



# Effects of Melatonin on Anterior Pituitary Plasticity: A Comparison Between Mammals and Teleosts

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Melatonin is a key hormone involved in the photoperiodic signaling pathway. In both teleosts and mammals, melatonin produced in the pineal gland at night is released into the blood and cerebrospinal fluid, providing rhythmic information to the whole organism. Melatonin acts *via* specific receptors, allowing the synchronization of daily and annual physiological rhythms to environmental conditions. The pituitary gland, which produces several hormones involved in a variety of physiological processes such as growth, metabolism, stress and reproduction, is an important target of melatonin. Melatonin modulates pituitary cellular activities, adjusting the synthesis and release of the different pituitary hormones to the functional demands, which changes during the day, seasons and life stages. It is, however, not always clear whether melatonin acts directly or indirectly on the pituitary. Indeed, melatonin also acts both upstream, on brain centers that control the pituitary hormone production and release, as well as downstream, on the tissues targeted by the pituitary hormones, which provide positive and negative feedback to the pituitary gland. In this review, we describe the known pathways through which melatonin modulates anterior pituitary hormonal production, distinguishing indirect effects mediated by brain centers from direct effects on the anterior pituitary. We also highlight similarities and differences between teleosts and mammals, drawing attention to knowledge gaps, and suggesting aims for future research.

**Keywords:** melatonin, adenohipophysis, photoperiod, melatonin receptors, seasonal reproduction, plasticity, endocrinology, light

## INTRODUCTION

Our environment is constantly changing. While some variations are fast and unpredictable (e.g. meteorological phenomena), others, such as solar cycles, moon phases, and seasons follow regular patterns. Photoperiod, the alternation of light and darkness, is the most reliable (noise-free, characterized by predictable rhythms over a long period of time) signal, allowing animals to synchronize their biological rhythms with both daily and seasonal changes. Photoperiod is conveyed by two types of signal: a neural message from photoreceptive structures to specific signaling centers in the brain, and a hormonal message (1, 2).

Melatonin is the key hormone that conveys rhythmic information from the environment, including photoperiod and temperature, to the organism. Circulating blood levels of melatonin exhibit a daily rhythm with higher levels during night than during day, and a seasonal rhythm with longer duration of the high level period during winter, as a consequence of the longer dark phase (**Figure 1**). Additionally, variations in temperature fine-tune those rhythms by modulating the amplitude of melatonin production. Duration and amplitude of melatonin release therefore provide clear information regarding time of the day and the year, and allow the synchronization of metabolic, physiological, and behavioral events, including growth, reproduction, and migration (3, 4).

Melatonin is synthesized from tryptophan in four enzymatic steps (4, 5). Tryptophan is first converted into 5-hydroxytryptophan by the tryptophan hydroxylase, then converted into serotonin by the 5-hydroxy-tryptophan decarboxylase. Afterwards, serotonin is acetylated by the arylalkylamine *N*-acetyltransferase (AANAT), producing *N*-acetylserotonin, which is finally converted into melatonin by the hydroxyindole-*O*-methyl transferase. AANAT has been reported to be the limiting enzyme driving the rhythm of melatonin production (6). It has been hypothesized that the functional shift of AANAT from amine detoxification to melatonin synthesis played a critical role in the evolution of melatonin as a night-time signal (7–9).

While the general mechanism of melatonin synthesis is conserved across vertebrates, the number of genes encoding

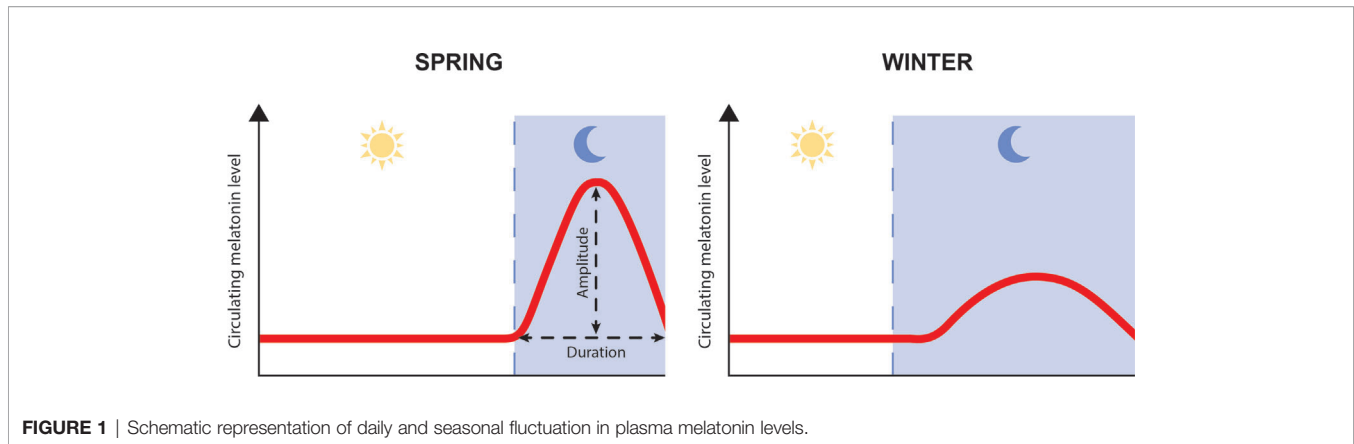
the different enzymes differs between mammals and fish, as a consequence of whole genome duplications that occurred in the vertebrate lineage. Indeed, after the two successive whole genome duplications (referred to as 1R and 2R) which occurred at the base of the vertebrate lineage (10–12), a third one (3R) occurred at the base of the teleost fish lineage (13), and a fourth one (4R) occurred independently in both the cyprinid and salmonid lineages (14, 15). Following a genome duplication, one of the paralogous genes may be lost or duplicated paralogues may acquire differential specialized functions over time, and an increase in the number of paralogues, expands the hormone-receptor combinations (16). In contrast to mammals, all actinopterygians, including the teleosts, possess at least two *aanat* genes (*aanat1* and *aanat2*) (9, 17), resulting probably from the whole genomic duplications that occurred in the vertebrate lineage (18). Additionally, *aanat1* and *aanat2* have also been duplicated during the 3R (18). While one of the *aanat2* paralogues was lost early after the 3R, this was not the case for the *aanat1* paralogues and, to date, some fish possess two *Aanat1* isoforms (*aanat1a* and *aanat1b*) or either one of them. While *aanat1* genes are mostly expressed in the retina, brain, and peripheral tissues, *aanat2* expression is specific to the pineal gland (19, 20), the site of production of circulating melatonin in both mammals (21) and teleosts (22, 23). Melatonin is then released from the pineal gland into the blood and cerebrospinal fluid to be transported to its target organs.

Melatonin acts through several different receptors (MTNR), belonging to the G-protein coupled receptor superfamily (24). Four sub-groups of *Mtnr*, arising from the 1R and 2R, have been characterized in vertebrates: MTNR1A (Mel1a or MT1), MTNR1B (Mel1b or MT2), MTNR1C (Mel1c or GPR50), and MTNR1D (Mtnr1A-like or Mel1d) (25–28). In mammals, melatonin action is mediated only through two MTNR paralogues, MTNR1A and MTNR1B, since the *Mtnr1d* gene was lost in the mammalian lineage and MTNR1C lost its ability to bind melatonin (28). Teleosts may possess up to 7 *Mtnr* paralogues (excluding the polyploid cyprinids), arising from the 3R and 4R (25, 28). MTNR affects different intracellular signaling pathways, including cAMP/PKA, via G<sub>i</sub> proteins (MTNR1A and MTNR1B) (29, 30), PLC/PKC via G<sub>q</sub>-proteins (MTNR1A and MTNR1C) (31) and cGMP via G<sub>1/0</sub> proteins (MTNR1B) (32, 33). In medaka (*Oryzias latipes*), all four *Mtnr* subtypes are functional and decrease cAMP in response to melatonin exposure (27). Interestingly, melatonin receptors in Atlantic salmon (*Salmo salar*) increase cAMP when activated by melatonin (25). The broad distribution of MTNR expression in the central nervous system (including the pituitary) and peripheral tissues suggests melatonin can have widespread effects (28, 34).

The pituitary is a key endocrine gland in all vertebrates, involved in the regulation of many important physiological processes (35). These include growth, puberty, seasonal sexual maturation, metabolism, and homeostasis, which exhibit cycling components over the day, the year and the life cycle. Located below the hypothalamus, the pituitary is composed of two main parts with different developmental origins (36): the anterior pituitary (adenohypophysis) and the posterior pituitary (neurohypophysis) (**Figure 2**). The neurohypophysis originates from a down-growth of the diencephalon and is mainly composed of nerve terminals from

**Abbreviations:** 1R to 4R, 1st to 4th whole genome duplication; AANAT, Arylalkylamine *N*-acetyltransferase; AC, Adenyl cyclase; ACTH, Adrenocorticotrophic hormone; ARC, Arcuate nucleus; ATP, Adenosine 5'-triphosphate; cAMP, Cyclic adenosine 5'-monophosphate; cGMP, Cyclic guanosine monophosphate; CREB, Calcium/cAMP response element binding protein; Cry1, Cryptochrome1; DIO2/3, Deiodinase 2/3; ER, Endoplasmic reticulum; EYA, Eyes absent homologue; FSH/FSHB, Follicle-stimulating hormone/FSH beta subunit; GH, Growth hormone; GnIH, Gonadotropin inhibiting hormone; GnRH, Gonadotropin releasing hormone; GnRHR, Gonadotropin releasing hormone receptor; LP/SP, Long photoperiod/Short photoperiod; LH/LHB, Luteinizing hormone/LH beta subunit; LL/DD, Constant light/Constant darkness; ME, Median eminence; MSH, Melanocyte-stimulating hormone; MTNR, Melatonin receptors; PD, Pars distalis; Per1, Period1; PI, Pars intermedia; PKA, Protein kinase A; PKC, Protein kinase C; PLC, Phospholipase C; POA, Preoptic area; POMC, Pro-opiomelanocortin; PRL, Prolactin; PT, Pars tuberalis; RFRP, RFamide related peptide; SCN, Suprachiasmatic nucleus; SL, Somatolactin; T3, Triiodothyroxine; T4, Thyroxine; TEF, Thyrotroph embryonic factor; TH, Thyroid hormone; TRH, Thyrotropin-releasing hormone; TSH/TSHB, Thyroid stimulating hormone/TSH beta subunit.

**Gene and protein nomenclature:** The present review follows the ZFIN nomenclature conventions for protein and gene names in mammals and fish (e.g. Mammalian protein: LHB; Mammalian gene: *Lhb*; fish protein: *Lhb*; fish gene: *lhb*).



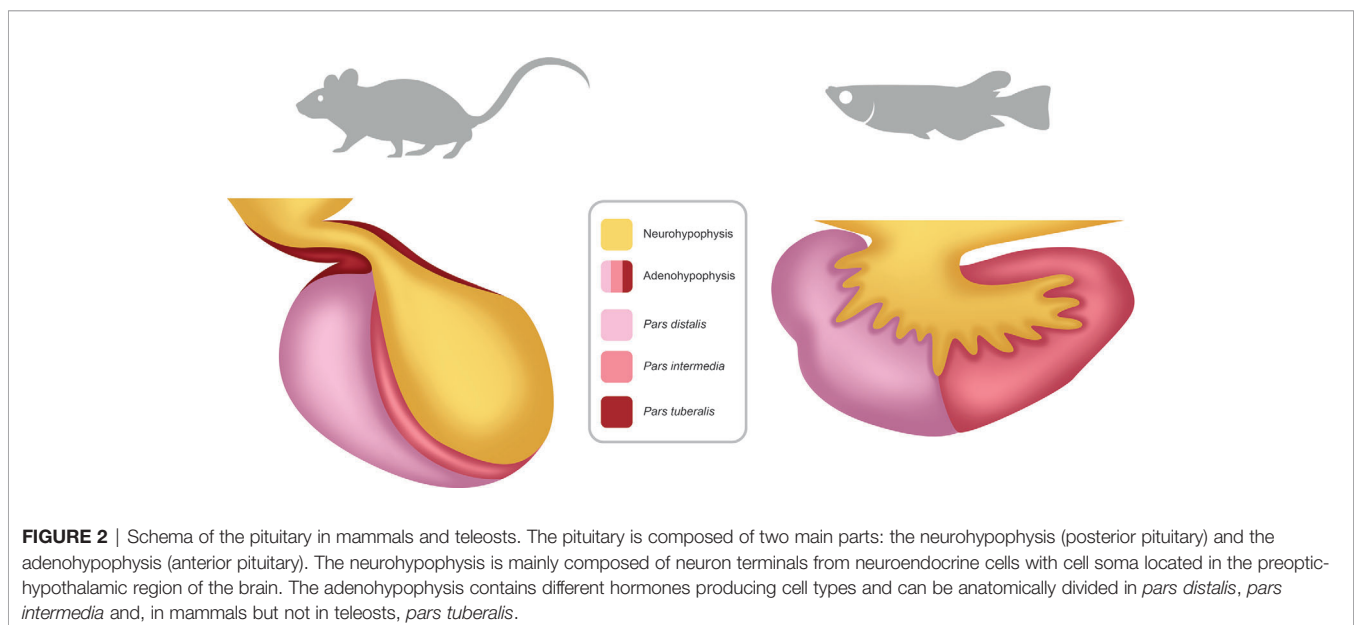
**FIGURE 1** | Schematic representation of daily and seasonal fluctuation in plasma melatonin levels.

neuroendocrine cells in the preoptic area (POA) and the hypothalamus of the brain, which are considered today as two distinct regions (37). The adenohypophysis originates from an up-growth of the pharyngeal ectoderm and endoderm (38) and can be histologically divided in the *pars intermedia* (PI), the *pars distalis* (PD), and the *pars tuberalis* (PT), the latter present in mammals but not in teleosts. The adenohypophysis hosts several hormone-producing cell types: gonadotropes (producing the gonadotropins: follicle-stimulating and luteinizing hormones, FSH and LH), lactotropes (prolactin, PRL), somatotropes (growth hormone, GH), thyrotropes (thyrotropin, TSH), corticotropes (adrenocorticotropin, ACTH), and melanotropes (melanocyte-stimulating hormone, MSH) (39). Teleosts also possess one additional cell type, the somatolactotropes responsible for the production of somatolactin (SI) (40).

The activity of pituitary endocrine cells is constantly changing over time, adjusting the hormonal production to changing physiological needs. It is controlled by factors produced from

signaling centers in the brain, mainly the POA and hypothalamus, and from peripheral organs, which provide positive and negative feedback to these centers and to the pituitary (41, 42). In mammals, POA/hypothalamic neurons project to the median eminence (ME) of the hypothalamus, releasing their hormones into the hypophysial portal system where they are transported *via* the blood stream to the pituitary endocrine cells (42). Teleosts, on the other hand, lack the hypophysial portal system, and instead the POA/hypothalamic neurons innervate the pituitary, releasing their neurohormones directly at target cells or into pituitary blood vessels (41, 43). Pituitary hormonal production is regulated through both modulation of the activity of individual cells, and regional reorganizations of the anterior pituitary in terms of structure or cell composition, as discussed previously for gonadotropes (38, 44).

While pituitary plasticity is influenced by environmental factors, the role that melatonin plays in translating fluctuations of environmental conditions into pituitary hormonal production



**FIGURE 2** | Schema of the pituitary in mammals and teleosts. The pituitary is composed of two main parts: the neurohypophysis (posterior pituitary) and the adenohypophysis (anterior pituitary). The neurohypophysis is mainly composed of neuron terminals from neuroendocrine cells with cell soma located in the preoptic-hypothalamic region of the brain. The adenohypophysis contains different hormones producing cell types and can be anatomically divided in *pars distalis*, *pars intermedia* and, in mammals but not in teleosts, *pars tuberalis*.

is not always clear. In addition, the mechanisms of melatonin action are complex, as both direct effects on pituitary endocrine cells and indirect effects through neuro/hormonal signaling centers combine to regulate pituitary activity. In this review, we describe the known pathways through which melatonin modulates anterior pituitary hormonal production, distinguishing between indirect effects mediated by brain centers and direct effects on the anterior pituitary. We also highlight similar and divergent features between teleosts and mammals, and emphasize important unsolved questions for future research.

## BRAIN-MEDIATED EFFECTS OF MELATONIN ON ANTERIOR PITUITARY ENDOCRINE CELLS

### Mammals

Endocrine pituitary cells are primarily controlled by brain signaling centers, mainly the preoptic and hypothalamic area (42) (Figure 3, Table 1), which integrate nervous and hormonal signals of different origins. These brain regions are characterized by the presence of numerous melatonin binding sites as shown in rodents and ruminants (60–66). Although the suprachiasmatic nucleus (SCN) of the hypothalamus drives the rhythmic production of melatonin in mammals (67), the present review will focus on known effects of melatonin on brain centers directly regulating pituitary endocrine production, as discussed below.

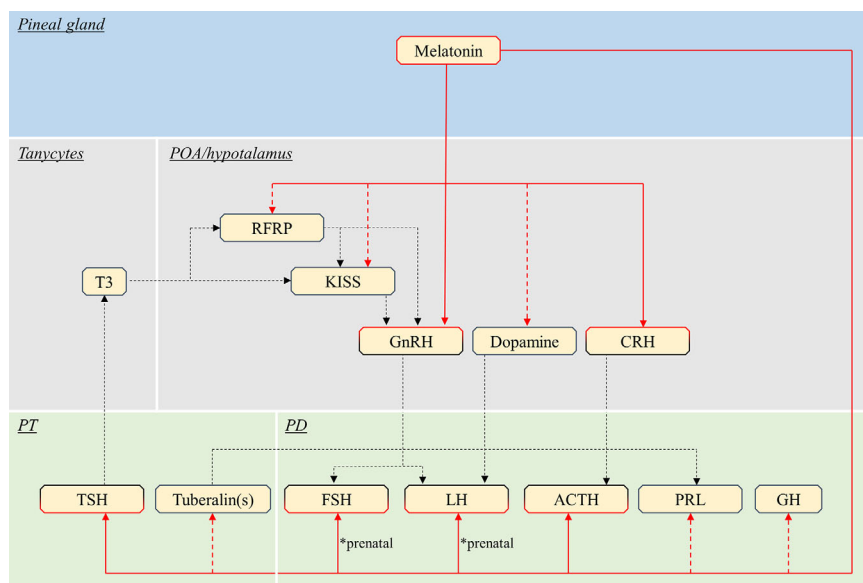
### Gonadotropes

Gonadotropes are the most investigated pituitary cell type in relation to melatonin, due to the high scientific and economic interest around the seasonal control of reproduction. Indeed, gonadotropes produce the two gonadotropins (FSH and LH), key hormones in the control of reproduction, which are heterodimeric glycoproteins composed of a common  $\alpha$ -subunit (GPH $\alpha$ , also shared with TSH) and a hormone-specific  $\beta$  subunit (LH $\beta$  or FSH $\beta$ ) conferring the specific biological activity (42).

### GnRH

Mammalian gonadotropin-releasing hormone (GnRH1 or mGnRH-I), a 10-amino acid neuropeptide produced from POA/hypothalamic neurons, is the main regulator of gonadotropin synthesis and secretion (42). Most mammals also possess a second form (GnRH2 or cGnRH-II), expressed in the midbrain and other organs, which is primarily involved in other functions than regulating gonadotropin release. Vertebrates also possess two major types of GnRH receptors (type I with the GnRHR1a and II with the GnRHR2c) (68), however in many mammalian species, GnRHR2c receptor is not functional (69).

Melatonin influences GnRH production and thus the reproductive axis in seasonal breeders. Melatonin administration and short photoperiod (SP) cause testicular regression in the male summer breeder jerboa (*Jaculus orientalis*), a desert hibernating rodent, by inhibiting GnRH release (47). In contrast, melatonin administration in the ewe (*Ovis aries*, a winter breeder) increases the pulsatile GnRH secretion from hypothalamus, and pituitary LH



**FIGURE 3** | Schematic view of the putative pathways through which melatonin influence pituitary endocrine activity in mammals. Red continuous lines indicate cell types directly targeted from melatonin. Dashed red lines indicate cells influenced by melatonin *via* yet unidentified interneurons, paracrine signals or MTNR. Note that melatonin might act only on a few of the illustrated pathway, in different species (see text). Black dashed lines indicate all other interactions between brain and pituitary. POA, preoptic area; PT, *pars tuberalis*; PD, *pars distalis*; T3, triiodothyronine; RFRP, RFamide-related peptide; KISS, kisspeptin; GnRH, gonadotropin-releasing hormone; CRH, corticotropin-releasing hormone; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; ACTH, adrenocorticotropic hormone; PRL, prolactin; GH, growth hormone.

**TABLE 1 |** Summary of the known effects of melatonin POA/hypothalamic neurons controlling pituitary hormonal production in mammals.

Target	Effect of melatonin	Species	Breeding season/ Photoperiod	Description	Reference
<b>Mammals</b>					
GnRH	Stimulates	Sheep	Winter/SP	Melatonin administration increases GnRH secretion	Bittman et al. (45) Viguié et al. (46)
	Inhibits	Jerboa	Summer/LP	Short photoperiod and melatonin administration downregulate GnRH release	El Qandil et al. (47)
	Inhibits	GT1-7 mouse GnRH cell line		Melatonin reduces GnRH mRNA and protein levels in GT1-7 cell line	Roy et al. (48)
	Modulates	Rat	non-seasonal breeder	Melatonin augments/reduces GABA-induced currents in GnRH neurons in a sex dependent way	Sato et al. (49)
KISS	Inhibits	Syrian hamster	Summer/LP	Melatonin reduces KISS1 mRNA	Revel et al. (50) Ansel et al. (51)
		Turkish hamster	Summer/LP	Melatonin reduces KISS1 mRNA	Piekarski et al. (52)
		Striped hamster	Summer/LP	Melatonin reduces KISS1 mRNA	Li et al. (53)
		Rat	non-seasonal breeder	Melatonin reduces KISS1 mRNA	Oliveira et al. (54)
RFRP	Inhibits	Syrian hamster	Summer/LP	Melatonin (and SP) reduces RFRP-3 mRNA and protein	Mason et al. (55) Revel et al. (56)
		Siberian hamster	Summer/LP	Melatonin (and SP) reduces RFRP-3 mRNA and protein	Ubuka et al. (57) Revel et al. (56)
Dopamine	Stimulates	Syrian hamster	Summer/LP	Melatonin administration stimulates tyrosine hydroxylase activity in males	Alexiuk et al. (58)
	Inhibits	Sheep	Winter/SP	Melatonin implants inhibit tyrosine hydroxylase activity	Viguié et al. (59)

secretion (45, 46). While suggesting a connection between melatonin level and GnRH production, these *in vivo* experiments do not reveal whether melatonin acts directly on GnRH neurons, indirectly *via* interneurons or through a combination of both. However, *in vitro* experiments using the GT1-7 mouse hypothalamic GnRH cell line reveal that GnRH neurons express MTNR1A (MT1) and MTNR1B (MT2) (48) and demonstrate that melatonin inhibits both GnRH mRNA expression and protein secretion (48, 70).

Melatonin action might be modulated in a sexually dimorphic way in rodents as higher mRNA levels of *Mtnr1a* (MT1) are detected in male than female rat (*Rattus norvegicus*) GnRH neurons, while *Mtnr1b* (MT2) is not expressed in either sex (71). Sexual dimorphism of the melatonin response in GnRH neurons is supported by another *in vitro* study, where melatonin augmented the membrane current induced by gamma-aminobutyric acid (GABA<sub>A</sub>) in 70% and attenuated it in 18% of neurons from adult males, while it augmented the current in only 25% and attenuated it in 61% of the neurons from adult females (49). Nevertheless, the physiological relevance of the direct actions of melatonin on GnRH neuron activity *in vivo* remains controversial, as melatonin might additionally act on upstream signals, such as KISS1, RFRP3 and T3, as discussed below.

### RFRP3 (GnIH)

RFamide related peptide3 (RFRP3) is the mammalian orthologue of avian GnIH, which was originally identified in birds as an inhibitory factor of gonadotropin synthesis and release, by acting on both GnRH neurons and gonadotropes. RFRP3 neurons are located in the paraventricular nucleus of the hypothalamus (42). Interestingly, the effects of RFRP3 on gonadotropin synthesis are deeply influenced by sex and timing of administration in mammals. For instance, in Syrian hamsters (*Mesocricetus auratus*), RFRP3 inhibits gonadotropin secretion in ovariectomized females (72) while it

stimulates GnRH and gonadotropin secretion in males (73). In male Siberian hamster (*Phodopus sungorus*), RFRP3 directly injected into the third ventricle inhibits LH release when applied under LP, but has excitatory effects under SP (57), suggesting that melatonin might differentially influence the activity of RFRP3 neurons over the seasons.

In summer breeders, such as Siberian and Syrian hamster, both SP and melatonin injection reduces RFRP3 protein and mRNA levels, as well as decrease RFRP3 fibre density and number of projections to GnRH neurons (55–57). These studies also show that pinealectomy abolishes the effects of photoperiod manipulation, while subsequent melatonin exposure re-establishes them. While sex steroids are known to induce positive or negative feedback on hypothalamic signaling centers, the SP-induced reduction in RFRP3 protein and mRNA levels observed in male hamsters is not a consequence of reduced circulating steroid levels, since neither castration nor testosterone implants alter RFRP3 synthesis. These data therefore strongly suggest that melatonin is responsible for the inhibition of RFRP3.

In winter breeders, such as sheep, SP decreases both RFRP3 mRNA and protein levels, and RFRP3 neuron projections to GnRH neurons (74, 75). Similarly, in brushtail possum (*Trichosurus vulpecula*) females, the number of RFRP3 neurons decreases during winter (76). Interestingly, in the laboratory Wistar rat, a non-photoperiodic breeder, no effect of photoperiod manipulation was detected on RFRP3 neurons (56). These results suggest that the photoperiodic control of melatonin on RFRP3 is conserved among mammals, with inhibiting effects in both summer and winter breeders, while the downstream effects of the RFRP3 system on gonadotropin secretion might diverge to adapt to long-day or short-day breeding strategies.

Whether melatonin acts directly on RFRP cells in mammals requires further investigations as there is still a lack of evidence for

colocalization with MTNR, or studies clearly demonstrating a direct action of melatonin on RFRP3 neurons, as previously discussed by Kriegsfeld and collaborators (77).

### **Kisspeptin**

KISS neurons produce the neuropeptide kisspeptin (KISS) and stimulate GnRH synthesis and secretion, thereby regulating gonadotrope cell activity (78). Located in two discrete hypothalamic nuclei, the arcuate nucleus (ARC) in all mammals and the anteroventral periventricular area around the 3<sup>rd</sup> ventricle in rodents or the POA in non-rodent mammals, the activity and number of KISS neurons display a marked photoperiodic/seasonal pattern, as shown below.

In the winter breeding sheep, SP upregulates both ARC *KISS1* mRNA and protein, and increases the number of both ARC KISS neurons and synaptic connections from KISS to GnRH neurons (75). In contrast, melatonin inhibits the activity of KISS neurons in summer breeders. For instance, using a combination of photoperiod manipulation, pinealectomy and melatonin administration Revel and colleagues (50) and Ansel and colleagues (51) demonstrated that melatonin clearly reduces ARC *KISS1* mRNA in Syrian hamsters, an effect further modulated by the negative steroid feedback. Similar inhibitory effects of melatonin on *KISS1* mRNA were detected in Turkish (*Mesocricetus brandti*) (52) and striped (*Cricetulus barabensis*) (53) hamsters but also in the rat, a non-seasonal breeder (54). Interestingly, in the Siberian hamster, ARC *KISS1* mRNA levels are lower under LP due to a robust negative sex steroid feedback overriding the melatonin signal, since castration in LP animals restores high *KISS1* mRNA levels (79). Therefore, the role of melatonin among different species, or different reproductive stages, might be difficult to identify considering the impact of steroid feedbacks on ARC KISS neurons.

Although a direct effect of melatonin on *KISS1* mRNA levels was detected in a hypothalamic cell line from rat (80), *Mtnr* expression has not been found in sheep KISS neurons, neither during the breeding nor during the non-breeding season (81). These results suggest that the effects of melatonin on KISS neurons could be mediated upstream.

### **Dopamine**

The activity of the dopaminergic neurons located within the POA/hypothalamic area, which are involved in the inhibition of gonadotropin synthesis and release (82), also appears to be regulated by melatonin. For instance, in the ewe, a winter breeder, melatonin implants inhibit the activity of tyrosine hydroxylase (the rate-limiting enzyme in the dopamine synthesis pathway) in the median eminence, while stimulating LH release (59). In contrast, in male Syrian hamsters, in which SP elicits testicular regression, melatonin administration stimulates tyrosine hydroxylase activity in the median eminence, increasing dopamine synthesis and release (58).

### **Other Endocrine Cells in the Pars Distalis**

Melatonin plays a role in the regulation of other pituitary endocrine cell types in mammals by regulating their main hypophysiotropic factors.

Corticotrope cells produce ACTH, a hormone involved in various physiological processes including the stress response

(promoting the release of cortisol from the adrenal gland) and the control of numerous daily and seasonal physiological rhythms (including sleep) (83). Corticotropes are mainly regulated by corticotropin releasing hormone (CRH) neurons located in the paraventricular nucleus. Melatonin exerts a stress-protective effect in mammals (84, 85). Daily melatonin administration reduces the ACTH secretory response to acute and chronic stress in rat (86, 87). In humans (*Homo sapiens*), oral melatonin administration in blind individuals normalizes the temporal pattern of ACTH and cortisol plasma concentrations during sleep, suppressing the pituitary-adrenal activity during early sleep and activating it during late sleep (88). Melatonin might modulate ACTH production by acting directly on hypothalamic CRH neurons, which express the MTNR1A in humans (89).

Lactotrope cells produce PRL, a peptide hormone involved in reproduction (lactation), moulting, metabolism, and immune responses. PRL secretion is stimulated by releasing factors from the PT and inhibited by dopamine secreted by tubero-infundibular dopaminergic neurons located in the dorsomedial arcuate nucleus (90–92). Exogenous melatonin administration and SP decrease the PRL secretion in ruminants. For instance, oral melatonin administration inhibits PRL secretion in lactating ewes (93). SP reduces PRL secretion in cows [*Bos taurus* (94)], while melatonin oral administration reduces PRL release in both prepubertal (95) and mature (96) cows. The pathway involved in the melatonin-mediated PRL inhibition seems to be mediated through a dopamine-independent mechanism, since melatonin administration inhibits PRL release even in rams where the hypothalamo-pituitary connection has been surgically disrupted (97, 98) and melatonin implants reduce PRL secretion without altering dopamine content in ewe (59).

Despite the involvement of both somatotropes and thyrotropes in seasonal physiological activity, there is no clearly established role for melatonin signaling to their POA/hypothalamic regulators. Somatotrope cells produce GH, a peptide hormone involved in numerous physiological processes including growth, metabolism and cellular proliferation. The main hypothalamic regulators of somatotropes are growth hormone releasing hormone (GHRH) and somatostatin, which stimulates and inhibits GH production, respectively (99). Thyrotrope cells produce TSH, a heterodimeric glycoprotein hormone, composed of an  $\alpha$ - (GPH $\alpha$ ) and a  $\beta$ - (TSH $\beta$ ) subunit, involved in different seasonal physiological functions including reproduction and growth (100). Two distinct populations of thyrotropes, with distinct morphology and secretory activity are located in the PT and PD (101–103). Thyrotropin-releasing hormone (TRH) produced by hypothalamic neurons is the main regulator of PD TSH synthesis (104). By contrast, TRH has no effect on PT thyrotrope activity (105), which is controlled by other signals including melatonin, as discussed in section 3 below on direct effects of melatonin.

### **Teleosts**

In teleosts, endocrine pituitary cells are also mainly controlled by brain signaling centers in the preoptic and hypothalamic areas (41), which are characterized by the presence of numerous melatonin binding sites (106–108). The effects of melatonin on

these brain centers, and thus indirectly on pituitary activity, have been studied mainly in the context of reproduction in teleosts, such as in the salmon (109) and eel (110) where melatonin has been shown to play an important role in puberty. Therefore, the available knowledge and thus the discussion in the present review, only concern gonadotropes (Figure 4, Table 2).

## Gonadotropes

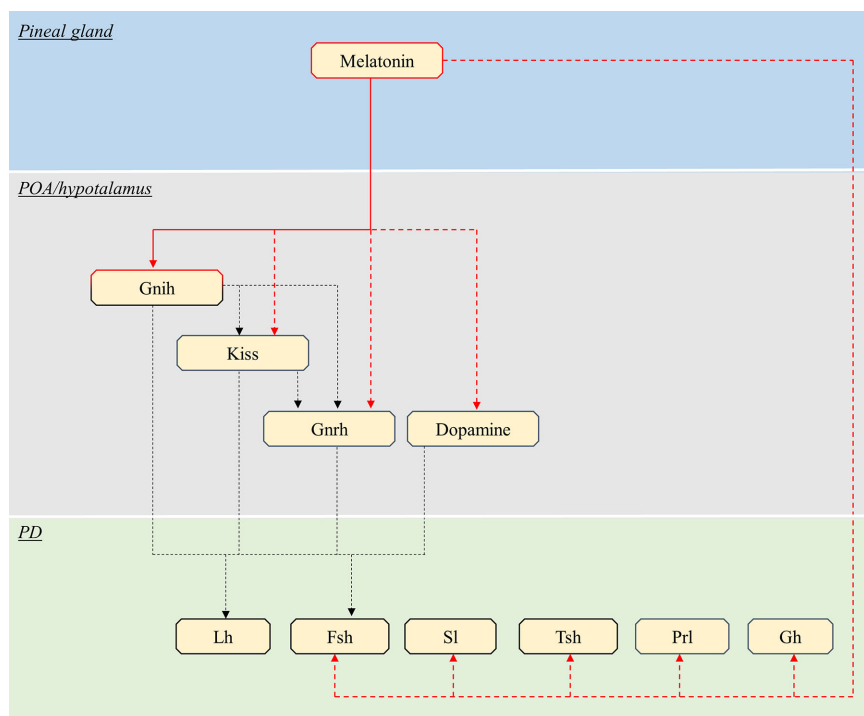
In contrast to mammals, the teleost gonadotropes mainly produce Lh and Fsh in distinct cells, with only a small portion of gonadotropes producing both hormones in some species (43). However, like in mammals, pituitary gonadotropin synthesis and release are regulated by POA/hypothalamic signaling centers, including GnRH, GnIH, Kiss, and dopamine neurons (41, 123, 124).

## Gnrh

Fish possess up to three genes encoding GnRH (*gnrh1*, *gnrh2*, *gnrh3*) (16, 41). In some teleost species, melatonin stimulates gonadotropin production by upregulating GnRH expression. For instance, in adult female zebrafish (*Danio rerio*), melatonin exposure *via* immersion increases the mRNA levels of brain *gnrh3* and pituitary *lhb* (111). In a second study on adult zebrafish females, brain *gnrh3* mRNA levels were increased in both constant light (LL) and constant darkness (DD) as compared to normal light-dark cycles (117). The

inconsistent responses of *gnrh* highlight the importance of the experimental conditions, and suggest the presence of different regulatory mechanisms activated by melatonin exposure and photoperiod manipulation, as mentioned in the introduction.

In other teleost species, melatonin inhibits gonadotropin production by downregulating GnRH expression. In Nile tilapia (*Oreochromis niloticus*), whose development and reproduction are suppressed under SP (125, 126), intraperitoneal melatonin injections simultaneously reduce *gnrh1* mRNA in the brain and both *lhb* and *fshb* mRNA in the pituitary (112). Several studies were performed in male sea bass (*Dicentrarchus labrax*). Both intraperitoneal melatonin injections (114) and melatonin implants (115) downregulate brain mRNA levels of the two hypophysiotropic forms of GnRH, *gnrh1* and *gnrh3*. Remarkably, these genes show natural daily variations in mRNA levels, with lower levels during the mid-dark phase, when plasma melatonin is highest (114). Melatonin implants also decrease pituitary mRNA levels of GnRH receptors (named *gnrhr2ba1* and *gnrhr1cb*, according to recent phylogeny, (68) but named *gnrhr-II-1a* and *gnrhr-II-2b*, respectively, in the study), as well as *fshb* (115). Interestingly, pituitary GnRH1 protein content shows daily variation with minimum levels during night time, under both natural photoperiod and LP (127). While downregulating the GnRH system, melatonin implants also reduce plasma gonadotropins (Lh and Fsh) and androgens (testosterone, T and 11-keto-testosterone,



**FIGURE 4** | Schematic view of the putative pathways through which melatonin influence pituitary endocrine activity in teleosts. Red continuous lines indicate cell types directly targeted from melatonin. Dashed red lines indicate cells influenced by melatonin *via* yet unidentified interneurons, paracrine signals or Mtnr. Note that melatonin might act only on a few of the illustrated pathway, in different species (see text). Black dashed lines indicate all other interactions between brain and pituitary. POA, *preoptic area*; PD, *pars distalis*; Kiss, kisspeptin; GnRH, gonadotropin-releasing hormone; Lh, luteinizing hormone; Fsh, follicle-stimulating hormone; SI, somatolactin; Tsh, thyroid-stimulating hormone; PRL, prolactin; GH, growth hormone.

**TABLE 2 |** Summary of the known effects of melatonin POA/hypothalamic neurons controlling pituitary hormonal production in teleosts.

Target	Effect of melatonin	Species	Spawning season/ Photoperiod	Description	Reference
<b>Teleosts</b>					
Gnrh	Stimulates	Zebrafish	Spring/LP (Daily in captivity)	Melatonin exposure <i>via</i> water upregulates brain <i>gnrh3</i> expression (adult females)	Camevali et al. (111)
	Inhibits	Nile tilapia	Spring/LP	Melatonin injections downregulate brain <i>gnrh1</i> expression	Kim et al. (112)
		Masu salmon Sea bass	Autumn/SP Spring/LP	Oral melatonin administration (50 µg/g feed) decreases Gnrh release Melatonin injections downregulate brain <i>gnrh1</i> and <i>gnrh3</i> expression	Amano et al. (113) Servili et al. (114)
Gnih	None	European eel	Spring/LP	Melatonin implants downregulate brain <i>gnrh1</i> and <i>gnrh3</i> and <i>gnrh-11a -2b</i>	Alvarado et al. (115)
	Stimulates	Nile tilapia	Spring/LP	Melatonin implants have no effects on <i>gnrh</i> expression	Sébert et al. (116)
	Inhibits	Zebrafish	Spring/LP (Daily in captivity)	Melatonin injections upregulate brain <i>gnih</i> expression Melatonin downregulates <i>gnih</i> expression in cultured hypothalamus	Kim et al. (112) Yumnancha et al. (117)
Kiss	Stimulates	Zebrafish	Spring/LP (Daily in captivity)	Melatonin exposure <i>via</i> water upregulates brain <i>kiss1</i> and <i>kiss2</i> expression (adult females)	Camevali et al. (111)
	Inhibits	Sea bass	Spring/LP	Melatonin implants downregulate brain <i>kiss1</i> and <i>kiss2</i> expression	Alvarado et al. (115)
Dopamine		Inhibits	European eel	Spring/LP	Melatonin implants stimulate brain tyrosine hydroxylase activity
	Carp		Spring/LP	Melatonin inhibits dopamine release in cultured hypothalamus Melatonin injections inhibit brain dopamine release	Popek (118) Popek et al. (119)
	Asian catfish	Spring/LP	Melatonin inhibits hypothalamic tyrosine hydroxylase activity during preovulatory phase in female A higher dose of melatonin has no effect on tyrosine hydroxylase activity	Chaube and Joy (120) Senthilkumaran and Joy (121)	
	Rainbow trout	Autumn/SP	Melatonin decreases hypothalamic-pituitary dopamine turnover	Hernández-Rauda et al. (122)	

11KT) levels, thus impairing sexual maturation (115). Servili and collaborators (128) show that in sea bass, the non-hypophysiotropic Gnrh2 neurons send their projections to the pineal gland, and directly stimulate melatonin secretion. Taken together, these results suggest that melatonin in male sea bass, downregulates the production of the hypophysiotropic Gnrh forms (Gnrh1 and Gnrh3) and their release in the pituitary. This, combined with the reduction of Gnrh receptors in the pituitary, result in gonadotropin downregulation. The use of different concentrations of exogenous melatonin can modulate its effects on Gnrh and gonadotropin content. For example, in underyearling masu salmon (*Oncorhynchus masou*), oral administration of melatonin (50 µg/g feed) under LP increases Fsh and T plasma content but has no effect on Lh (129), suggesting that mimicking SP by melatonin administration stimulates testicular development. However, a 10-fold higher dose (500 µg/g feed) decreases pituitary Gnrh and Lh content together with plasma T levels (113). In contrast, the Gnrh system does not respond to melatonin in some teleost species such as European eel (*Anguilla anguilla*) where melatonin implants had no effects on brain *gnrh1* and *gnrh2* mRNA levels (116).

The specific pathways through which melatonin affects Gnrh are largely unknown. In sea bass, the effects of melatonin on Gnrh neuron activity are most likely mediated *via* interneurons (114), since the distribution of melatonin receptors does not match the distribution of *gnrh1* and *gnrh3* cells (106). In masu salmon, melatonin binding sites were localized in the POA (113), however no colocalization study was performed to investigate their presence in Gnrh neurons.

### Gnih

Melatonin modulates the activity of Gnih neurons by stimulating or inhibiting Gnih expression in different species. In adult zebrafish females, exogenous melatonin treatment reduces *gnih* mRNA levels in cultured whole brain, while DD decreases *in vivo* brain *gnih* and increases both *lhb* and *fshb* mRNA in the pituitary (117). In contrast, in Nile tilapia (mixed sex), brain *gnih* mRNA levels increase during the night, in parallel with plasma melatonin levels in mature fish (130). Additionally, intraperitoneal melatonin injections increase *gnih* and *mtnr1c* mRNA in the brain and simultaneously decrease *lhb* and *fshb* mRNA in the pituitary.

Kim and colleagues (130) suggest that, like in birds, melatonin might act on Gnih neuron activity *via* Mtnr1c (131). Indeed, in the cinnamon clownfish (*Amphiprion melanopus*), Gnih neurons express Mtnr1c (named from the authors MT-R1) (132). However, whether this is a species-specific case, or a general condition for all teleosts, remains to be investigated.

### Kiss

In teleosts, contrary to in mammals, Kiss neurons directly regulate pituitary endocrine cells rather than acting through Gnrh neurons (133). Teleosts possess two genes encoding kisspeptins (*kiss1*, *kiss2*) (16, 134). Melatonin is also involved in the control of *kiss* expression in teleosts. In adult female zebrafish, melatonin exposure *via* immersion increases mRNA transcript levels of both *kiss1* and *kiss2* in the brain, and *lhb* in the pituitary (111). While *kiss1* does not respond to photoperiod manipulations, *kiss2* mRNA is induced under LL when melatonin plasma levels are at their minimum



(117). In contrast to in zebrafish, prolonged exposure to melatonin *via* implants decreases brain mRNA levels of *kiss1* and *kiss2* in male sea bass (115). The heterogeneity of *kiss* response, as seen for *gnrh*, highlight the influence of experimental conditions and suggest the possible involvement of different pathways influenced by the hormonal and nervous photoperiodic signal.

It is not known whether melatonin acts directly on kiss neurons or operates *via* interneurons in teleosts. In sea bass, Kiss1 and Kiss2 immunoreactive neurons were identified in the lateral tuberal nucleus and parvocellular nucleus, respectively (135), two locations that also express melatonin receptors (106). However, a clear colocalization of the melatonin receptors in Kiss neurons has not been demonstrated.

### Dopamine

In several teleost species, dopaminergic neurons from the POA exert a strong negative control on gonadotropes, especially Lh-producing cells (82). Melatonin, in turn, influences the activity of hypophysiotropic dopaminergic neurons. In European eel melatonin implants stimulate the dopaminergic system in the POA, increasing tyrosine hydroxylase activity, the rate-limiting enzyme of dopamine synthesis (116). As a consequence, this treatment downregulates both *lhb* and *fshb* mRNA levels. In contrast to the eel, melatonin inhibits the dopaminergic system in other fish species. For instance, in mature female carp (*Cyprinus carpio*), melatonin decreases dopamine release, both in *in vitro* cultured hypothalamus (118) and *in vivo* by direct injection into the third cerebral ventricle (119). The *in vivo* inhibition of dopamine release was registered during the spawning period in summer, but not during sexual regression in winter, suggesting that the effect of melatonin on the dopaminergic system might depend of the maturation stage. Inhibiting effects of melatonin on the dopaminergic systems were also observed in other species, including the threespot wrasse (*Halichoeres trimaculatus*), where intraperitoneal melatonin injections downregulate brain dopamine content (136), and rainbow trout (*Oncorhynchus mykiss*), where melatonin decreases the hypothalamic-pituitary dopamine turnover (122). In preovulatory female catfish (*Heteropneustes fossilis*), melatonin injections for three days inhibit tyrosine hydroxylase enzymatic activity in the hypothalamus (120). However, in a previous study using the same species, reproductive phase and melatonin injection dose, but administrated over a longer period (20 days), failed to affect hypothalamic dopamine turnover (121). This indicates that the length of the treatment with melatonin might affect the response of the dopaminergic system.

Melatonin binding and *mtnr* mRNA distribution studies in rainbow trout (108) indicate that it is very unlikely that Mtnr is present on hypophysiotropic dopaminergic neurons. Therefore, the effects of melatonin might be mediated by interneurons in this species. Studies in Atlantic salmon (137) goldfish (*Carassius auratus*) (138) and Japanese catfish (*Silurus asotus*) (139), identify melatonin binding sites in the POA, where hypophysiotropic dopaminergic neurones are located (82); however, a clear colocalization has not been demonstrated.

### Summary

Melatonin affects pituitary hormonal production in both mammals and teleosts by regulating upstream brain factors. As

gonadotropes play a crucial role in the control of reproduction, which often depends on environmental conditions, it is not surprising that especially their response to indirect melatonin signaling has been studied extensively.

In mammals, melatonin modulates gonadotropin expression by acting on POA/hypothalamic signaling centers. It downregulates KISS and GnRH production and stimulate dopaminergic activity in summer breeders, while it upregulates KISS and GnRH production and inhibits dopaminergic activity in winter breeders. Interestingly, melatonin reduces GnIH neuronal activity in both summer and winter breeders, indicating downstream differences in the signaling cascade.

In teleost fish, melatonin affects these brain signaling hubs in a more complex manner, both inhibiting and activating the gonadotrope axis, depending on the species. In some species, melatonin activates the gonadotrope axis by simultaneously stimulating the production of GnRH and Kiss, while inhibiting GnIH; in others, melatonin exerts a negative action on reproduction. Melatonin may downregulate dopamine production resulting in increased gonadotropin synthesis, or it can stimulate the dopaminergic system and inhibit gonadotropin production. Nevertheless, in both teleosts and mammals, a clear picture of the cell types directly targeted by melatonin in the brain is still scarce. In light of such opposing forces, it is urgent to identify the specific cell types targeted by melatonin in both mammals and teleosts, by determining which ones express MTNR. This is a requirement before being able to fully elucidate the mechanisms involved in the integration of environmental signals in the brain neuroendocrine centers.

## DIRECT EFFECTS OF MELATONIN ON THE ANTERIOR PITUITARY

### Mammals

In addition to the effects mediated by the brain, melatonin can act directly on the pituitary gland in mammals (Figure 3, Table 3).

### Melatonin Receptors in Mammalian Pituitary

The main target for melatonin within the mammalian pituitary is the PT, as indicated by the important presence of melatonin binding sites in all mammalian species investigated so far. Those include, for instance, Siberian hamster (154, 155); Syrian hamster, (154–156); rat, (154, 155, 157, 158); red deer (*Cervus elaphus*) (159); ferret (*Mustela putorius furo*) (160), rhesus monkeys (*Macaca mulatta*) (161) and human (89). MTNR1A (MT1) is the main form of melatonin receptor present in the PT. *Mtnr1a* mRNA was detected by *in situ* hybridization in the PT of sheep, Siberian hamster and rat (154) and in primary PT cell cultures of sheep (162). MTNR1A has also been detected in human PT, *via* immunostaining (89). Identification of the specific cell types expressing melatonin receptors is a key requisite to discriminate the direct effects mediated by melatonin. Double labelling combining *in situ* hybridization and immunohistochemistry shows that *Mtnr1a* is expressed in most, but not all, thyrotrope cells within the PT, while it is absent from the other endocrine cells types in the anterior

**TABLE 3** | Summary of the known effects of melatonin on pituitary *in vitro* and *ex vivo* cultures in mammals.

Species	Type of preparation	Effects of melatonin	Reference
<b>Mammals</b>			
Sheep	PT cell culture	Acute: inhibits forskolin-induced secretion of tuberalin	Morgan et al. (140)
	PT cell culture	Acute: inhibits forskolin-induced cAMP	Hazlerigg et al. (141)
	PT cell culture	Prolonged: increase basal and forskolin-induced cAMP	Hazlerigg et al. (141)
	PT cell culture	Reduces <i>Mtnr1a</i> mRNA	Barret et al. (142)
	PT explants	Reduces <i>Mtnr1a</i> mRNA	Fustin et al. (143)
Rat (neonatal)	PT explants and cell culture	Reduces <i>Egr1</i> expression	Fustin et al. (143)
	PD organ cultures	Inhibits LH and FSH release	Martin and Klein (144)
	PD cell culture	Inhibits GnRH-induced Ca <sup>2+</sup> signal and LH secretion	Martin and Sattler (145)
	PD cell culture	Inhibits GnRH-induced cFOS	Vaněček and Klein (146)
	Organ cultures	No effect on TRH-induced TSH/PRL or SRIF-induced inhibition of GH	Sumova et al. (147)
Rat (maturing)	PD cell culture	No effect on GnRH-response	Martin and Klein (144)
Rat (Adult)	TP/ME explants	Inhibits Lh release	Rivest et al. (148)
	GH3/GH4 cell line	Inhibits secretion of PRL and GH (no effect on cAMP)	Nakazawa et al. (149)
	GH3 cell line	Inhibits basal and forskolin-induced PRL secretion and expression	Griffiths et al. (150)
Baboon	PD cell culture	No effect on LH or FSH secretion	Ogura-Ochi et al. (151)
Baboon	PD cell culture	Stimulates GH and PRL expression and release	Ibáñez-Costa et al. (152)
	PD cell culture	Increases expression of receptors for GhRH and ghrelin, decreases receptors for somatostatin	Ibáñez-Costa et al. (152)
	PD cell culture	No effect on ACTH or TSH	Ibáñez-Costa et al. (152)
Mouse	AT120 cell line	Inhibits cAMP and ACTH release	Tsukamoto et al. (153)

pituitary in European hamster (*Cricetus cricetus*) (163) and rat (157). This suggests that thyrotropes of the PT are the main pituitary target of melatonin action in mammalian species.

Interestingly, the expression of *Mtnr* within the PT varies across the year, in response to different neuroendocrine factors (34), modulating the endocrine response to melatonin between the different seasons. For instance, *Mtnr* expression increases during the reproductive season, peaking under LP in summer breeders or SP in winter breeders. Simulating winter season in the summer breeder Syrian hamster, using artificial SP (164) or melatonin injections (156, 165) induces a marked decrease in MTNR density in the PT of Syrian hamster. Melatonin injections decrease MTNR1A density in both Syrian and Siberian hamster PT (156). Similar effects of SP were shown in European hamster (163, 166) and hedgehog, *Erinaceus europaeus* (167). On the contrary, in winter breeders such as the mink (*Mustela vison*), the density of melatonin binding sites in the PT plummets in July and peaked in October, in concomitance with reactivation of sexual activity (168).

Melatonin and the pituitary also regulate daily physiological rhythms. As a consequence, variations in the presence of MTNR within the PT are not limited to annual cycles, but also occur within the span of a single day. *Mtnr1a* mRNA levels vary during the day in the PT of Siberian and Syrian hamster, peaking during daytime and decreasing at night (156).

Finally, in the PD of foetal rat, *Mtnr1a* mRNA was also identified by *in situ* hybridization before activation of the GnRH system, but not in postnatal stages (169). Bae and colleagues (170) demonstrate that *Mtnr1a* transcripts are present in the mice  $\alpha$ T3-1 gonadotrope cell line, but their expression is downregulated after exposure to GnRH. The activation of the GnRH system in postnatal stages might therefore be responsible for the lack of MTNR in the adult PD reported in rat. Melatonin binding sites were also detected in the PD of adult sheep (171,

172), red deer (159) and ferret (160). A weak staining of *MTNR1A* was detected in human PD by *in situ* hybridization (89). To date, the identity of the cellular targets of melatonin within the PD and their contribution to the hormonal regulation of the gland remain largely unknown.

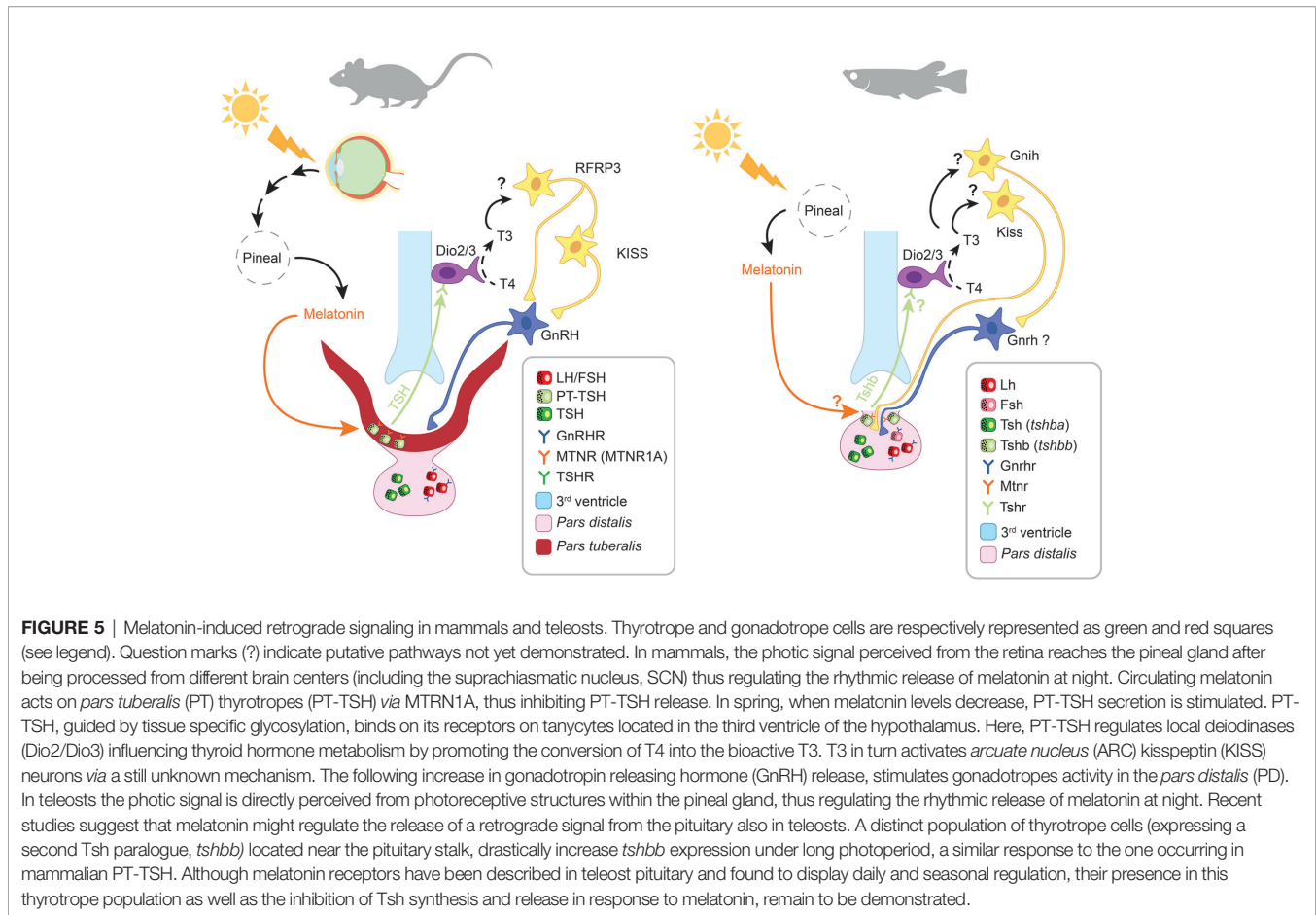
### Effects of Melatonin on the *Pars Tuberalis*

As mentioned above, melatonin pituitary binding primarily takes place in the PT. Through these cells, melatonin seems to regulate the PD activity *via* at least two different routes, a retrograde route from the PT to the brain (Figure 5) and an anterograde route from the PT to the PD, as discussed below.

#### Retrograde Route

Studies in rodents demonstrate the inhibitory effects of melatonin on PT-TSH synthesis (173) *via* MTNR1A (174). During the long days in spring/summer, PT-TSH rises independently from TRH stimulation (175) due to reduced circulating melatonin levels. In the retrograde route (Figure 5), the expression of PT-TSH is rapidly induced, after LP exposure, by the transcription factor EYA3, which works with the circadian transcription factor thyrotroph embryonic factor (TEF) (176, 177). Melatonin acutely inhibits *Eya3* expression, but at the same time induces a peak of *Eya3* 12 h later. This leads to a strong morning peak of *Eya3* (and subsequently TSH) during long days. Although several other collaborating transcription factors are involved in the precise circannual regulation of TSH secretion from PT, EYA3 seems to be the one regulated by photoperiod *via* melatonin.

PT-TSH then reaches the brain where it binds to its receptors in tanycytes, specialized ependymal cells within the mediobasal hypothalamus, thus regulating the enzymatic activity of local deiodinases (Dio2-Dio3) (173, 178). This controls local thyroid hormone (TH) metabolism by converting thyroxine (T4) to the bioactive triiodothyroxine (T3), serving as key regulator of



seasonality (173). Ikegami and collaborators (175) demonstrate that specific post-translational glycosylations allow PT-TSH to exclusively target the hypothalamus, and not the thyroid. While the cellular and molecular targets remain to be clearly identified, recent findings indicate that the increase of T3 in the mediobasal hypothalamus acts on KISS1 and RFRP3 neurons, which in turn modulate GnRH secretion (78). The molecular pathway from melatonin to T3 production appears to be conserved in mammalian species regardless of their reproductive strategy as summer or winter breeders (67, 179). Therefore, species-specific differences might occur downstream of this common pathway.

### Anterograde Route

In the anterograde route, melatonin regulates PRL synthesis and secretion in the PD by inhibiting the release from the PT of one or more PRL-releasing factors named “tuberalin” (67). To date, the PT-specific factor(s) are still undetermined, as more than 30 different factors are known to stimulate PRL secretion (92). Several candidates have been proposed including tachykinin-1 and neurokinin A in sheep (180) or endocannabinoids in hamster (179, 181). Notably, these factors might act through folliculo-stellate cells to regulate lactotropes (182).

Tuberalin secretion can indeed be stimulated in ovine PT cell cultures by forskolin (140), an activator of adenylyl cyclase (AC),

the enzyme catalysing the conversion of ATP to cyclic AMP (cAMP). The forskolin-induced secretion of tuberalin from PT cells was assessed by adding medium from the PT culture to a PD culture and measuring the amount of PRL secreted in response. Melatonin acutely inhibited the forskolin-induced secretion of tuberalin but had no effect alone. In support, melatonin inhibited the forskolin-induced cAMP production in ovine PT cells (141). Furthermore, melatonin downregulated the expression of its own receptor in PT cells from rat (183) and sheep (142). In ovine PT cells, the downregulation of *Mtnr* expression involves the cAMP signaling pathway (143). Together, these results imply that melatonin works through the MTNR/Gi/cAMP pathway to inhibit tuberalin secretion and subsequently regulating PRL production in the PD. Interestingly, incubation with melatonin for 16 h sensitizes AC, increasing both basal and forskolin-induced cAMP production (141). After the prolonged melatonin exposure, acute application of melatonin still inhibits the forskolin-induced cAMP increase.

For melatonin to inhibit secretion of tuberalin, there must be a stimulating factor that melatonin can oppose. This “tuberalin releasing factor” has not been identified but was named StimX by Morgan and Williams (184). Dardente and colleagues (67) proposed dopamine as a promising candidate for StimX, arguing that it might act through the dopamine receptor D1 expressed in PT

cells, whose activation increases the intracellular cAMP level in neurons.

Downstream of cAMP, melatonin up-regulates or down-regulates the expression of a range of genes (67). Several of them are clock genes, including Period1 (*Per1*) and Cryptochrome-1 (*Cry1*) (185). This implies that PT cell activity might be regulated by an internal clock and that the clock itself may be modulated by melatonin. Interestingly, the same clock genes are not affected by melatonin in the suprachiasmatic nucleus (SCN) of the hypothalamus, indicating that the SCN clock is working more independently than peripheral clocks (186–188). In ovine PT cell cultures and explants, the expression of the immediate early gene *Egr1* is acutely suppressed by melatonin, which otherwise follows a daily rhythm (143). EGR1 in turn regulates several genes, some being upregulated, such as *Cry1*, others downregulated such as *Mtnr1a*. In contrast to *Mtnr1a*, the expression of *Cry1* was not affected by changes in cAMP levels.

Other PT endocrine cells beside thyrotropes might also be regulated by melatonin. Nakazawa and collaborators (149) found that melatonin inhibits LH release from male rat tissue explants (consisting of PT and median eminence) in a dose-dependent manner. This in turn increases the release of GnRH from the median eminence part of the explant.

## Effects of Melatonin on the *pars distalis*

### Gonadotropes

In rodents, the effects on PD gonadotropes seem highly age-specific, with clear inhibitory effects in neonatal animals and no effects in adults. Melatonin (1–10 nM) reduces the GnRH-induced LH and FSH release in pituitary organ cultures from neonatal rats (144, 145). Furthermore, Vanecek and Klein (146) demonstrate that melatonin (10 nM) reduces the GnRH-induced  $Ca^{2+}$  signal and subsequently LH secretion. Similarly, Pelisek and Vanecek (189) demonstrated that melatonin (2 nM) reduces GnRH-induced LH release, as well as the forskolin-induced cAMP production, in cell cultures from neonatal rats. Melatonin (1 nM) directly inhibits GnRH-induced  $Ca^{2+}$  signaling in neonatal gonadotropes, both *via* plasma membrane  $Ca^{2+}$  channels and endoplasmic reticulum  $Ca^{2+}$  release channels (190). The inhibitory effect of melatonin on the GnRH-induced  $Ca^{2+}$  oscillations might not be uniform over the gonadotrope cell population as the responses differ between cells, indicating a complex regulatory pathway (191, 192). The role of MTNR in neonatal PD may not be limited to gonadotrope regulation. In light of the previously described role of melatonin on the regulation of clock genes, Johnston and colleagues (169) suggest that *Mtnr1a* expression may reflect a developmental requirement for circadian synchronization between tissues before mature regulatory pathways become established. Additionally, the promoter region of rat *Mtnr1a* contains response elements for transcription factors involved in pituitary cell differentiation and regulation (169). Melatonin might therefore be involved in the correct development of the embryonic PD. Indeed, melatonin (100 nM) inhibits GnRH-induced increase of *cFos* (a proto-oncogene involved in cellular proliferation and differentiation) immunoreactivity in neonatal rat pituitary PD culture (147).

During development and maturation, melatonin binding is reduced, and in adults, melatonin does not have the same direct

effect on the pituitary. Rivest and collaborators (148) found that melatonin incubation (5 nM) of pituitary cell cultures from sexually maturing rats does not modify the GnRH response. Likewise, Ibáñez-Costa and colleagues (152) found no effect of melatonin (pM to  $\mu$ M range) on the FSH and LH secretion in primary pituitary cultures from adult female baboons.

### Other Endocrine Cells in the *pars distalis*

Regarding the effects of melatonin on other PD endocrine cells, the results are even scarcer. Melatonin ( $10^{-8}$  to  $10^{-6}$  M) reduces the production and secretion of both PRL and GH from the rat pituitary cell line GH4C1, but has no effect on basal or stimulated cAMP levels (150). Similarly, Ogura-Ochi and collaborators (151) show that melatonin suppresses both basal and forskolin-induced PRL secretion and mRNA abundance in the closely related GH3 cell line. In contrast, in primary pituitary cell cultures from adult female baboons, melatonin increases GH and PRL expression and release in a dose-dependent manner, an effect blocked by somatostatin (152). Both the common (AC/PKA/Ca-channels) and distinct (PLC/Ca-release) pathways seem to be involved. Melatonin (10 nM) also affects the expression of GHRH receptors, ghrelin and somatostatin, but not expression or release of ACTH or TSH. Also in pituitary organ cultures from neonatal rats, melatonin has no effect on TRH-induced TSH/PRL release or somatostatin-induced inhibition of GH release (144, 145). In the mice corticotrope cell line AtT20, melatonin reduces the levels of ACTH, alongside a reduction in cAMP (153).

## Teleosts

As in mammals, melatonin can also act directly on the pituitary gland in teleosts (Figure 4, Table 4).

### Melatonin Receptors in Teleosts Pituitary

Multiple *Mtnr* paralogues are expressed in the pituitary of teleosts (28). For instance, qPCR analysis detected the mRNA of four *Mtnr* paralogues in the pituitary of medaka (27). Three were described in Senegalese sole (*Solea senegalensis*) (200), goldfish (201), and Atlantic salmon (25). Two were detected in chum salmon (*Oncorhynchus keta*) (202) and pike (*Esox lucius*) (196). One was detected in European sea bass (203), suggesting possible multiple effects of melatonin which might also vary between species.

The exact location of melatonin receptor/binding sites in teleosts is not clear. Despite the aforementioned identification of *mtnr* mRNA in goldfish pituitary, Martinoli and colleagues (107) observe no specific binding of melatonin. On the other hand, rainbow trout (197) and pike (196) pituitaries have 2-[ $^{125}$ I]iodo-melatonin binding sites. However, the assay used was aimed at characterizing the binding capacity rather than their localization within the pituitary, although a regional distribution was reported, with binding sites clustering together in close proximity.

Like in mammals, the abundance of pituitary *Mtnr* in teleosts varies with the season and the day, suggesting a correlation with physiological state. The Senegalese sole (200) shows seasonal fluctuations with higher *mtnr* mRNA levels during the summer spawning period. While a first study in Atlantic salmon carried out in autumn indicated the absence of melatonin binding sites

**TABLE 4** | Summary of the known effects of melatonin on pituitary *in vitro* and *ex vivo* cultures in teleosts.

Species	Type of preparation	Effects of melatonin	Reference
<b>Teleosts</b>			
Goldfish	Primary cell culture	No effect on AC activity	Deery et al. (193)
	Perfused fragments	No effect on secretion of Lh, Fsh or Gh.	Somoza and Peter (194)
European eel	Primary cell culture	No effect on <i>fshb</i> and <i>lhb</i> mRNA levels	Sébert et al. (116)
Atlantic croaker	Perfused fragments	Stimulates Lh (GthII) secretion	Khan and Thomas (195)
Pike	Whole pituitary	Inhibits forskolin-induced cAMP	Gaildrat and Falcón (196)
Rainbow trout	Primary cell culture	Low dose: inhibits forskolin-induced cAMP and Gh secretion	Falcón et al. (197)
	Primary cell culture	High dose: stimulates Gh secretion	Falcón et al. (197)
	Primary cell culture	High dose: inhibits Prl secretion	Falcón et al. (197)
European sea bass	Primary cell culture	Increases <i>Cry1</i> and <i>Cry2</i> mRNA levels	Herrero and Lepesant (198)
Medaka	Whole pituitary organ culture	Reduces <i>fshb</i> , <i>tshb</i> and <i>sl</i> mRNA levels (not <i>lhb</i> , <i>gh</i> , <i>prl</i> or <i>pomc</i> )	Kawabata-Sakata et al. (199)

(137), a later study shows that *Mtnr* exhibits both seasonal and daily fluctuations in the male parr pituitary (25). In spring during sexual maturation, pituitary *mtnr* mRNA peaks during the day and drops at night, while in autumn minimal levels are constantly maintained throughout the day. In medaka, where SP inhibits reproduction, pituitary *mtnr1a*, *mtnr1c*, and *mtnr1d*, but not *mtnr1b* mRNA levels show daily fluctuations with higher levels at night under LP but not SP (27). The presence of multiple *Mtnr* paralogues whose concentrations vary across the season indicates a complex role of melatonin in teleost pituitary physiology. It is not yet clear precisely which cell types express *mtnr* in teleosts. Indeed, the seasonal and daily variations in *mtnr* mRNA levels observed in sole, sea bass, salmon, and medaka suggest a relation with the reproductive status of the fish. These fluctuations also highlight the importance of both the timing of sampling and the application of different techniques for the successful identification of the cells expressing *Mtnr* within the pituitary.

## Effects of Melatonin in Teleosts Pituitary

### Putative Retrograde Signal

Unlike mammals, teleosts do not possess an anatomically distinct PT. Nakane and Yoshimura (204) propose that, in salmonids, the translation of the photoperiodic signals into pituitary hormonal messages might instead take place in the *saccus vasculosus* (SV), a secretory organ located posterior to the pituitary and directly connected to the third ventricle of the hypothalamus. In masu salmon, specialized cells within the SV, the coronet cells, possess all the components involved in the regulation of seasonal reproduction *via* the Tsh pathway (Tsh $\beta$ , Tsh receptors and Dio2). However, the exact photoperiodic role of the SV (and the involvement of melatonin in it), remains controversial. First, the SV signal pathway is presumably directly activated by photo-transduction through photoreceptive pigments without the requirement of melatonin (205). Additionally a recent study in juvenile Atlantic salmon reported no photoperiodic effects on SV *tshb* and *dio2b* mRNA levels (206). Finally, the SV is not present in all fish [e.g. it is absent in zebrafish (207, 208)]. Therefore, a different mechanism might be involved in the photoperiodic control of seasonality in fish.

Several teleosts possess two *tshb* paralogues resulting from the 3R, *tshba* and *tshbb* (209) (named by the authors *tsh $\beta$*  and *tsh $\beta$ 3*). In Atlantic salmon, both are expressed in the pituitary, but only

*tshbb* is expressed in the SV (210). Interestingly, while pituitary *tshba* mRNA levels are relatively constant, *tshbb* mRNA level vary profoundly, with a peak concomitant with the onset of downstream migration, in spring. Since the two paralogues also show expression at distinct locations in the pituitary, Fleming and colleagues (210) propose that *tshbb*-expressing cells, located near the pituitary stalk, are analogous to the mammalian PT-TSH cells and possibly regulate the retrograde diffusion of Tsh to the hypothalamus (Figure 5).

Irachi and collaborators (206) demonstrate a significant increase in pituitary *tshbb* mRNA levels followed by a rise in *dio2b* mRNA levels in the midbrain/optic tectum and hypothalamus in response to increased daylength, providing additional evidence that the pituitary Tshb (formed by the *tshbb* subunit) is a key contributor to photoperiodic signaling in fish, similar to the mammalian PT-TSH. However, whether like in mammals, melatonin signal is directly integrated by the pituitary Tshb (*tshbb*-expressing) cells in teleosts, is not known.

### Other Endocrine Cells in the Pars Distalis

The direct effects of melatonin on other endocrine cell types have not been extensively investigated in teleosts and the few studies available indicate different effects between species.

In goldfish, melatonin ( $10^{-6}$ – $10^{-3}$  M) has no effect on AC activity in homogenized pituitary samples (193). Although AC is part of the most common signaling pathway triggered by melatonin receptors, this result does not rule out the possibility that melatonin may trigger effects *via* other pathways. The conclusion that melatonin most probably had no direct effect on the pituitary was further supported by a study on perfused goldfish pituitary fragments, from which melatonin did not affect secretion of gonadotropins or Gh (194). Similarly, Sébert and colleagues (116) report from unpublished *in vitro* experiments that melatonin has no effect on *fshb* and *lhb* mRNA levels in primary pituitary cultures from European eel.

However, effects of melatonin have been observed in other species. Melatonin (0.2 ng/ml) stimulates Lh (Gth II) secretion from pituitary fragments from mature Atlantic croaker (195). In trout pituitary organ- and cell cultures, high concentration of melatonin [close to the night-time circulating levels as determined by Gern and colleagues (211)] induces a dose-dependent Gh secretion in the absence of forskolin, along with a decrease in the secretion of Prl (197). In contrast, low melatonin

concentration (close to daytime circulating levels) inhibits the forskolin-induced increase in cAMP levels and Gh secretion. Finally, melatonin exposure ( $10^{-5}$  M) in *ex vivo* whole pituitary organ culture from sexually mature medaka, decreases *fshb*, *tshba* and *sl* mRNA levels but has no significant effects on *lhb*, *gh*, *prl*, and *pomc*, (199).

## Summary

The presence of melatonin receptors indicates that melatonin can directly regulate pituitary cells. According to the receptor localization, the PT thyrotropes are the main targets of melatonin in the mammalian pituitary. A few mammalian species also have melatonin binding sites in the PD, suggesting a possible direct control of melatonin on PD endocrine production. The teleost pituitary also expresses several Mtnr paralogs, however their localization is not clear.

In mammals, most of the direct effects of melatonin on the pituitary take place in the PT, in particular on thyrotropes (**Figure 5**). Here, melatonin acting *via* MTNR1A (MT1) affects the expression levels of a set of clock genes that in turn regulate synthesis and secretion of TSH and the hitherto unidentified tuberalin, for retrograde and anterograde seasonal regulation of gonadotropes and lactotropes in the PD, respectively. The signaling pathway from MTNR1A activation to transcriptional regulation seems to mainly be *via* inhibition of AC/cAMP and possibly CREB. Studies on the direct effects of melatonin in the PD are still scarce, but there is solid evidence that melatonin inhibits LH secretion from PD gonadotropes in neonatal stage, but not in adults.

Fewer studies on the direct effects of melatonin on the teleost pituitary have been performed. They report different effects depending on the species and the experimental conditions. Nevertheless, recent works described a new pituitary Tsh population responding to variation in photoperiod similarly to PT-TSH in mammals, suggesting that a Tsh retrograde signaling might also occur in teleosts. It is therefore crucial that future research investigate the presence of melatonin receptors and the responsiveness to melatonin in this cell type to verify whether, similar to in mammals, melatonin signal is directly integrated by Tshb (*tshbb*-expressing) cells in teleosts.

## DISCUSSION

As shown in the present review, the response of the pituitary to melatonin is highly plastic and differs between seasons, time of the day, physiological status, and reproductive strategies. The comparison between mammals and teleosts reveals a greater knowledge gap in the latter group, leaving many open questions on the role of melatonin in regulating the pituitary hormonal production. In both mammals and teleosts however, the exact pathways and cell types targeted by melatonin are largely unknown. It is therefore crucial to clearly describe the integration of the melatonin signal, and identify the cell types expressing melatonin receptors, in the pituitary as well as in the brain. Multi-color *in situ* hybridization or immuno-labelling and single cell transcriptomic approaches are relevant techniques that can be applied to identify the cell types directly targeted by melatonin.

To validate the effects of melatonin on the different cell types a combination of *in vivo*, *ex vivo* and *in vitro* studies will be necessary, as no single approach can produce a complete and reliable picture by itself. For instance, caution should be taken when investigating dissociated endocrine pituitary cells in culture, as a recent study shows that dissociation leads to a quick cellular phenotypic change in the pituitary cells (212). Additionally, when deciding on animal model and experimental conditions, one should also consider the important biological differences that might influence, or be influenced by, a time-keeping hormone as melatonin, such as nocturnal versus diurnal habits, different reproductive seasons or hibernation periods. Indeed, the response in animals adapted during numerous generations to stable laboratory conditions, such as mice, rats, zebrafish and medaka, might diverge from the ones in the wild.

In addition, given the seasonality of the processes regulated by melatonin, the localization of MTNR appears to be heavily influenced by factors such as physiological status, season, but also time of the day. It is therefore reasonable to assume that the expression of MTNR in some key cell types might be characteristic of specific physiological conditions and might still remain undetected when analyzed outside a particular time window.

Finally, when investigating the effects of melatonin on neuroendocrine system activity, teleosts show a remarkable plasticity as their response is more sensitive to variation in environmental conditions as compared to mammals (1, 213). As a consequence, it is harder to draw a general picture of the role of melatonin on teleosts brain and pituitary, as the choice of the season or the time of the day to perform the experiment appear to influence the response of the pituitary gland in teleosts.

Because of this sheer number of physiological and environmental variables, as well as significant inter-specific variation, unravelling the full impact of melatonin on the pituitary gland remains a challenge.

## AUTHOR CONTRIBUTIONS

EC, TH, and RF contributed to the conception and design of the review. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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