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EARLY CAREER PERSPECTIVE

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Maternal photoperiodic programming enlightens the internal regulation of thyroid-hormone deiodinases in tanycytes

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Seasonal rhythms in physiology are widespread among mammals living in temperate zones. These rhythms rely on the external photoperiodic signal being entrained to the seasons, although they persist under constant conditions, revealing their endogenous origin. Internal long-term timing (circannual cycles) can be revealed in the laboratory as photoperiodic history-dependent responses, comprising the ability to respond differently to similar photoperiodic cues based on prior photoperiodic experience. In juveniles, history-dependence relies on the photoperiod transmitted by the mother to the fetus in utero, a phenomenon known as "maternal photoperiodic programming" (MPP). The response to photoperiod in mammals involves the nocturnal pineal hormone melatonin, which regulates a neuroendocrine network including thyrotrophin in the pars tuberalis and deiodinases in tanycytes, resulting in changes in thyroid hormone in the mediobasal hypothalamus. This review addresses MPP and discusses the latest findings on its impact on the thyrotrophin/deiodinase network. Finally, commonalities between MPP and other instances of endogenous seasonal timing are considered, and a unifying scheme is suggested in which timing arises from a long-term communication between the pars tuberalis and the hypothalamus and resultant spontaneous changes in local thyroid hormone status, independently of the pineal melatonin signal.

KEYWORDS
circannual, deiodinase, maternal programming, pars tuberalis, tanycytes, TSH

1 | INTRODUCTION

Organisms living in temperate latitudes express seasonal cycles in physiology and behaviour (eg, reproduction, metabolism, moult, hibernation or migration) to adapt to the Earth's seasonally changing environment. For successful adaptation, the biological rhythms must anticipate the changing seasons. Animals have therefore evolved intrinsically generated long-term (circannual) rhythms[1,2] that proceed independently of and can be synchronised by changes in the external environment. The highly predictable annual cycle of daylength (photoperiod) is the predominant synchronising signal (Figure 1A). In the laboratory, internal timing can be revealed in the form photoperiodic history-dependent responses or as partial/full circannual rhythms by manipulating photoperiodic conditions (Figure 1B,C).

Seasonal species acquire information about previous photoperiodic exposure, so-called "photoperiodic history", and compare it with a subsequent signal. This strategy allows individuals to respond appropriately to intermediate daylengths present around the equinoxes, developing the adequate response at each time of the year based on their prior experience.[3,4] Photoperiodic history-dependence is critical for setting up the timing of puberty in newborns. In this context, the mother transfers photoperiodic information to the pups in utero, modulating the developmental trajectory of the young and allowing them to prepare for the upcoming season. This

phenomenon is known as maternal photoperiodic programming[5-8] (MPP).

This review summarises the current knowledge about photoperiodic history and MPP in seasonal reproduction, as well as the neuroendocrine system underlying MPP in mammals. Finally, the regulation of MPP is compared with other instances of endogenous rhythmicity with respect to the hypothesis that internal long-term timing arises from the long-term communication between the pituitary and the hypothalamus, resulting in spontaneous changes in hypothalamic thyroid status.

2 | MATERNAL PHOTOPERIODIC PROGRAMMING: PRIMED BY MATERNAL MELATONIN

Long-day breeding species typically present a breeding season that expands from early spring to late summer, with some species of rodents producing up to three litters in this period. The young of these species follow a different pattern of growth and reproductive development depending on the part of the season in which they were born (Figure 2).[9,10] Individuals born at the beginning of the season normally attain reproductive maturity and attempt to breed in the same year, whereas progeny born in late summer delay growth and reproductive development and overwinter before achieving puberty.[11] Cohorts born very late in the season typically do not survive the winter, unless they encounter nutrient rich fluctuations in the environment.[11] This suggests that the dual strategy could allow late summer offspring to sufficiently grow and accumulate energy for winter survival, instead of going through the energetically costly reproductive process. However, the functional significance of this adaptation remains unclear. Similarly, sheep, with a typical breeding season during autumn and winter (ie, short-day breeders), are normally born in spring and attain sexual maturity the next autumn, when they are approximately 30 weeks old. Lambs born out of season, in autumn, delay puberty to the following breeding season when they are approximately 1 year of age.[12]

Developmental studies on voles and hamsters (ie, long-day breeders) exposed prenatally to long (15-16 h light [L] day^{-1}) or short photoperiods (SPs; shorter than 12 h L day^{-1}) and raised postnatally in photoperiods of intermediate duration (12.5-14 h L day^{-1}) demonstrated that the maternally transmitted photoperiodic-history during gestation is critical for setting the individual's growth trajectory and reproductive development (delay or advance development, respectively).[5,6,13,14] Contrastingly, alteration of photoperiod during lactation does not influence the pubertal development programmed by prenatal experience, demonstrating that prenatal programming works independently of the lactational photoperiod.[14,15] Thus, the physiological responses elicited by intermediate daylengths after weaning depend on a relative interpretation of the photoperiod based on prior photoperiodic exposure and not on its absolute duration (Figures 1B and 2).

Photoperiodic history-dependent responses have been observed in the seasonal cycle of reproduction also in adult individuals.[3,4] This phenomenon has been mostly studied in Siberian hamsters. In these species, a minimum of 2 weeks of long photoperiodic exposure is necessary to establish an efficient photoperiodic history that determines subsequent reproductive responses to intermediate photoperiod (IP).[16] In adult mammals, the exclusively nocturnal secretion of melatonin from the pineal gland inversely reflects daylength duration and thus serves as the internal link to measure photoperiod[17]

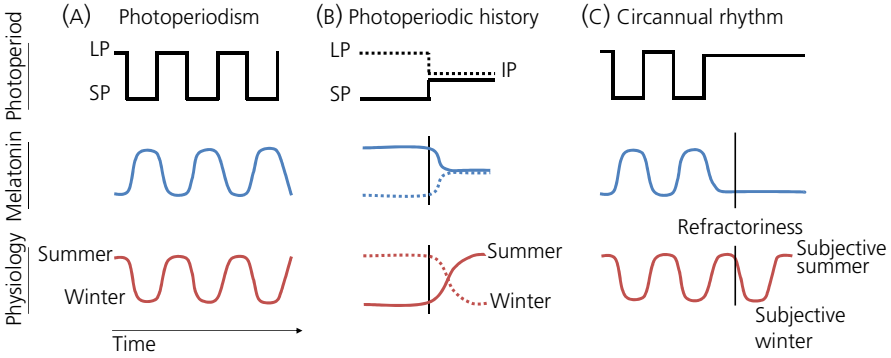

FIGURE 1 Photoperiodic and internal long-term timing cycles in physiology as demonstrated in photoperiodic manipulation experiments. A, Photoperiodism is the ability to use the seasonal cycle of daylength (photoperiod) to entrain rhythms in physiology to a year. Alternating cycles of long (LP) and short photoperiod (SP) (top) are internally represented by the nocturnal secretion of the hormone melatonin from the pineal gland (middle), which leads cycles in physiology and behaviour to oscillate between summer and winter states (bottom). B, Internal rhythms are revealed as photoperiodic history-dependent responses when animals kept in either LP (dotted line) or SP (continuous line) are transferred to photoperiod of intermediate duration (IP), present in nature around the equinoxes (top). Melatonin secretion under these conditions remains similar, reflecting the duration of the prevailing photoperiod (middle). The seasonal physiology elicited in IP depends on prior photoperiodic exposure. Animals previously exposed to LP interpret IP as a decrease in photoperiod and show winter physiology, whereas animals previously exposed to SP interpret IP as an increase in photoperiod and show summer physiology (bottom). C, Internal timing is revealed as full/partial circannual rhythms when photoperiod is maintained constant (top). Under these conditions, the profile of melatonin secretion also remains constant, reflecting the prevailing fixed photoperiod (middle). Despite this continuous signal, cycles in physiology become refractory to the constant photoperiod and continue to oscillate between "subjective" summer and winter states (bottom)

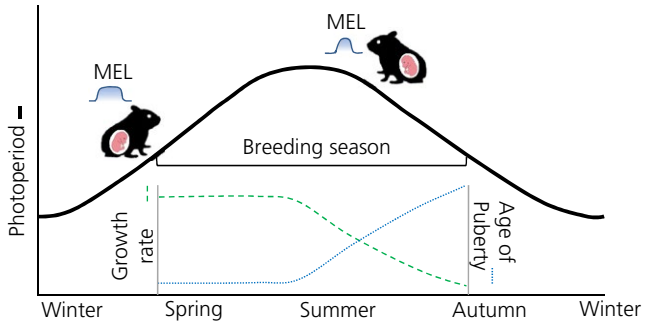

FIGURE 2 Maternal photoperiodic programming of reproduction and growth rate in small mammals. In temperate environments, breeding initiates at the beginning of spring, when photoperiod (black line) is increasing, and the breeding season lasts into the end of the summer when photoperiod decreases. Pups born in either part of the season undergo two different life-history strategies. Dams pregnant at the beginning of the season transmit a long melatonin (MEL) signal to their pups in utero. These pups show fast growth rates (green dashed line) and achieve puberty at a young age (blue dotted line). Dams that are pregnant when the photoperiod is long transmit short melatonin profiles to their pups in utero. These pups have low growth rates and delay their time of puberty, often until the next season

(Figure 1A). Mimicking photoperiodic history-dependent responses, melatonin infusions of intermediate duration (7 h day^{-1}) in adults are interpreted as inhibitory for reproduction in animals with a long photoperiodic history or as stimulatory in animals with prior short photoperiodic exposure.[16] The memory for previously acquired photoperiodic history fades with time. In adult pinealectomised Siberian hamsters with an acquired long photoperiodic history, 7 h day^{-1} melatonin infusions are no longer effective for inhibiting reproduction when initiated 20 weeks after pinealectomy. However, unequivocally winter-like melatonin signals (10 h day^{-1}) always lead to inhibitory reproductive responses. Thus, melatonin appears to be necessary to maintain this memory.[16] Nevertheless, it remains unclear how these observations apply in nature.

The transfer of photoperiodic information from a mother to her foetus occurs via melatonin-dependent mechanisms. Maternal melatonin crosses the placenta and acts on melatonin sensitive foetal brain regions and other tissues.[18,19] Also, melatonin injections in pregnant rodents are able to entrain pups' disrupted circadian rhythms,[20,21] showing that melatonin can be used by the mothers to signal time to their foetuses.[22] In Siberian hamsters, the foetal pituitary is responsive to melatonin from gestational day 16.[23,24] How this gestational signal influences postnatal development has been studied mostly in these species. Offspring of pinealectomised dams kept in a long photoperiod (LP) fail to develop gonads when reared in an IP, demonstrating that they do not receive information about the gestational or prior maternal photoperiodic exposure.[25] However, offspring of pinealectomised dams receiving 8 h day^{-1} (long) melatonin infusions during pregnancy interpret a postnatal IP as stimulatory for gonadal growth, whereas those receiving shorter infusions interpret it as inhibitory.[25] These infusions are maximally effective when given during the last 3-6 days of pregnancy for a minimum of 4 days, defining a narrow sensitive window in which the reproductive axis of the foetus is responsive to the programming effects of melatonin.[26] During lactation, the level of maternal melatonin found in the plasma of pups is very low, showing no day-night differences.[27,28] The pups themselves do not secrete melatonin rhythmically until postnatal day (P) 15 in hamsters, regardless of photoperiodic experience,[29,30] supporting the concept that they are effectively blind to photoperiod during lactation.[14,15] Furthermore, reproductive development proceeds in accordance with prenatal photoperiodic exposure and independently of pre-weaning photoperiod in pinealectomised Siberian hamsters,[31] suggesting that the memory of prenatal photoperiodic history is maintained during this time. This indicates that the foetal melatonin-responsive neuroendocrine system is functional prior to birth and uses the maternal melatonin rhythm as a calendar signal.

Several alternative hypotheses to account for these history-dependent effects have been considered. Based on timed-melatonin infusions, it has been proposed that maternal melatonin could be altering the pups' circadian regulation of juvenile melatonin production.[32] Alternatively, the postnatal melatonin pattern could be interpreted differently depending on prenatal photoperiodic history.[33] Functional studies show that the developmental trajectory set by the prenatal photoperiodic experience continues in juveniles pinealectomised or reared in constant light, and thus in the absence of postnatal melatonin.[15,31,34,35] In our recent study, we observed that juvenile Siberian hamsters gestated in either LP (16 h L day^{-1}) or SP (8 h L day^{-1}) and transferred to IP (14 h L day^{-1}) at weaning (Figure 3A) presented melatonin peaks of similar duration, regardless of their experience[36] (Figure 3B), as observed previously.[37] These results suggest that MPP does not arise from altered circulating melatonin patterns in juveniles, although it may result from a change in their sensitivity to melatonin signalling. To understand this phenomenon, we should then focus on the neuroendocrine system that transduces the melatonin message.[22,33]

3 | NEUROENDOCRINE CONTROL OF PHOTOPERIODISM IN MAMMALS

3.1 | The pars tuberalis: interface between melatonin and the hypothalamus

Several regions of the brain and pituitary were discovered to be melatonin sensitive in mammals using both radiolabelled melatonin binding assays[38,39] and the study of melatonin receptor expression and functionality.[40,41] The most conserved melatonin sensitive tissue is the pars tuberalis (PT) of the pituitary gland,[42-45] which has subsequently become a central site for the study of the mechanisms underlying the physiological responses to photoperiod or photoperiodism.

The PT is located directly below the basal hypothalamus where it is in contact with the nerve endings at the median eminence (ME) and with the capillaries of the primary plexus of the portal system.[46] Melatonin receptor 1 in the pituitary is exclusively

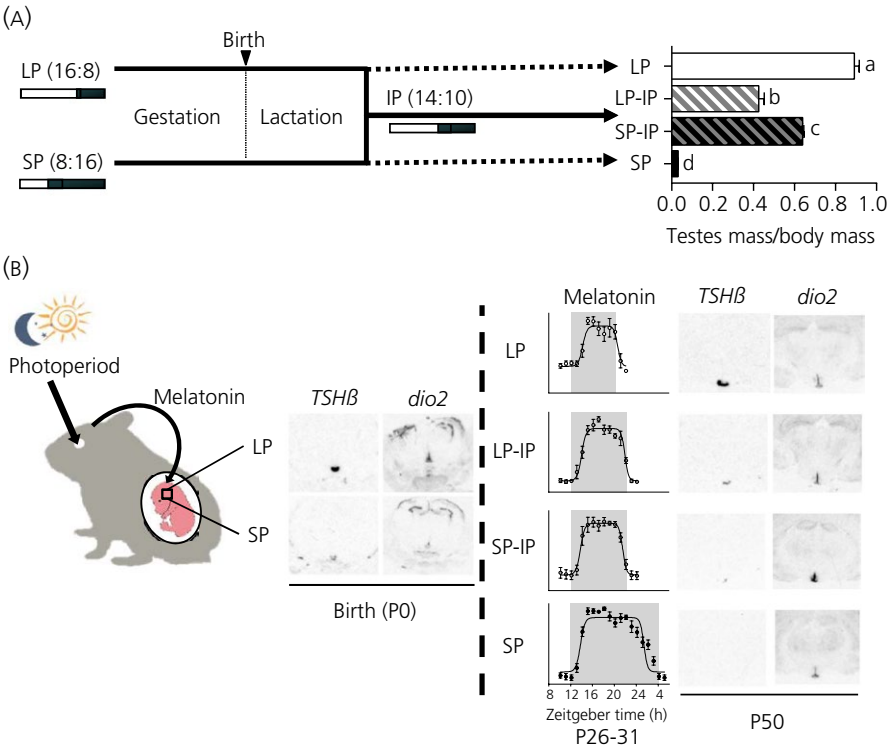

FIGURE 3 Maternal photoperiodic programming neuroendocrine pathway. A, Timeline and photoperiodic conditions used to explore the effects of maternal photoperiodic programming.[36] Animals gestated and maintained during lactation in either long photoperiod (LP: 16:8 h light/dark) or short photoperiod (SP: 8:16 h light/dark) are maintained in the same photoperiod or transferred to an intermediate photoperiod (IP: 14:10 h light/dark) at weaning. At 50 days of age, the reproductive development in animals gestated in SP and transferred to IP (SP-IP) is larger than in animals gestated in LP and transferred to IP (LP-IP). Different lowercase letters in the graph indicate significant differences between groups. B, Maternal transfer of melatonin to fetal brain in utero programs developmental pituitary/hypothalamic gene expression in offspring independently of the offspring's own melatonin profile. Representative in situ hybridisation autoradiography images of *TSH*β and *dio2* gene expression from birth (P0) to postnatal age (P)50. Average melatonin profiles of offspring at P26-31. Modified from previous data[5-8]

expressed on PT-specific thyrotroph secretory cells that produce thyroid-stimulating hormone (TSH).[47-49] In seasonal species, TSH expression in the PT, specifically the β subunit (TSHβ), is rapidly induced by exposure to LP and inhibited by SP, which, in mammals, depends on melatonin.[48-51] Although, in European hamsters, the photoperiodic entrainment of PT-TSH is also possible in the absence of melatonin,[52] this phenomenon has not been explored in other mammals. In non-mammalian vertebrates, the photoperiodic network is conserved but does not involve melatonin and, instead, the light-input is transmitted via deep brain photoreceptors in birds or photoreceptive coronet cells in the saccus vasculosus in fish.[53]

PT-TSH acts in a retrograde fashion on the hypothalamus to reactivate summer physiology via functional TSH receptor (TSH-R) expressed in the tanycytes lining the third ventricle (3V).[51,54] Acute i.c.v. TSH injections lead to induction of thyroid hormone deiodinase 2 (*dio2*) expression,[51,54] whereas the photoperiodic and melatonin-induced increase in *dio2* expression is blocked in *TSH-r* knockout mice.[49] Long-term TSH i.c.v. infusions in SP-maintained individuals reactivate summer physiology (ie, activation of the reproductive axis in hamster and quail and inhibition in sheep) via induction of *dio2* and decrease in thyroid hormone deiodinase 3 (*dio3*) expression in tanycytes.[51,54,55] These specialised glial cells, for which the bodies are strategically located in the ependymal wall of the 3V, extend their projections towards the capillaries in the arcuate nucleus (ARC) and to the external border of the ME with the PT, forming a functional blood-brain barrier in this region.[56] Several other genes and cellular pathways are photoperiodically regulated in tanycytes, such as neuromedin U, retinoic acid or glutamate transport.[56]

3.2 | Thyroid hormone: required for expression of summer physiology

Dio2 is the primary thyroid hormone (TH) activating enzyme in the brain, converting the circulating thyroxine (T4) to the more active form of TH, triiodothyronine (T3). Contrastingly, Dio3 is the main TH inactivating enzyme, degrading both T3 and T4 to the inactive metabolites diiodothyronine and reverse T3, respectively.[58] Although the dynamic regulation of hypothalamic deiodinase expression differs between species and experimental protocol (see below), transfer to LP generally increases *dio2* and down-regulates *dio3*, whereas transfer to SP leads to increased *dio3* and decreased *dio2* expression.[49,54,59,60] This change has been associated with a local increase

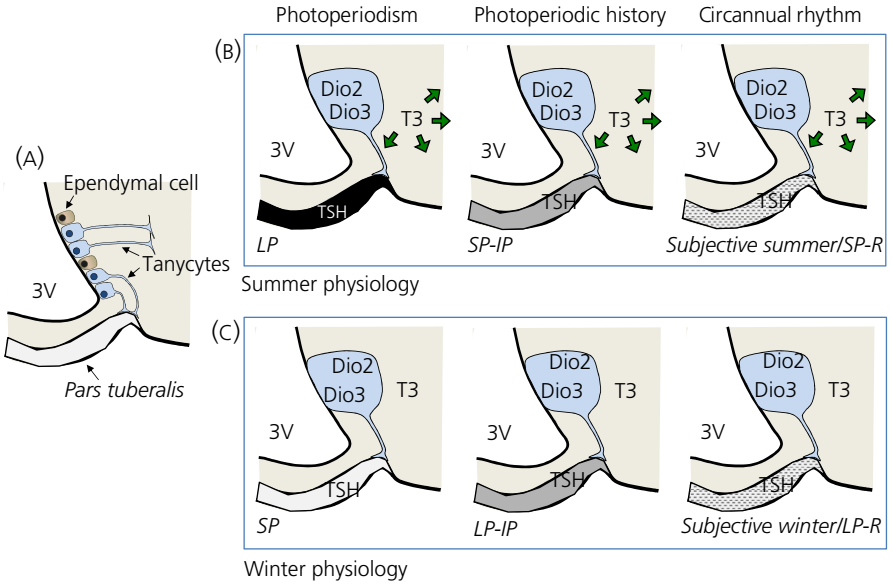

FIGURE 4 Photoperiodism and internal timing control seasonal changes in physiology via long-term communication between the pars tuberalis (PT) and the hypothalamus that leads to similar regulation of deiodinases and triiodothyronine (T3) status in the hypothalamus. A, Cartoon depicting the cytoarchitecture of the ependymal layer of the third ventricle (3V), where tanycytes and ependymal cells are located. Tanycytes extend their projections into the mediobasal hypothalamus or to the median eminence, where they contact portal vessels. A tanycyte is magnified in the other panels to show changes in deiodinase gene expression. B, The transition to summer physiology involves an increase in deiodinase-induced T3 signalling in the hypothalamus. In photoperiodism, the long photoperiod (LP)-induced increase in PT thyroid-stimulating hormone (TSH) (black) leads to a high *dio2/dio3* expression ratio in tanycytes (blue) and thus increased T3 signalling (green arrows). Similarly, in history-dependent timing, animals in intermediate photoperiod with short photoperiod (SP) history (SP-IP), show a spontaneous increase in the *dio2/dio3* ratio in tanycytes, which, in maternal photoperiodic programming, has been linked to intermediate PT TSH expression (grey). In circannual rhythms, animals in a subjective summer state show high TSH production in the PT, as observed in European hamsters, although this increase has not been observed in short-day refractory (SP-R) sheep or Siberian hamsters (dotted). In both cases, there is an increase in the *dio2/dio3* ratio in tanycytes that leads to increased T3 signalling. C, The transition to winter physiology involves a decrease in hypothalamic deiodinase-induced T3 signalling, mediated by a decrease in PT TSH expression. In photoperiodism, the long melatonin profile present in animals in SP inhibits PT TSH expression (white), which leads to a low *dio2/dio3* expression ratio in tanycytes and a low T3 level in the hypothalamus. Similarly, in history-dependent timing, animals in IP with LP history (LP-IP) show a spontaneous decrease in the *dio2/dio3* ratio in tanycytes, which, in maternal photoperiodic programming, has been linked to intermediate PT TSH expression (grey) and reduced sensitivity to its action. In animals displaying circannual rhythms, PT TSH expression is reduced (dotted) during the subjective winter state, as observed in European hamsters and long-day refractory (LP-R) sheep. This decrease in TSH signalling leads to reduced *dio2/dio3* ratio in tanycytes and thus reduced T3 signalling

in T3 and T4 levels in LP compared to SP,[55,59,61] which is a conserved feature in vertebrates, regardless of the breeding season of the species[62] (Figure 4).

Locally regulated TH levels controlled by deiodinase activity serve as an ancestral signal in vertebrates, being involved in postembryonic organ development and life-cycle events such as metamorphosis[63] or puberty[64]; such events are endogenously driven but can be environmentally modulated. A role for TH in seasonal reproduction was first suggested by studies in ducks, where thyroidectomy blocks the increase in gonadal growth induced by exposure to long daylength.[65] In sheep, thyroidectomy does not affect the onset of the breeding season but prevents the spring transition into anoestrous.[66,67] This effect can be reversed by T4 treatment,[66-68] which is effective only during a sensitive window between spring and mid-summer,[68] coincident with the increased presence of hypothalamic *dio2* and the absence of *dio3* expression.[69] T3 injections in sexually inhibited Siberian hamsters reactivate the reproductive axis.[70] T3 microimplants only in the basal hypothalamic region (but not in other brain regions) reverse the effects of thyroidectomy or transfer to SP on seasonal reproduction,[71,72] also restoring growth and the metabolic axis.[73] TH is thus required for the initiation and maintenance of the summer reproductive physiology, comprising sexual quiescence in short-day breeders and activity in long-day breeders, an effect that is explained by the dynamics of tanycyte deiodinase activity. The RFamides kisspeptin and RFamide-related peptide (RFRP) expressed in the mediobasal hypothalamus show photoperiodic changes in expression and have been implicated in the seasonal effects on the reproductive axis. These neuropeptides are regulators of gonadotrophin-releasing hormone (GnRH) secretion, integrating internal and external cues such as photoperiod, sex-steroid feedback and metabolic cues.[74] In hamsters, TSH and T3 infusions restore the summer reproductive phenotype and kisspeptin and RFRP expression.[55,75] Hence, the seasonal TH pattern in the hypothalamus, modulated by the PT-TSH message coordinates the neuroendocrine systems that regulate reproduction and metabolism.[55,73]

4 | MATERNAL PHOTOPERIODIC PROGRAMMING OCCURS IN TANYCYTES

4.1 | Programming of hypothalamic deiodinases

The neuroendocrine mechanisms involved in photoperiodic history and MPP remain unknown. Adult Siberian hamsters transferred from LP or SP to IP show history-dependent changes in hypothalamic *dio3* gene expression, reflecting the subjective interpretation of the photoperiodic signal, rather than its actual duration. This was the first indication that hypothalamic TH signalling reflects photoperiodic history dependence.[76]

We recently investigated the neuroendocrine mechanisms involved in the MPP response with the working hypothesis that the neuroendocrine TSH/dio system downstream of melatonin will reflect the programming effect of photoperiodic history lived in utero. Using a developmental approach to induce the MPP phenomenon,[36] Siberian hamsters gestated and raised in LP or SP were transferred at weaning to IP (LP-IP and SP-IP, respectively) (Figure 3A). LP-gestated newborns expressed higher *TSHβ* in the PT, together with a higher *dio2* mRNA level in the tanycytes than those gestated in SP, indicating that the maternal melatonin binding to foetal pituitary and the PT-hypothalamic retrograde communication lead to regulation of local TH metabolism in the newborn's tanycytes (Figure 3B). *Dio3* gene expression was first observed by mid-lactation only in the SP animals.[36]

As soon as 3 days after weaning and transfer to IP, LP-IP animals showed reduced *TSHβ* expression in the PT and *dio2* expression in the tanycytes, which was associated with a decrease in follicle-stimulating hormone levels, whereas a strong increase in *dio2* and decrease in *dio3* expression was observed in the SP-IP animals, although without any observed increase in *TSHβ* expression. This result does not represent a transitory response to the switch in photoperiod but, instead, the initiation of a long-term programming of the offspring's interpretation of its own melatonin pattern. At P50, after 25 days in identical IP conditions, SP-IP animals showed increased gonadal development compared to LP-IP animals. At this time, *dio2* mRNA expression was strongly stimulated and *dio3* inhibited in SP-IP animals, with *dio3* mRNA expression being stimulated in LP-IP animals, whereas no changes were observed in PT *TSHβ* mRNA expression between these groups (Figure 3B). This result localises the persistent programming effect to deiodinase expression in tanycytes.

4.2 | Programming changes tanycyte sensitivity to TSH

We hypothesised that a switch in tanycyte sensitivity to TSH signalling underlies the MPP effect. To test this hypothesis, we injected i.c.v. increasing doses of TSH previously shown to cause minimal effects on *dio2* expression.[55] Accordingly, 0.5 mIU of TSH induced *dio2* mRNA expression in both LP-IP and SP-IP animals, whereas 1 mIU of TSH further increased *dio2* mRNA expression in SP-IP animals, although not in the LP-IP group, demonstrating a decreased sensitivity to TSH in LP-IP animals, which is an effect that was not associated with changes in *TSH-r* mRNA expression, nor circulating TH feedback on deiodinase expression.[36] This change in the level of *dio2* expression to a given *TSH* mRNA level was recently reported in a study exploring critical photoperiods in sheep.[77] The mechanistic origin of this change in sensitivity to TSH signalling remains to be determined. Programming effects of prenatal stress experience have been associated with epigenetic regulation of gene expression.[78] Both deiodinase genes are targets of epigenetic modifications[79,80] and both *dio3* promoter methylation and the level of epigenetic enzymes are altered by photoperiod in Siberian hamsters.[81,82] Early photoperiodic exposure, as mediated by TSH-dependent or -independent signalling, could induce epigenetic mechanisms that lead to the long-term shift in TSH sensitivity in tanycytes.

5 | MATERNAL NEUROENDOCRINE PROGRAMMING

At present, the study of maternal programming of neuroendocrine function focuses primarily on the long-term consequences of early life altered stress and metabolic environments for offspring health, where mismatching environments and hormonal status between foetal and adult life often lead to pathology. Prenatal stress exposure produces offspring with increased levels of depressive behaviour and anxiety.[83] An excess of glucocorticoids in utero leads to impaired negative-feedback on the hypothalamic-pituitary-adrenal axis and, consequently, higher vasopressin and corticotrophin-releasing hormone expression in the hypothalamus.[83] The long-term effects of early-life stress have been linked to altered epigenetic regulation of gene expression in the hypothalamus and lymbic system.[78]

Maternal undernutrition during pregnancy and lactation produces obese and leptin-resistant offspring, especially when fed a high-fat diet,[84] an effect that can be reversed with neonatal leptin treatment.[84] Similarly, overnutrition during this time leads to metabolic syndrome in offspring.[85] Interestingly, adults born to overfed dams develop resistance to leptin, insulin and ghrelin signalling in the ARC, reducing the ability of these hormones to induce an intracellular response,[86-88] as well as altering the development of neuroendocrine projections from the ARC.[89] This developmental plasticity, considered as pathological in the view of a increasingly obese society, serves as an adaptive response for preparing the physiology to match a future environment predicted by the early environmental cues: the so-called predictive-adaptive response.[90] This strategy appears of particular value in predictable seasonally changing environments,[91] accounting for the evolution of MPP as an adaptive trait.

6 | HISTORY-DEPENDENT CHANGE IN HYPOTHALAMIC DEIODINASES: UNIFYING OUTPUT OF INTERNAL LONG-TERM TIMING

In addition to history-dependent changes in photoperiodic responsiveness, endogenous long-term timekeeping is revealed by

exposure to constant photoperiodic conditions. In these conditions, full circannual rhythms (Figure 1C) are manifested in seasonal species that normally live for several breeding seasons, although these rhythms are only partially manifested in short-lived species, and not likely to survive for more than one or two breeding seasons. Short-lived species typically maintain the ability to spontaneously revert to a spring reproductive phenotype under prolonged winter daylengths, although without going through a full cycle, comprising a phenomenon known as photorefractoriness.[92] The term refractory is often applied to the individual phase switches in a circannual rhythm.[93]

Similar to the melatonin-independent switch in the expression of hypothalamic deiodinases underlying MPP of seasonal reproduction (Figures 3B and 4), recent work on the control of circannual timing has also unveiled long-term switches in the TSH/dio2-3 system independently of melatonin signalling (Figure 4). In circannually cycling sheep, the melatonin signal continues to reflect the prevailing photoperiod.[93] Sheep that become refractory to constant SP exposure (SP-refractory) switching to summer physiology (ie, reproductive axis inhibition) show a decrease in *dio3* and an increase in *dio2* mRNA level in the ME, with no increase observed in PT *TSHβ* expression.[69] Similarly, SP-refractory Syrian or Siberian hamsters undergo a spontaneous switch to summer physiology[94] (ie, reactivation of the reproductive axis), whereas their melatonin pattern remains unchanged.[95] This switch involves a decrease in *dio3* gene expression, with no obvious change in *dio2* or *TSHβ* expression, followed by reactivation of the reproductive axis a few weeks later.[96-99] These endogenous switches, which apparently occur independently of TSH signalling, mimic the observed change in SP-IP animals where a strong drive towards the recovery of TH signalling (increased *dio2* and decreased *dio3* gene expression) takes place via a greatly enhanced sensitivity to TSH signalling. This evidence suggests that the endogenous switch to summer physiology is *dio2*-dependent and might originate in the hypothalamic response to pituitary signals, or be intrinsic to the hypothalamus[36] (Figure 4B).

When sheep become refractory to constant LP exposure (LP-refractory), switching to winter physiology, they show a decrease in *dio2* and an increase in *dio3* expression in the hypothalamus, together with a decrease in *TSHβ* expression in the PT.[69,100] Similarly, European hamsters kept in constant LP show a decrease in *TSHβ* and *dio2* expression during the "subjective winter state", when they have endogenously switched towards a winter nonreproductive state.[101] However, prolonged LP exposure in Syrian or Siberian hamsters does not cause a reversion to a winter-like anestrous state,[94] nor a switch in *dio2* or *dio3* expression.[97] Nonetheless, the switches observed in LP-IP animals, where the spontaneous increase in *dio3* expression is preceded by a dynamic decrease in *TSHβ* mRNA levels,[36] parallel to other endogenous winter-like switches. Therefore, species considered noncircannual show LP-refractory phenomena leading to decreased hypothalamic TH signalling. Thus, the capacity of a species to undergo an entire circannual cycle might reside in the ability of the PT to decrease TSH expression in the winter switch independently of melatonin signalling, driving an increase in *dio3* expression to decrease hypothalamic TH levels (Figure 4C). Future work should aim to test this hypothesis.

7 | HOW DOES HYPOTHALAMIC T3 ACT ON SEASONAL REPRODUCTION?

Outstanding challenges include identifying the long-term (rheostatic) neuroendocrine mechanisms downstream of tanycyte programming, which lead to history-dependent changes in reproduction, and understanding how T3 availability influences GnRH release. RFamides are presently the main candidates for mediation between the photoperiodic control of T3 and seasonal GnRH regulation.[102] However, reactivation of gonadal growth in LP-refractory Siberian and Syrian hamsters takes place prior to an increase in expression of the reproductive neuropeptides RFRP and kisspeptin.[99] This early (homeostatic) step could be more directly mediated by changes in firing activity[103] leading to GnRH release. Tanycytes are involved in the formation of the blood-brain barrier in the ME, where they undergo structural changes that allow regulation of neuroendocrine secretions.[104] Photoperiod and T3 regulate tanycyte endfeet remodelling in Siberian hamster and quail, allowing GnRH terminals to access the basal lamina in LP and blocking this access in SP.[105,106] However, this phenomenon is also evident in LP-refractory sheep with respect to reactivating the reproductive axis, and so it is linked to the phase of reproduction and not the T3 status.[100] A recent study identified several genes that are independently regulated by photoperiod and TH in sheep tanycytes (*Tmt252*, *evolv3*, *cndp1*), suggesting that they could serve as a bridge between the seasonal TH message and the regulation of GnRH,[107] although this remains to be investigated in other species.

T3 plays a direct role in both the control of neural cell proliferation and neuroglial differentiation in brain proliferative areas.[108,109] Tanycytes express proliferation and differentiation markers under seasonal (eg, vimentin, nestin)[105,110] and T3-mediated control (eg, *shh*)[107] and have been proposed as the substrate for neurogenic activity in the hypothalamus, stimulated by metabolic cues and growth factors.[111-116] Moreover, seasonal differences exist in hypothalamic cell proliferation[117-119] and neuronal differentiation.[114,120] Although the functional significance of this restructurating remains to be demonstrated, seasonal histogenesis has been proposed as a mechanism for endogenous timing.[121] It could be speculated that, in MPP, pools of proliferating cells differently programmed during gestation react differently to the same photoperiodic signal perceived in adults. Cell fate-mapping studies using reporter genetic models in photoperiodic responsive species[54,59,60,72] or mice and rat strains[49,61] would be required to explore this hypothesis.

8 | CONCLUSIONS AND PERSPECTIVES

Despite dynamic differences, all of the studies conducted to date highlight the central role of hypothalamic deiodinase regulation

and TH metabolism in seasonal timekeeping in mammals, regardless of the life-history strategies of the species. Internal timing is characterised by spontaneous switches towards hypothalamic TH signalling in the spring and away from this in autumn, arising from the long-term communication between the PT and the hypothalamus (Figure 4), independently of the prevailing melatonin signal, whereas these switches are driven by melatonin in photoperiodism. Determination of the molecular mechanisms responsible for the spontaneous changes in endogenous timing strategies remains one of the largest challenges in the field. Recent work in LP-refractory sheep has highlighted a number of molecular markers, signalling networks and structural changes taking place in the PT associated to this endogenous change,[100] offering new avenues to understand the spontaneous switch to winter physiology. Otherwise, tanycytes appear as a strong cellular candidate for exploring the molecular origin of the spontaneous change towards summer physiology, as evident in all of the manifestations of endogenous timing. Furthermore, the characterisation of history-dependent and photoperiodic molecular changes taking place in tanycytes could shed light on how the equivalent switch in the TSH/dio pathway is associated with apparently opposite effects on reproductive physiology in long-day vs short-day breeders. A recent model proposes that this variation would arise from different dynamics in the net result of two photoneuroendocrine processes: a photo-inductory process dependent on prevailing photoperiod and a gradually increasing long-term photo-inhibitory process.[122]

Finally, the MPP phenomenon is a strong model for exploring the seasonal effects on brain plasticity. Moreover, it is also an effective paradigm for understanding how the early environment affects reproductive and metabolic development and its hypothalamic control. TH are essential for neural postnatal development, being involved in processes such as neural progenitor proliferation, migration and differentiation of neurones and glia.[123] The clear change in hypothalamic TH signalling and the associated physiological response means that MPP comprises a useful nonpathological paradigm for exploring the effects of altered endogenous TH signalling during hypothalamic development.

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CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest.

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