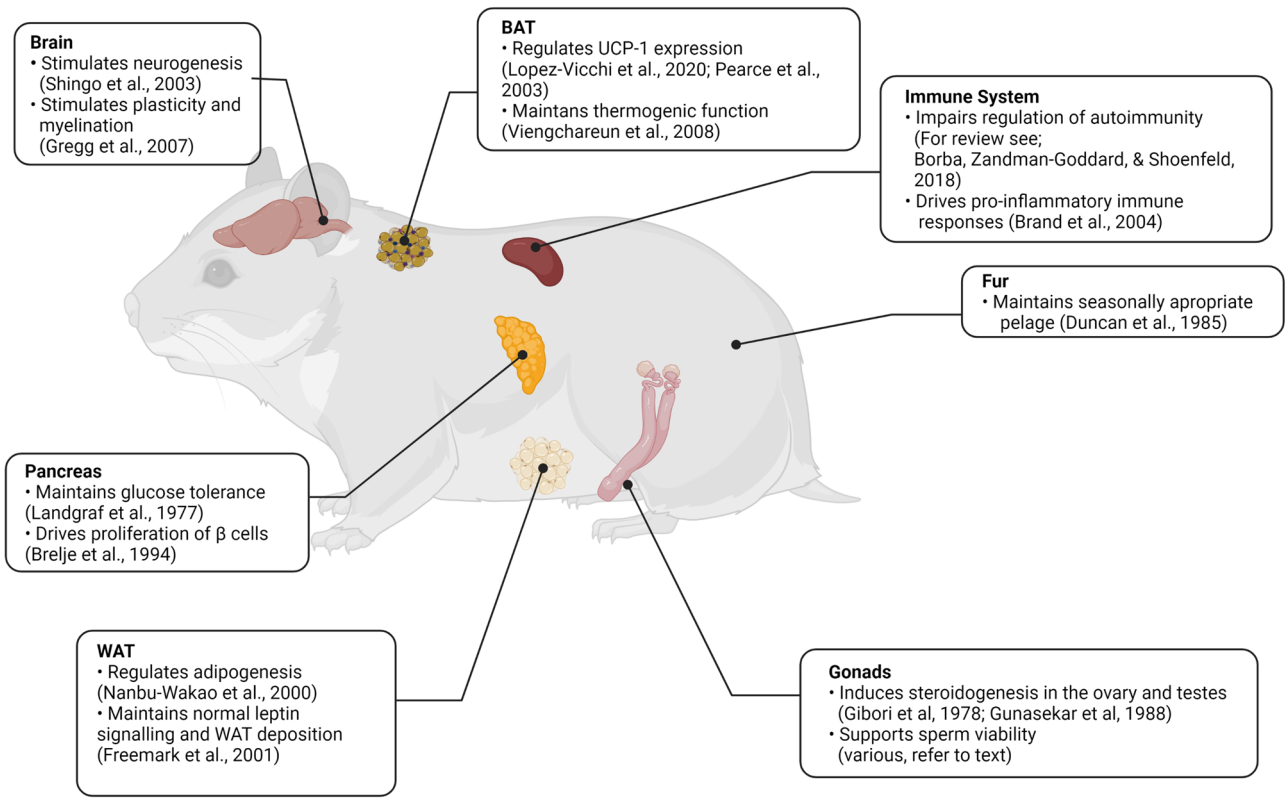

FIGURE 1 The peripheral effects of prolactin signaling. The peripheral effects of prolactin in select peripheral tissues (pancreas, WAT, BAT, immune system, gonads, and fur) and central effects of prolactin

mechanism of DA action on the lactotroph, demonstrating the necessity of the D_2 receptor which, if nonfunctional, leads to hyperprolactinaemia (Kelly et al., 1997; Saiardi et al., 1997). This DA inhibition-based regulation is made possible by endogenous electrical properties of lactotroph which possess voltage-gated calcium channels generating spontaneous electrical activity, even when isolated from external inputs. Their spontaneous electrical activity is inhibited by DA and leads to decreased prolactin expression and secretion (Elsholtz et al., 1991; Gregerson et al., 1994; Gregerson, 2003; Lledo et al., 1990).

The neuroanatomy of the cell populations generating neuroendocrine DA secretion in mammals is well defined by a plethora of rodent studies, belonging to the A12 and A14 groups of catecholamine neurons based on categories established by Dahlström and Fuxe (Dahlstroem & Fuxe, 1964) (Figure 2). These neurons are subcategorized further based upon their projection targets. Tuberoinfundibular DA (TIDA) neurons are scattered throughout the dorsomedial arcuate nucleus (A12 group) of the hypothalamus, projecting axons to the median eminence (Björklund et al., 1973) where terminals release DA into the vasculature via fenestrated capillaries and delivered to the anterior pituitary through long portal vessels. Tuberohypophyseal DA (THDA) neurons are confined to the rostral arcuate nucleus (A12) and extend their axons to the intermediate and posterior lobes of the pituitary (Holzbauer et al., 1978). Finally, the periventricular hypophyseal DA (PHDA) neurons originate in the periventricular nucleus of the hypothalamus (A14) and project exclusively to the intermediate lobe of the pituitary (Goudreau et al., 1995). DA secreted by the THDA and PHDA neurons is transported to lactotrophs in the anterior pituitary via short portal vessels extending between the lobes (Peters et al., 1981). While THDA and PHDA neurons play a role in regulating the secretion of prolactin, TIDA neuron output accounts for the bulk of the inhibition of prolactin release (De Greef & Neill, 1979; de Greef et al., 1981). Factors such as their release patterns and overlap in dendritic field have typically led researchers to conclude that these populations, while distinct, likely play a similar role in terms of their regulation and function. In addition to neurosecretory DA neurons, noradrenaline neurons have been implicated in regulating the secretion of prolactin in sheep. Axons from noradrenergic neurons terminate in the ovine median eminence, appear to secrete into portal blood and suppress prolactin release (Thomas, Cummins, Doughton, et al., 1989; Thomas, Cummins, Smythe, et al., 1989; Tillet & Thibault, 1989). However, receptor antagonist studies on sheep in vivo demonstrate a stronger and more sustained rise in secreted prolactin using DA receptor antagonists compared with adrenoceptor receptor antagonists (Lincoln & Clarke, 2002; Meyer & Goodman, 1985), implicating DA as the dominant prolactin inhibitory factor.

In contrast to DA-mediated inhibitory control in mammals, prolactin secretion in avian species is a more typical stimulatory neuroendocrine axis. Neurons located in the basal hypothalamus that project to the median eminence and synthesise vasoactive intestinal peptide (VIP) have been described in several avian species including the Japanese quail (*Coturnix japonica*) (Yamada et al., 1982), bantam hen (*Gallus domesticus*) (Macnamee et al., 1986), domestic turkey (*Meleagris gallopavo*) (Mauro et al., 1989), and ring dove (*Streptopeliarisoria risoria*) (Cloues et al., 1990). VIP is detectable in the portal blood of domestic turkeys which supports that these neurons are neuroendocrine in nature and not simply innervating other secretory cells in the median eminence (Youngren et al., 1996). Furthermore, portal VIP concentrations reflect the level of circulating prolactin across various reproductive states in hens (Youngren et al., 1996). Studies utilizing immunoneutralization have demonstrated the necessity of VIP signaling by injection of antibodies raised against avian VIP into the hypothalamus of bantam and turkey hens, which blocks prolactin release in various physiological states (El Halawani et al., 1996; Sharp et al., 1989). DA signaling has also been implicated in prolactin release in birds, with putative DA signaling increasing in the hypothalamus of incubating birds (Lea et al., 2001; Macnamee & Sharp, 1989).

The presence of prolactin receptor in DA neurosecretory cells and other brain populations suggests prolactin can enter the brain, despite being a large molecule (~22 kDa) preventing passive entry into the brain by the blood-brain-barrier (Oetting et al., 1989). A likely mechanism permitting this is through receptor-mediated active transport of prolactin into the cerebrospinal fluid (CSF) (Login & MacLeod, 1977; Nicholson et al., 1980; Walsh et al., 1987). The prolactin receptor is highly expressed in the choroid plexus which lines the ventricles of the brain and secretes CSF, implicating this as a likely transport pathway (Pi & Grattan, 1998; Walsh et al., 1990). Regions with high densities of prolactin receptor expression such as the arcuate and medial preoptic nuclei are typically located adjacent to ventricles where prolactin may readily diffuse from the CSF via the "leaky" ependymal cell lining. Additionally in the arcuate nucleus where TIDA neurons reside, fenestrated capillaries create permeability in the blood-brain-barrier which may allow passage of prolactin directly—a mechanism that has been proposed for other hormone signaling pathways in this region (Leon-Mercado et al., 2017; Schaeffer et al., 2013). The ability of prolactin to access the brain allows it to act to regulate its own release via the neural substrates that gate its secretion, a process termed "short-loop" feedback. prolactin receptors are present in neuroendocrine DA neurons (Lerant & Freeman, 1998), and prolactin increases DA synthesis in the hypothalamus (Hökfelt & Fuxe, 1972) as well as DA content in the median eminence and portal vasculature (Gudelsky & Porter, 1979; Lookingland et al., 1987). These activities are particularly well studied in TIDA neurons where prolactin is observed to rapidly increase firing rate (Brown et al., 2012; Lyons et al., 2012). In addition to rapid electrical effects, prolactin may also regulate DA neuron activity by inducing synthesis and posttranslational phosphorylation of tyrosine hydroxylase (Arbogast & Voogt, 1991, 1997; Ma et al., 2005), the rate-limiting enzyme involved in DA synthesis. The capacity for prolactin to control its own secretion via these mechanisms allows for appropriate feedback to occur in the absence of a single downstream endocrine tissue that is present in other neuroendocrine axes.

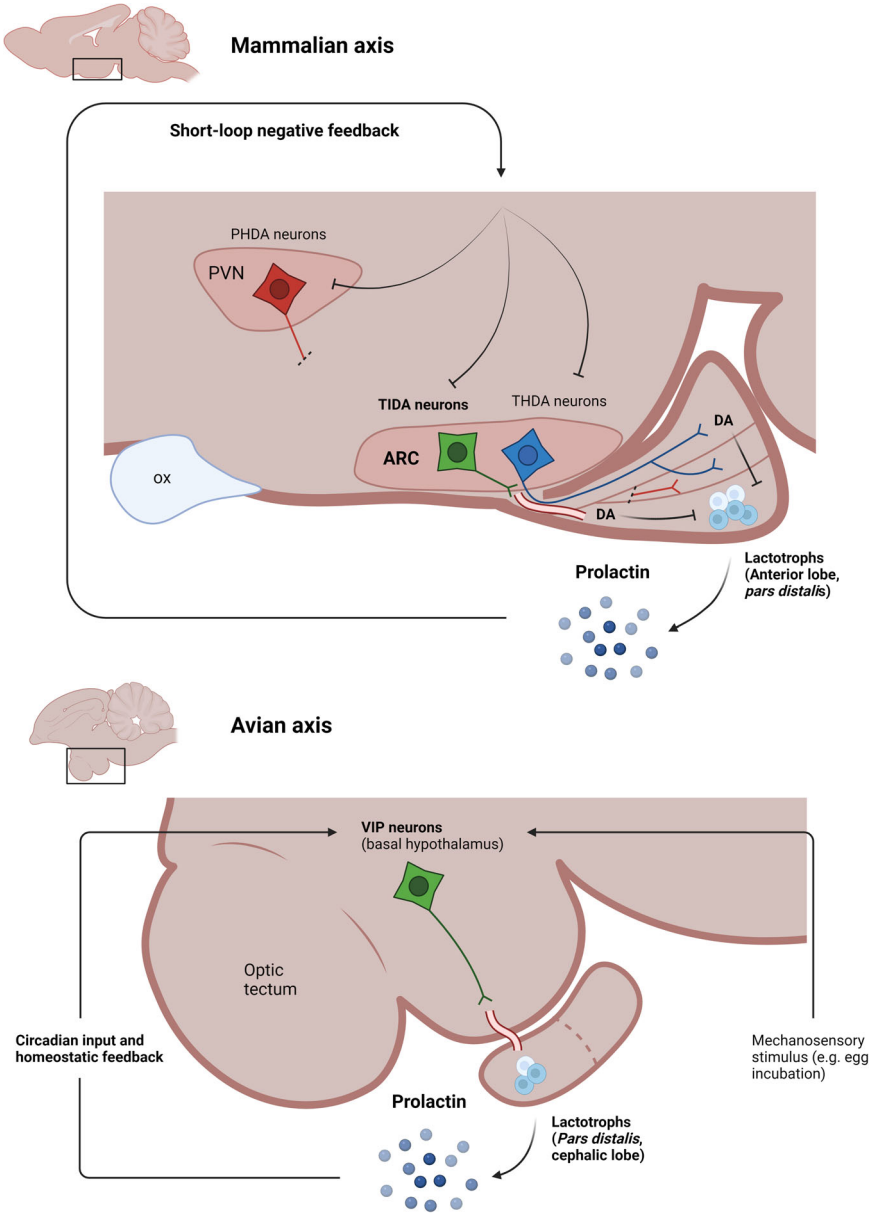

FIGURE 2 The central homeostatic control of prolactin secretion. (Top) A schematic representation of the mammalian hypothalamic-prolactin axis with bold text highlighting the principal components of the axis. Three subpopulations of dopamine neurons are represented in the hypothalamus as well as their distinct projection targets. Tuberoinfundibular dopamine (TIDA, green) neurons in the arcuate nucleus (ARC) terminate in the median eminence where dopamine (DA) is released into the portal blood circulating toward the anterior pituitary to inhibit prolactin release. Lactotrophs secrete prolactin into the general circulation where it can act upon target peripheral tissues and drives inhibitory DA release in a short-loop feedback mechanism. Ancillary neural populations, namely the tuberohypophyseal dopamine (THDA, blue) and periventricular hypophyseal dopamine (PHDA, red) neurons are also involved in the inhibition of prolactin release, terminating in the intermediate and posterior lobes of the pituitary gland. (Bottom) The avian hypothalamic-prolactin axis differs as prolactin release is driven by a stimulatory hypothalamic output. During incubating season, the activity of vasoactive intestinal peptide (VIP) expressing neurons increase, releasing VIP into the portal blood. VIP stimulates a large rise in prolactin secretion during this season, and circulating prolactin typically remains high until posthatching

3 | PROLACTIN AS AN ENERGETIC HORMONE

A growing body of literature has highlighted critical metabolic functions of prolactin. The prolactin receptor is expressed in a number of hypothalamic regions associated with energy balance, such as the arcuate nucleus (ARC), dorsomedial nucleus (DMH) and paraventricular nucleus (PVN) (Chen & Smith, 2004; Sirzen-Zelenskaya et al., 2011). In the ARC, prolactin has been shown to down regulate the expression of pro-opiomelanocortin (POMC), an anorexigenic neuropeptide (Tong & Pelletier, 1992). Some conflicting findings have been reported regarding regulation of orexigenic NPY

within the arcuate nucleus. Within the DMH, but not the arcuate nucleus, prolactin administration appears to drive orexigenic neuropeptide Y expression (Chen & Smith, 2004). However, likely due to altered energetic state, chronic hyperprolactinaemia appears to drive increases in NPY and AgRP expression within the arcuate nucleus, (Lopez-Vicchi et al., 2020). An increase in NPY expression is consistent with the physiological effects of increased food intake with prolactin administration (Naef & Woodside, 2007). In addition to direct actions, prolactin may influence primary energy circuits by acting on afferent neurons. Oxytocinergic neurons within the PVN, which project to the ARC where they drive POMC signaling (Maejima et al., 2014), generate a hyperpolarising current after prolactin administration (Sirzen-Zelenskaya et al., 2011).

In humans, obesity has been associated with hyperprolactinaemia resulting from pituitary adenomas (Greenman et al., 1998). Prolactin has been implicated in driving adipogenesis, having been found to enhance expression of critical early adipogenic transcription factors; peroxisome proliferator activated receptor γ and CCAAT enhancer binding protein beta (C/EBPβ) (Nanbu-Wakao et al., 2000). Prolactin receptor knockout models have revealed decreased fat mass, altered lipid metabolism and impaired leptin signaling in mice (Freemark et al., 2001). Several studies have shown prolactin to increase food intake in a dose dependent manner in multiple species (Gerardo-Gettens et al., 1989a, 1989b). The effect of prolactin administration appears to be nucleus specific within the hypothalamus, with administration to PVN specifically driving an increase in food intake and body weight, while VMH and POA injections show no response (Sauvé & Woodside, 2000); this may suggest prolactin acts by influencing the canonical energy balance circuits. Interestingly, the degree to which prolactin drives food intake may be sex dependent as female rats displaying a greater response to prolactin than their male counterparts (Heil, 1999). Ovariectomy appears to have no impact on the ability of prolactin to modulate food intake, implying that ovarian hormones are not involved in the mechanism by which prolactin acts on energy balance (Sauve´ & Woodside, 1996) (Freemark et al., 2001).

Uncoupling proteins, critical in nonshivering thermogenesis, are upregulated by prolactin signaling in neonates (Pearce et al., 2003). However, adult mice display reduced *ucp1* expression after chronic hyperprolactinaemia which may indicate a response to prolonged altered metabolic status driven by increased prolactin (Lopez-Vicchi et al., 2020). Prolactin receptor signaling is crucially important for establishing normal thermogenic function of brown adipose tissue (Viengchareun et al., 2008). Blockage of leptin receptor on prolactin releasing peptide neurons within the hypothalamus prevents the thermogenic effect of leptin, suggesting that leptin may mediate its thermogenic effect through prolactin (Dodd et al., 2014). Adipocytes themselves have been shown to express prolactin, expression is attenuated by obesity and may have implications for adverse metabolic states which develop during obesity (Brandebourg et al., 2007). Normal pancreatic function also depends upon prolactin signaling. Human patients suffering prolactin producing tumors display reduced glucose tolerance which may result from reduced insulin tolerance (Landgraf et al., 1977). Additionally, prolactin is known to drive the proliferation of insulin producing beta cells and drive an increase in pancreatic insulin secretion (Brelje et al., 1994).

4 | PROLACTIN AS A REPRODUCTIVE HORMONE

As we will discuss later in this review, prolactin is unlikely to play a primary role in seasonal variation of reproductive function. It does, however, act upon multiple levels of the neuroendocrine axis that governs fertility, and perhaps plays an ancillary role in seasonal reproduction. Prolactin has a multitude of demonstrated direct effects on the gonads in both male and female mammals. The role of prolactin in the maintenance of the corpus luteum following ovulation is well-established in non-primate females. This is achieved in combination with luteinizing hormone (LH) signaling by increasing the expression of LH receptor in the corpus luteum, in turn stimulating steroidogenesis pathways to induce progesterone synthesis (Bachelot et al., 2009; Gåfvels et al., 1992; Gibori & Richards, 1978; Segaloff et al., 1990). Prolactin is also directly implicated in the synthesis of oestradiol in the corpus luteum, as well as increasing the expression of oestrogen receptors in this tissue (reviewed in Stocco et al., 2007). Through stimulation of these steroidogenic pathways, prolactin facilitates the survival of the corpus luteum which in turn is crucial for the success of fertilization following ovulation. This critical role of prolactin signaling is highlighted in studies in which prolactin, or its receptor gene, are knocked out. For example, female prolactin receptor knockout mice are infertile as a result of embryonic implantation failure (Ormandy et al., 1997).

In male mammalian reproduction there is a range of evidence to suggest that physiological levels of prolactin play a stimulatory role at multiple levels. In the testes, prolactin increases androgen production in Leydig cells, as well as decreasing androgenic conversion to oestrogens by suppressing aromatase activity (Gunasekar et al., 1988; Papadopoulos et al., 1986; Purvis et al., 1979) implicating a role in gonadal testosterone output. It also appears to facilitate signaling between the pituitary gonadotrophs and the testes; prolactin has been shown to increase sensitivity to LH in Leydig cells and follicle-stimulating hormone (FSH) in Sertoli cells by increasing the presence of their respective receptors (Dombrowicz et al., 1992; Guillaumot et al., 1996). There are also studies suggesting prolactin increases mobility and energy metabolism of spermatozoa (Fukuda et al., 1989; Pedrón & Giner, 1978), presumably increasing their viability and thus the likelihood of successful fertilization occurring. An interesting consideration is whether prolactin of female origin during copulation can also elicit these effects on sperm viability. Prolactin further facilitates fertility by its effects on accessory sex organs. For example, prolactin is known to increase the weight, metabolism and androgen sensitivity of both the prostate gland and seminal vesicles (Arunakaran et al., 1988; Prins, 1987; Thomas et al., 1976). These roles in the testes and accessory organs suggest prolactin signaling

could play a role in the marked variation of testes weight and circulating testosterone that is present in many seasonal males (see Table 1).

In birds, prolactin is implicated in the switch from breeding to brooding behavior. There is a concomitant rise in circulating prolactin which may facilitate the success of incubation during brooding. The role of this rise in prolactin is somewhat complicated by the fact that the timing of this rise over the course of incubation is not always consistent between species. In the domestic chicken (*Gallus gallus*) for example, there is a distinct and sharp rise in serum prolactin at the onset of egg incubation (Sharp et al., 1998). However, in other species such as the ring dove and zebra finch (*Taeniopygia guttata*),

TABLE 1 A selection of publications detailing seasonality in avian and mammalian species

Publication	Species	Prolactin timing	Concurrent physiology
Mammals			
(Smale et al., 1988)	Prairie Vole (*Microtus ochrogaster*)	SP Decrease	winter pelage
(Yellon & Goldman, 1984)	Siberian Hamster (*Phodopus sungorus*)	SP Decrease	Nonbreeding, winter pelage, decreased body mass
(Bartness et al., 1987)	Syrian Hamster (*Mesocricetus auratus*)	SP Decrease	Decreased body mass
(Dark et al., 1983; Nelson & Blom, 1994)	Deer mice (*Peromyscus maniculatus*)	Likely SP decrease	Nonbreeding
(Lincoln & Baker, 1995)	Soay Sheep (*Ovis aries*)	SP Decrease	Breeding, decreased body mass
(Dahl et al., 2012)	Cow (*Bos taurus*)	SP Decrease	Increased lactation
(Webster & G. K., 1985)	Red Deer (*Cervus elaphus*)	SP Decrease	Winter pelage,
(Martinet et al., 1992)	Mink (*Mustela vison*)	SP Decrease	Nonbreeding, decreased body mass, winter pelage
(Holekamp et al., 1988)	California ground squirrel (*Spermophilus beecheyi*)	Winter Decrease	Nonbreeding, winter moult
(Kreeger et al., 1991)	Gray wolves (*Canis lupus*)	Winter Decrease	N/A
(Thompson & Oberhaus, 2015)	Horse (*Equus ferus*)	SP Decrease	Nonbreeding
(Ryan & Robinson, 1989)	Ferret (*Mustela furo*)	SP Decrease	Prevents puberty
(Howell-Skalla et al., 2002)	Polar bear (*Ursus maritimus*)	Winter Decrease	Nonbreeding, decreased testis size
(Curlewis, 1991)	Wallaby (*Macropus rufogriseus*)	SP Decrease	Decreased testosterone, LH, decreased prostate weight
(Crawford et al., 2006)	Brushtail Possum (*Trichosurus vulpeca*)	SP Decrease	Nonbreeding
Birds			
(Goldsmith & Hall, 1980)	Japanese Quail (*Coturnix japonica*)	LP increase (pituitary)	Gonadal growth
(Boswell et al., 1995)	European Quail (*Coturnix coturnix*)	Delayed LP increase	Gonadal regression
(Sreekumar & Sharp, 2008)	Bantam (*Gallus domesticus*)	LP increase	No reproductive effect
(Blache et al., 2001)	Emu (*Dromaius novaehollandiae*)	Delayed SP increase	Gonadal regression
(Concannon et al., 1999)	Woodchuck (*Marmota monax*)	Delayed LP increase	Gonadal regression, increased food intake, increased body weight
(Ebling et al., 1982)	European Starling (*Sturnus vulgaris*)	Delayed LP increase	Gonadal regression
(Goldsmith & Williams, 1980)	Mallard (*Anas platyrhynchos*)	Delayed LP increase	Decreased LH, Gonadal regression
(Burke & Dennison, 1980)	Turkeys (*Meleagris gallapavo*)	Delayed LP increase	Broodiness, Gonadal regression
(Goldsmith, 1982)	Australian Black Swan (*Cygnus atratus*)	Delayed LP increase	Incubation behavior
(Silverin & Goldsmith, 1997)	Great tit (*Parus major*)	Delayed LP increase	Regressed Gonads
(Stokkan et al., 1988)	Svalbard ptarmigan (*Lagopus mutus*)	LP increase	Decreasing Testosterone, LH
(Saarela et al., 1986)	Pigeon (*Columba livia*)	Winter spike	Decreased LH

Abbreviations: LP, long photoperiod; SP, short photoperiod.

this rise is not present until late incubation (Buntin et al., 1996; Smiley & Adkins-Regan, 2016). What is clear, however, is that there is a rise in prolactin in all bird species where this phenomenon has been examined by late incubation. This rise in prolactin appears to be partially regulated by the hypothalamus as both immunodetection of VIP and VIP messenger RNA is increased during this period (Mauro et al., 1989; Sharp et al., 1989; You et al., 1995). Several functions for this rise in prolactin have been postulated, however, its necessity has yet to be definitively demonstrated. There is evidence that prolactin suppresses gonadotrophin-releasing hormone-I and -II content in the hypothalamus of turkey hens (Rozenboim et al., 1993), but this may not be necessary for all avian species, such as those where gonadal regression occurs before prolactin rises. There is more compelling evidence for the role that prolactin plays in the maintenance and readiness of egg incubation. Prolactin drives the formation of the brood patch that facilitates heat transfer from the body to the eggs (Hutchison et al., 1967; Hutchison, 1975). The act of incubating stimulates sensory nerves on the brood patch that have been postulated to further drive the release of prolactin in a type of positive feedback loop that may reinforce this behavior (Figure 2) (Sharp et al., 1998). This role of prolactin is supported by studies where immunoneutralization of prolactin signaling prevents incubation behavior (March et al., 1994); inversely, exogenous prolactin can induce incubation behavior (El Halawani et al., 1986).

5 | SEASONALITY OF PROLACTIN SIGNALING IN MAMMALS

Prolactin signaling is supressed by short photoperiod (SP) in almost all seasonally responsive mammals studied, though the physiological response to this suppression is species specific (Table 1). Seasonality of prolactin is characterized by an initial decrease upon exposure to SP, followed by spontaneous refractory period wherein levels recover (Lincoln et al., 1996). Some animals also display a refractory response to a long photoperiod (LP) signal, wherein levels eventually drop after prolonged exposure (Lincoln et al., 1996), while others display refractoriness only to SP signals (Kauffman et al., 2003). In species such as sheep, genuine circannual rhythms allow for prolonged rhythmicity over multiple years without further photoperiod changes (Lincoln et al., 1996), while others such as the Siberian hamster display only one cycle (Kauffman et al., 2003) (Figure 3). While this review will mostly focus on the effects of photoperiod on prolactin secretion it should be noted that multiple supplementary cues also drive seasonal changes (Reviewed in Tolla & Stevenson, 2020).

Soay sheep display very robust rhythms of plasma prolactin in free living conditions; plasma prolactin levels are increased after exposure to LP for only 1 day and precipitate a progressive increase in prolactin levels (Hazlerigg et al., 2004). Indeed, several sheep breeds display similar changes in prolactin concentrations (Gómez-Brunet et al., 2008). Seasonal prolactin timing in sheep does not correlate with FSH signaling, suggesting discrete regulation (Lincoln, 1990). Sheep under artificial LP display significant disassociation between prolactin concentrations and seasonal ovulatory cycling (Gómez-Brunet et al., 2008). Soay sheep show a strong endogenous circannual rhythm of prolactin secretion under artificial LP when hypothalamic and pituitary signaling is disrupted (Clarke et al., 2006). Deer mice (*Peromyscus maniculatus*) display SP driven decreases in reproductive factors such as testes mass and spermatogenesis (Dark et al., 1983). The California deermouse (*Peromyscus californicus*), a winter breeder, displays seasonal changes in prolactin driven by water scarcity rather than photoperiod (Nelson et al., 1995).

Golden hamsters show a similar seasonal reduction in plasma prolactin and endogenous recrudescence, not timed concurrently with seasonal reproductive changes (Donham et al., 1994). Anterior pituitary extracts from Siberian hamsters display significant seasonal decrease in prolactin release which can be, in part, attenuated by coculture with hypothalamic extracts from LP animals, though is unable to recover prolactin to levels similar to LP controls (Badura & Goldman, 1997). In Syrian and Siberian hamsters, a winter decrease in serum prolactin appears to have opposite effects, driving an increase and decrease in body weight, respectively (Bartness et al., 1987). Siberian hamsters display significant reduction in prolactin levels in response to SP exposure which coincides with large reductions in body mass, food intake and gonadal involution (Vitale et al., 1985; Yellon & Goldman, 1984). Long duration melatonin signaling has been demonstrated to drive a decrease in plasma prolactin concentrations. Pinealectomised Siberian hamsters do not display SP driven losses in body weight and show limited seasonal torpor (Vitale et al., 1985). Interestingly, pelage color change and testicular function possess different critical photoperiods in Siberian hamsters, with a photoperiod of 14L:10D driving testicular regression but not pelage change, this was accompanied by a reduced interval of prolactin inhibition (Duncan et al., 1985). Further evidence linking seasonality of prolactin and energy balance is that leptin signaling drives a dose dependent decrease in prolactin signaling in SP but an increase in LP (Zieba et al., 2008). Curiously, orexin-A, which has opposing effects on food intake to leptin, differentially regulates seasonal prolactin in a similar manner to leptin (Molik et al., 2008). While prolactin may play a role in seasonal energy balance, other factors also play a major role. Siberian hamsters treated with thyroid hormone fail to display the normal SP decreases in body mass and reproductive fitness and can rapidly recover both to LP levels when introduced part way through the seasonal cycle (Barrett et al., 2007; Murphy et al., 2012). Traditional hypothalamic regulators of energy balance such as POMC also play a major role in seasonal energy balance (Helfer & Stevenson, 2020).

Exogenous pituitary implants in Golden hamsters limit, but do not eliminate, seasonal reproductive changes (Bartke et al., 1980). Under LP, golden hamsters treated with an inhibitor of prolactin secretion display significant decreases in body weight, but limited change in testicular function (Bex et al., 1978). Curiously, this same study identified that prolactin administration drove increases in testes mass, testes LH receptor density and plasma testosterone levels, potentially indicating a role for prolactin in development of recrudescence (Bex et al., 1978). Prolactin may regulate GnRH

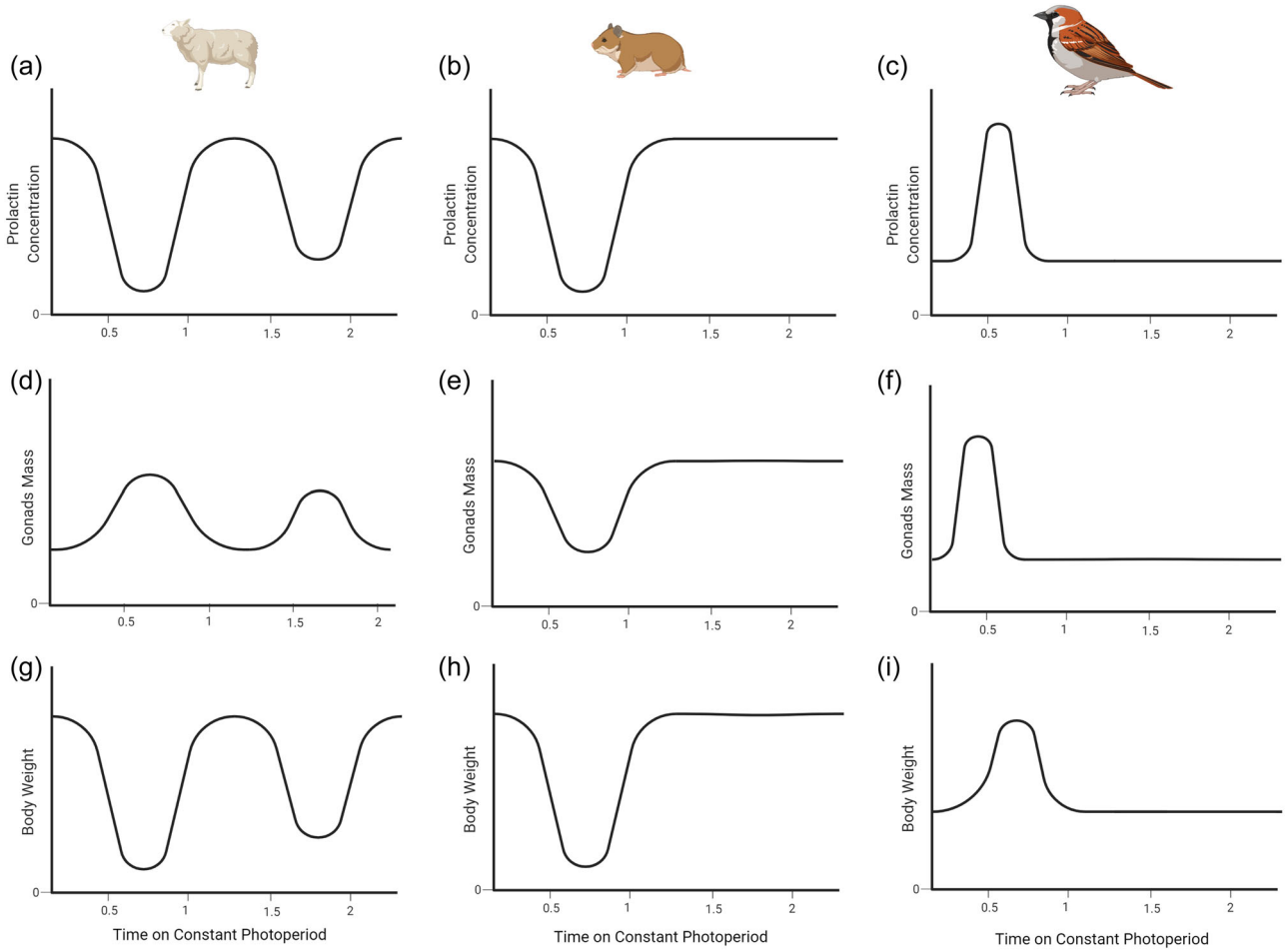

FIGURE 3 Seasonal patterns of prolactin, body weight and testes mass. (a) Representative figure displaying the seasonal rhythm of prolactin concentration in (a) Soay Sheep; (b) Siberian hamsters and (c) Sparrows under constant photoperiod for several years, showing the persistence of this rhythm in sheep but not hamsters. The rhythm of gonads mass in (d): Soay Sheep; (e) Siberian hamsters and (f) Sparrows under constant photoperiod display the temporal misalignment of prolactin and gonads mass in the sheep but not hamster. The seasonal rhythm of body weight in (g) Soay Sheep; (h) Siberian hamsters and (i) Sparrows under constant photoperiod once again showing the persistence of this rhythm in the sheep

secretion in mammals, though few GnRH neurons express prolactin receptor any effects are likely driven by afferent signaling (Grattan et al., 2007). Neurons coexpressing kisspeptin and the prolactin receptor have been identified in the arcuate nucleus of sheep (Li et al., 2011). Seasonality of kisspeptin signaling is associated with timing seasonal reproductive function (Simonneaux et al., 2013). Prolactin administration induces pSTAT5 signaling in these cells but does not drive kisspeptin signaling (Li et al., 2011). In Siberian hamsters, treatment with a DA antagonist or direct prolactin administration delays the development of a winter pelage, while treatment with an agonist accelerates it, however, neither treatment affects the timing of photorefractory return to summer pelage (Badura & Goldman, 1992). This pattern is matched by plasma prolactin secretions under the same treatments, though interestingly pinealectomised animals do not respond to treatment with the agonist (Badura & Goldman, 1992), suggesting this response is melatonin dependent. In Syrian hamsters, inhibition of prolactin release attenuates photoperiod driven seasonal obesity, insulin resistance and glucose tolerance to levels similar to that of LP or photorefractory animals (Cincotta et al., 1991) and drives an increase in body weight which mimics the SP response in this species (Bartness et al., 1987). Daily injections of prolactin are sufficient to eliminate winter torpor in Siberian hamsters, but not torpor driven by food restriction. This suggests differential thermoregulation driven by food availability and seasonality, for the latter of which prolactin may be more relevant (Ruby et al., 1993).

A key set of experiments examined the role of hypothalamic-pituitary signaling in prolactin seasonality by generating hypothalamo-pituitary disconnected (HPD) sheep. HPD sheep maintain normal prolactin cyclicity both as an endogenous cycle and in response to photoperiod, though display higher peaks of prolactin concentration, perhaps due to a loss of inhibitory dopaminergic signaling (Lincoln & Clarke, 1994; Lincoln & Richardson, 1998). They develop severe obesity and lose seasonal cyclicity in body weight and food intake (Lincoln & Richardson, 1998). HPD sheep display greatly reduced testes mass and loss of FSH

signaling, testes in such animals display extremely minor cycling, the peak of which is misaligned with control animals (Lincoln & Richardson, 1998). The SP induced peak of testes mass in sheep is typically not aligned with a LP induced peak in prolactin secretion, however, in HPD sheep testes mass peaks under LP concurrent with a peak in prolactin; this occurs along with a loss of reproductive hormones LH, FSH and testosterone (Lincoln et al., 1996). This implies that in intact sheep, the LP gonadotropic effects of prolactin are masked by reductions in these dominant classic reproductive hormones. HPD sheep are metabolically atypical, with loss of cyclicity of plasma β-endorphin, GH and IGF1 (Lincoln & Richardson, 1998). Additionally, they are hyperinsulemic and display increased adipose tissue deposition (Lincoln & Richardson, 1998). This evidence would lead Lincoln et al. to argue that the circannual pacemaker exists within the pars tuberalis (PT) and that prolactin signaling is a read out of this system (Clarke et al., 2006), though, as we will discuss later, this pacemaker may not necessarily be PT specific.

6 | SEASONALITY OF PROLACTIN SIGNALING IN BIRDS

The seasonal cycle of birds is somewhat different to that of mammals. Birds generally possess a far narrower window in which breeding takes place, followed by rapid gonadal involution, driven generally by development of photorefractoriness (Dawson & Sharp, 2010). Tree sparrows (*Passer manticus*) display LP driven increases in testicular and body mass which persist for only one cycle (Dixit & Singh, 2011) (Figure 3). In free living European starlings (*Sturnus vulgaris*), plasma prolactin concentrations spike in mid-summer shortly before the development of photorefractoriness to LP (Dawson & Sharp, 2010). In starlings, testis mass and plasma LH concentrations increase rapidly after exposure to LP while prolactin levels display a delayed rise and may be involved in gonadal regression (Ebling et al., 1982). In free living male starlings, increased plasma LH concentration is temporally associated with testicular growth, while prolactin peaks later in the seasonal cycle (Dawson & Goldsmith, 1982). In gallinaceous birds, serum prolactin levels rise throughout the egg laying period and spike at the cessation of egg laying and onset of parental behavior (El Halawani et al., 1984). Similar associations between incubation behavior and increased plasma prolactin have been noted in swans (Goldsmith, 1982), mallards (Goldsmith & Williams, 1980) and Turkeys (Youngren et al., 1991).

European quail (*Coturnix coturnix*) display a SP driven increase in prolactin, which occurs after migration associated fat gain ends and body weight begins to regress (Boswell et al., 1995). The Japanese quail displays a slight gradual increase in pituitary prolactin occurs after exposure to LP (Goldsmith & Hall, 1980). In white-crowned sparrows (*Zonotrichia leucophrys*), ovariectomy inhibits vernal fat deposition but has no impact on prolactin levels, again suggesting misalignment of the two systems (Schwabl et al., 1988). Interestingly, ovariectomy performed on white-crowned sparrows in November before photostimulation inhibits maximum prolactin levels, while ovariectomy in January does not (Schwabl et al., 1988), suggesting an interplay on ovarian hormones and photoperiod on prolactin levels. Plasma prolactin levels in the Great tit (*Parus major*) spike in summer in free living conditions and under LP in laboratory conditions regardless of time of year (Silverin & Goldsmith, 1997). Sensitivity of prolactin signaling to photoperiod varies by season, and great tits show a similar increase in plasma prolactin in response to 14 and 20 h light, however, during the winter the prolactin increase under 14 h light is greatly delayed (Silverin & Goldsmith, 1997). In castrated bantams, plasma LH concentrations can be maintained under LP for over 100 days, while photorefractoriness of prolactin occurs well before this (Sreekumar & Sharp, 2008). This has been used to suggest a disassociation of prolactin secretion and seasonal reproduction in this species, similar to observations in mammals (Sreekumar & Sharp, 2008). While most birds breed under LP, Emus (*Dromaiu novaehollandiae*) are SP breeders. They display a SP driven increase in plasma LH, testosterone, and an increase in testes mass (Malecki et al., 1998). Remarkably, with respect to reproduction, the timing of prolactin secretion in emus remains the same, peaking at the onset of gonadal regression providing further evidence of the misalignment of gonadal growth and prolactin secretion (Blache et al., 2001; Malecki et al., 1998). In the ring dove, SP drives attenuation of reproductive factors (LH, testosterone) before becoming photorefractory to SP, however, prolactin does not vary by season in this species (Lea et al., 1986). Some evidence has mounted of an interaction between corticosterone and prolactin in controlling gonadal growth, in sparrows prolactin drives gonadal growth if injected shortly after corticosterone (Meier et al., 1971).

In starlings, immunization against the VIP carrier protein (VIP-PPD) significantly delays the photorefractory response of testicular regression but has no effect on photostimulatory gonadal growth (Dawson & Sharp, 1998). The same study also demonstrated that VIP immunization prevents postnuptial molt (Dawson & Sharp, 1998). These results imply prolactin is critical for establishing the photorefractory, but not poststimulatory, response in birds. VIP immunized turkeys fail to exhibit the typical increase in prolactin in response to DA administration, suggesting that dopaminergic regulation of prolactin depends upon VIP signaling (Youngren et al., 1996). Time dependent prolactin injection is highly relevant in birds, such as LP white-throated sparrows (*Zonotrichia albicollis*) where morning injections of prolactin depletes lipid stores mass while a midday injection increases mass (Meier, 1969). European quail develop increased body mass and food intake after prolactin injection, suggesting that prolactin in this species may play a role in body mass seasonality (Boswell et al., 1995). In the avian hypothalamus, prolactin binding efficiency in multiple nuclei is seasonal with a general decrease in summer animals, though it is unclear if this is due to increased prolactin receptor occupancy or a change in its expression (Smiley et al., 2020). In female bantams, photostimulatory egg laying is unaffected by immunization against prolactin, though delays or prevents the onset of incubation behavior (March et al., 1994). Intracranial administration of prolactin to turkeys drives an increase in incubation behavior and a decrease in egg laying (Youngren

et al., 1991). This is notable as incubation is often associated with a progressive loss of body mass (Criscuolo et al., 2002).

Thyroidectomised starlings, in which prolactin signaling may be lost, display a loss of the photorefractory regression in testes mass and testosterone and maintain a progressively increased plasma FSH, in direct contrast with intact starlings (Goldsmith & Nicholls, 1984). Though photorefractoriness is lost the initial gonadal response to photoperiod remains in recently thyroidectomised birds, however, after 13 weeks this initial response is also lost, suggesting that thyroidectomy may drive a progressive loss of response to all seasonal changes (Dawson, 1993). Thyroxine treatment in thyroidectomised starlings drives an increase in plasma prolactin and a decrease in plasma FSH and testicular width (Goldsmith et al., 1985). Thyroidectomised Japanese quail show a similar pattern with a loss of photorefractory response, which can be recovered by thyroxine treatment (Follett & Nicholls, 1985).

7 | THE MOLECULAR BASIS OF SEASONAL PROLACTIN SIGNALING

Pineal melatonin signaling has long been implicated in the molecular control of seasonal prolactin signaling in mammals. In Soay sheep, melatonin signaling appears to act directly upon the pituitary and is necessary to establish circannual rhythmicity in prolactin, but is not necessary to establish a response to SP (Clarke et al., 2006). Surgical separation of the hypothalamus and pituitary to generate HPD sheep preserves the pattern of melatonin receptor expression with the pituitary (Williams et al., 2003). In addition, prolactin secretion in HPD sheep maintains an endogenous seasonal rhythm, and remains responsive to SP and exogenous melatonin implants (Lincoln & Clarke, 1994). Indeed, HPD in sheep appears to disrupt all seasonal endocrine cycling with the exception of prolactin (Lincoln & Richardson, 1998). These findings point to a direct action of melatonin within the pituitary. However, lactotrophs present there do not express melatonin receptor (Williams et al., 2003) underlining a key missing step in the translation of the melatonin signal to lactotrophs. While prolactin release results from the pars distalis (PD) of the pituitary, the PT of the pituitary has been shown instead to be the site of pituitary melatonin binding in *Peromyscus* (Weaver et al., 1990), Syrian hamsters (Williams et al., 1989), Siberian hamsters (Weaver et al., 1989), and Soay sheep (Williams et al., 2003). In some ungulate species melatonin receptors have been localized to the PD and PT, suggesting that melatonin may act directly there to regulate prolactin seasonality, however, it is unclear if this represents expression within the lactotrophs (Nonno et al., 1995). In humans, which are not seasonal, the PT lacks melatonin receptors highlighting the importance of binding here for seasonal response (Weaver et al., 1993). In photorefractory Siberian hamsters, the binding affinity and signal transduction of melatonin in the PT is not altered, suggesting that photorefractory changes to melatonin signal arises not from reduced sensitivity, but altered response to the same signal (Weaver et al., 1991). Direct melatonin releasing implants in the PT of ovariectomised sheep inhibits prolactin release but has no effect on reproductive indicators (e.g., LH release), consistent with the hypothesis that prolactin signaling and seasonal reproduction are not directly linked (Malpaux et al., 1995).

Media from the PT can induce an increase in expression of immediate early gene c-fos and drives an increased prolactin concentration in PD cell culture (Morgan et al., 1996). Further treatment of PT with melatonin inhibits the ability of this media to drive c-fos expression. This led to the proposal of a low molecular weight molecule released from melatonin sensitive PT cells controlling prolactin expression, putatively named tuberalin (Morgan et al., 1996). The identity of tuberalin has yet to be confirmed, but there have been several proposals. The discovery of seasonal rhythmicity of *tac1*, which encodes preprotachykinin-1, a precursor of substance P and neurokinins (tachykinins), with a gradual increase of *tac1* expression upon LP exposure, provided a possible identity for tuberalin (Dupré et al., 2010). Tachykinin products are known to play a role in prolactin secretion, for example substance P administration is capable of both inducing prolactin expression (Vijayan & McCann, 1979) and modulating prolactin feedback via tuberoinfundibular dopaminergic neurons (Isovich et al., 1994). However, tachykinin receptors have yet to be identified on lactotrophs, suggesting that any potential effect of tachykinins would necessarily be mediated through intermediate cells (Dupré et al., 2010). In songbirds, castration attenuates a spring increase in hypothalamic *tac1* expression which may impart seasonal timing in birds (Sharma et al., 2020).

Another proposed identity of tuberalin is the endocannabinoid 2-arachidonoyl glycerol (2-AG). In tissue cultures of PD from seasonal Syrian hamsters, 2-AG is capable of driving prolactin expression when co-incubated with forskolin (Yasuo et al., 2014). A LP dependent increase in 2-AG expression has been demonstrated within the PT (Yasuo et al., 2010) along with peripheral tissues such as the retroperitoneal white adipose tissue and brainstem (Ho et al., 2012). The primary receptor of 2-AG, Cb1, has been detected in the PD of Syrian hamsters with some level of expression on lactotrophs (Yasuo et al., 2010). Treatment with the Cb1 antagonist SR141716 is sufficient to drive a decrease in food intake and body mass in Siberian hamsters, revealing a functional link between feeding behavior and 2-AG signaling (Ho et al., 2012). Tuberalin may also represent a host of molecules released together, the initial study which proposed tuberalin showed both low- (<1 kDa) and high- (>10 kDa) molecular weight fractions of PT media stimulated c-fos, raising the possibility of a multi-product identity for tuberalin (Morgan et al., 1996). Regardless of the exact identity of tuberalin they represent a key step in explaining the effect of melatonin, and therefore seasonality, on prolactin signaling.

A pituitary timer driving changes in prolactin seems likely (Figure 4), given findings derived from HPD sheep. It seems therefore necessary that an endogenous timer exists within an axis between melatonin signaling to the PT and prolactin release from the PD. The location and nature of this timer, however, remains somewhat elusive. One proposed mechanism for the generation of seasonal

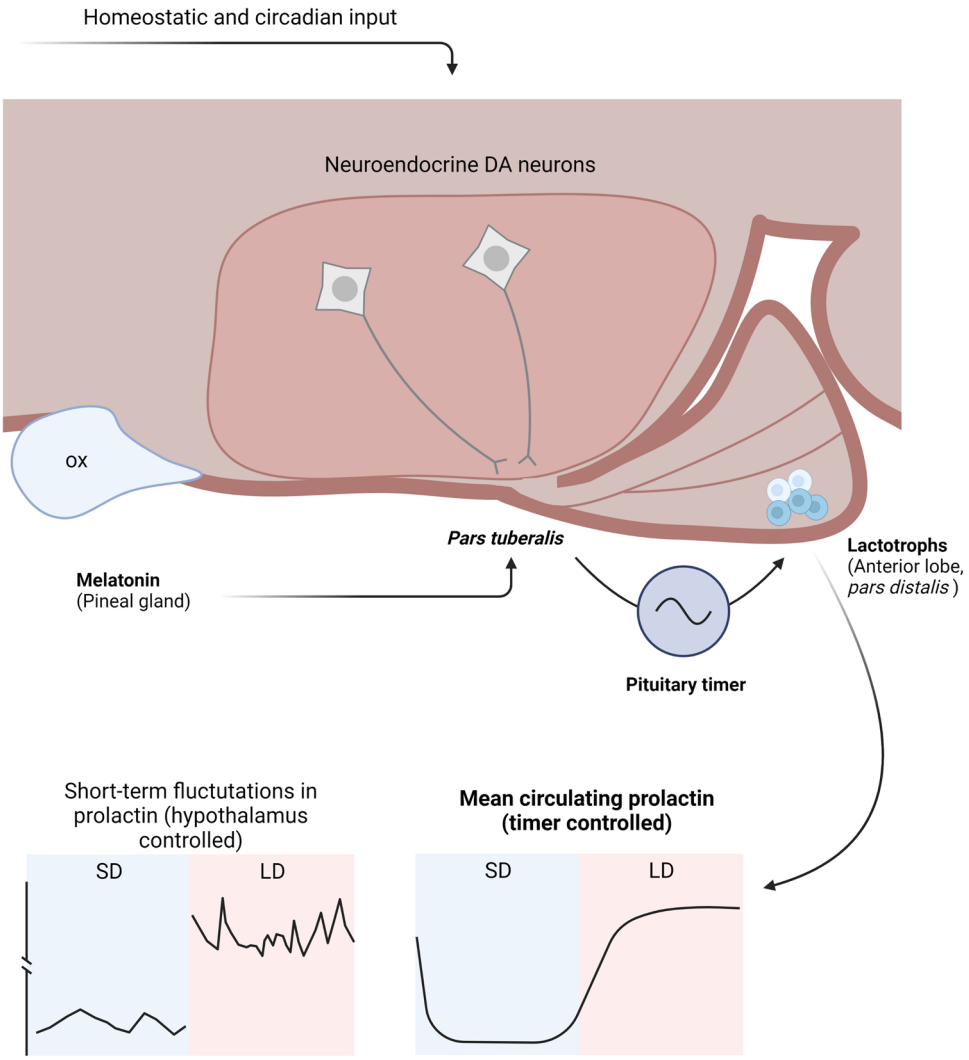

FIGURE 4 Integrated model of acute and circannual control of mammalian prolactin secretion. Outlined is a possible mechanism of how seasonal variations in mammalian prolactin secretion are generated. Circannual rhythms are generated in the anterior pituitary by an endogenous timer mechanism which is presently not completely understood but might be entrained by melatonin signaling in the *pars tuberalis*. This endogenous timer acts as a rheostatic controller which changes the set point of circulating prolactin levels to coincide with the long photoperiods (LP) of summer and short photoperiods (SP) of winter. In turn, this generates much higher mean prolactin concentrations (~20-fold) under LP conditions versus SP. This endogenous timer in the pituitary appears decoupled from the hypothalamus, where acute homeostatic and daily variations in prolactin secretion (towards the set point generated by the circannual timer) are controlled by inhibitory neuroendocrine DA neurons. DA, dopamine

prolactin signaling is a "delayed-feedback" model, in which the PT responds to photoperiod and drives an initial increase in PD prolactin, however, a delayed 15-week negative feedback inhibits prolactin, which in turn allows for the photoperiod response to once again predominate (MacGregor & Lincoln, 2008). This model, primarily based on data gathered from sheep, would allow for multiple year seasonal rhythmicity of prolactin secretion. However, it would fail to explain the response in species which display only one cycle (e.g., Siberian hamster), in which high levels of prolactin may persist. Two possibilities exist to explain this, either the molecular basis underlying seasonal prolactin signaling is highly species specific, or a mechanism other than negative feedback drives prolactin seasonality. In determining the location of the pituitary clock, the timing of tuberalin signaling is of critical importance.

Previous work investigating tuberalin has focused on its ability to drive an increase in PD prolactin and has demonstrated that its release is photoperiod dependent. However, tuberalin may only generate prolactin cyclicity if it were cyclic in the same, or a similar manner. In the hamsters, some evidence has suggested a lack of cyclicity of PT thyroid stimulating hormone (TSHβ) secretion under SP, despite pronounced cycles of body weight and gonadal size (Milesi et al., 2017). SP PD lactotrophs significantly increase prolactin synthesis after exposure to SP refractory and LP PT culture media, suggesting that release of tuberalin from the PT is a critical element in the development of photorefractoriness (Johnston et al., 2003). However, it should be noted that cultured PD cells maintain a seasonally appropriate pattern of prolactin secretion in the absence of tuberalin signaling (Johnston et al., 2003). This would suggest that

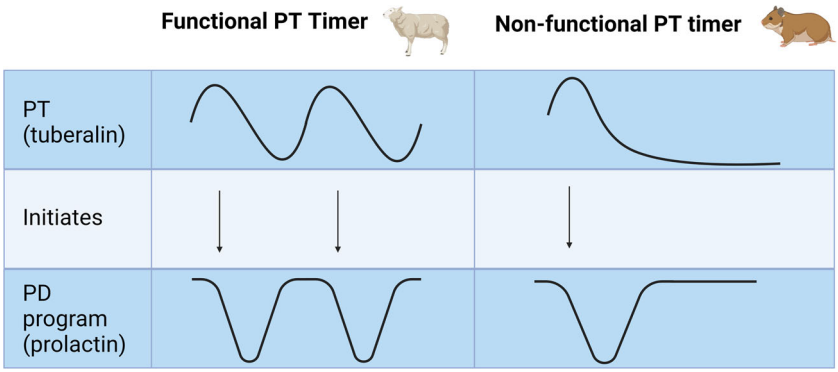

FIGURE 5 A potential model of seasonal prolactin rhythmicity. An outline of a potential model of prolactin seasonality involving two timers within the PT and PD. Some evidence has pointed to PT TSHβ signaling possessing limited rhythmicity in hamsters (Milesi et al., 2017). A similar pattern in tuberalin secretion could imply the existence of multiple timers. PD, pars distalis

the PT is an important site of control of prolactin secretion, however, this occurs without cycling in melatonin responsive genes *per1* or inducible cAMP early repressor (ICER) signaling (Johnston et al., 2003). This is in contrast to findings from ovine PT in which cyclicity of these genes appears to be relevant in photoperiod responsiveness (Dupré et al., 2008). Recent work has implicated a role for circadian clock components in decoding the melatonin signal within the PT. Wood et al. (2020) identified *bmal2*, an E-box regulator, as a seasonally regulated gene within the PT of sheep acting as a basis of a circadian driven E-box binding coincidence timer driving seasonal changes. Within the Siberian hamster PT, many classic clock genes, such as *cry1* and *per1*, appear to lack rhythmicity (Johnston et al., 2005). This is in contrast to findings from ovine PT which much broader rhythmicity of clock genes under different photoperiods (Dupré et al., 2008). This provides some evidence of species-specific rhythmicity with the PT.

It, therefore, seems likely that multiple timers orchestrate the seasonal response, a pituitary timer which orchestrates, and a second timer which may be initiated by PT signaling but in which refractoriness develops separately. We propose that it is possible that two timers similarly orchestrate the seasonal prolactin response (Figure 5). A first timer, which drives refractoriness, and a second timer which rhythmically generates annual cycles of prolactin signaling. Such a model may explain some of the differences observed between species. If this timer was nonfunctional in a species (e.g., Siberian hamster) but remained melatonin responsive then the prolactin output would appear as a single seasonal cycle, responding only to the photoperiod driven changes. If this timer was a functional timer entrained by melatonin signaling (e.g., sheep) then the prolactin output would appear as an endogenous cycle (Figure 5). It is notable that even though prolactin and reproductive seasonality can be dissociated, and that refractoriness of reproductive factors seems to develop independently of PT signaling (Milesi et al., 2017), long term circannual rhythmicity tends to exist for both simultaneously in any given species. We have recently suggested that multiple neuroendocrine systems act independently of each other to orchestrate seasonality and may allow for better evolutionary control of seasonality to allow for the development of species-specific programs (Stevenson et al., 2022). A "two-timer" model of prolactin seasonality would, similarly, allow for finer control of seasonal timing of prolactin secretion. In free living "one cycle" species, the seasonal cycle is reset by LP signaling rather than an inherent cycle. This "two timers" model may explain the difference between species which posses' endogenous circannual activity of prolactin signaling and ones in which the system must be reset.

Under normal homeostatic conditions, prolactin release is inhibited by hypothalamic dopaminergic signaling, raising the possibility that this mechanism drives seasonality of prolactin release. TIDA neurons are melatonin sensitive and display a circadian pattern of activity, entrained by melatonin signaling (Sellix & Freeman, 2003). Several publications have investigated the potential role of inhibitory dopaminergic signaling as a regulator of seasonal prolactin. Tissue cultures of SP Siberian hamster pituitaries display greater sensitivity to prolactin inhibition by DA than LP cultures (Badura, 1996). In the Syrian hamster, DA concentrations within the median eminence are not significantly affected by photoperiod in females but are significantly decreased by SP in males (Krajnak et al., 1994). However, TIDA neuron activity does not appear to be altered by SP (Krajnak et al., 1994) or by direct melatonin administration (Lyons et al., 2017). Given that HPD sheep maintain a circannual rhythm of prolactin secretion (Houghton et al., 1995; Lincoln & Clarke, 1994) it seems probable that hypothalamic signaling is not essential for seasonality of prolactin. Treatment with DA agonists and antagonists has the predicted effect on prolactin secretion in sheep but has no effect on the seasonal timing of prolactin (Lincoln, 2003). In contrast to the circannual rhythmicity of prolactin, the circadian rhythm of prolactin secretion in HPD sheep is lost (Houghton et al., 1995). Taken together these data suggest that dopaminergic inhibition of prolactin release has limited relevance for seasonal control of prolactin and may be more relevant in establishing circadian timing of prolactin release. DA agonists can ablate seasonal prolactin response and associated physiological changes (Cincotta et al., 1991). Though, this may not necessarily represent the same mechanism which acts to establish seasonal prolactin signaling. This argument would entail a hypothalamic circuit controlling short term circadian and homeostatic control of prolactin secretion (Lincoln & Clarke, 1994) while a longer-term pituitary mechanism drives seasonal changes in prolactin signaling (Figure 4).

8 | FUTURE DIRECTIONS

This review has focused on the effects of prolactin physiologically in mammals and birds and its roles in seasonal energy balance and reproduction. We have covered the signaling mechanisms which may translate melatonin signaling into prolactin. We postulate a discrete regulation of seasonal and homeostatic prolactin signaling and highlights the different roles prolactin appears to play in seasonal and homeostatic contexts. Most research highlighted uses traditional technologies such as qPCR, immunostaining, and ELISA. The advent of next generation sequencing technologies may allow for the identification of previously not investigated transcripts which may dictate seasonal prolactin signaling within the hypothalamus. Indeed, recently the Siberian hamster genome was sequenced along with hypothalamic-pituitary RNA sequencing to identify seasonal transcripts (Bao et al., 2019). Functional work investigating seasonality of prolactin has predominantly involved the manipulation of dopaminergic signaling to mimic seasonal prolactin changes, however, this may not be the same mechanism which controls seasonal prolactin signaling. The usage of CRISPR-Cas9 technologies will allow for functional interrogation of novel genes with a putative role in seasonality of prolactin signaling and allow for more precise mimicry of the seasonal response. Future studies may also capitalize on these technologies that are now a mainstay of molecular research to probe the location and nature of the pituitary timer.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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