Chapter 9

The pineal and reproduction of teleosts and other fishes

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ABBREVIATIONS

3rd V	third ventricle
11-KT	11-ketotestosterone
17αHP	17α-hydroxyprogesterone
^{125}IMel	2-[^{125}I]-iodomelatonin
AANAT	arylalkylamine *N*-acetyltransferase
AgRP	agouti-related peptide
ASMT	acetylserotonin-*O*-methyltransferase (formerly HIOMT)
AVT	arginine vasotocin
B_{max}	maximal number of binding sites
BPG	brain-pituitary-gonadal axis
Ca^{2+}	calcium
CSF	cerebrospinal fluid
cAMP	cyclic-3′,5′-adenosine monophosphate
cGMP	cyclic-3′,5′-guanosine monophosphate
D	darkness
Dio2	type-2 deiodinase
dpf	days postfertilization
DHP	17α,20β-dihydroxy-4-pregnen-3-one
E_1	estrone
E_2	17β-estradiol
Erα/β	estradiol receptor alpha/beta
FEO	food-entrained oscillators
FMRF	tetrapeptide Phe-Met-Arg-Phe-NH2
FSH	follicle-stimulating hormone
Fshβ	follicle-stimulating hormone (beta subunit)
GC	granulosa cells
GH	growth hormone
GnIH	gonadotropin-inhibitory hormone
GnRH	gonadotropin-releasing hormone
GnRHR	gonadotropin-releasing hormone receptor
GPCR G-	protein-coupled receptors
Gr	glucocorticoid receptor
GSI	gonadosomatic index
h	hour
HIOMT	hydroxyindole-*O*-methyltransferase (now ASMT) gene name or enzyme??
ICC	immunocytochemistry
i.c.v.	intracerebroventricular injection
i.m.	intramuscular injection
i.p.	intraperitoneal injection
ISH	in situ hybridization
k_D	dissociation constant
***K*p**	kisspeptin
L	light
LEO	light-entrained oscillators
LH	Luteinizing hormone
Lhβ	luteinizing hormone (beta subunit)
mRNA-Seq	mRNA sequencing
NPY	neuropeptide Y
PKA	protein kinase A
PGE_2	prostaglandin E2
POMC	proopiomelanocortin
PRL	prolactin
RHT	retinohypothalamic tract
RPE	retinal pigment epithelium
SCN	suprachiasmatic nuclei of the hypothalamus
Sl	somatolactin
T	testosterone
T_3	triiodothyronine
T_4	thyroxine
TH	tyrosine hydroxylase
TpOH	tryptophan hydroxylase
TSH	thyroid-stimulating hormone
Tshβ	thyroid-stimulating hormone (beta subunit)
TRPV	transient-receptor-potential channel vanilloid
VGCC	voltage-gated calcium channels
WGD	whole-genome duplication

Hormones and Reproduction of Vertebrates, Volume 1. https://doi.org/10.1016/B978-0-443-16009-7.00008-6

1 INTRODUCTION

Photoperiod is the most reliable indicator of the cyclic changes of our environment. It is thus no surprise that the timing of periodic events be synchronized by the alternation of the light (L) and dark (D) daily and seasonal fluctuations in most living species. This allows harmonization and anticipation in a flurry of rhythmic biochemical, physiological, and behavioral processes that occur in a single organism. Reproduction is one such precisely timed process. The first indications of photoperiod controlling the seasonal cycle of reproduction in fishes came from early studies in the bridle shiner, *Notropis bifrenatus*; the bitterling, *Rhodeus amarus*; and the European minnow, *Phoxinus laevis* (Bullough, 1941; Harrington Jr., 1957). Since then, numerous investigations using manipulated photoperiod have highlighted the major role this factor plays in fish reproduction (Bromage et al., 2001; Carrillo et al., 1993; de Vlaming & Olcese, 1981; Doyle et al., 2021; Migaud et al., 2010). It is worth mentioning that other factors may interact with photoperiod, particularly temperature and food availability, to control this seasonal cycle (Bushnell et al., 2010; Isorna et al., 2017; Shimizu, 2003; Shimizu et al., 1994; Vasal & Sundararaj, 1976). In the equatorial areas, photoperiod is constant, and synchronization is achieved via, e.g., rainfalls, water salinity, monsoons, feeding, social cues, lunar, or tidal cycles (Abesamis et al., 2015; Bushnell et al., 2010; Claydon et al., 2014; Guerrero et al., 2009; Ikegami et al., 2014; Ohta & Ebisawa, 2015, 2017; Oliveira & Sánchez-Vázquez, 2010).

Photoperiod acts at different timescales from daily to once in a life (Juntti & Fernald, 2016). In seasonal breeders, fish may display one or two spawning windows, with months of preparation preceding, and a phase of arrest following the window (Falcón & Zohar, 2018). Equatorial species tend to spawn throughout the year (Abesamis et al., 2015; Claydon et al., 2014; Oliveira & Sánchez-Vázquez, 2010). Spawning occurs either in the morning (e.g., zebrafish, *Danio rerio*), or afternoon (e.g., seabream, *Sparus aurata*), or (most often) at night (e.g., European sea bass, *Dicentrarchus labrax;* Senegal sole, *Solea senegalensis*) depending on the species (Claydon et al., 2014; Meseguer et al., 2008; Oliveira & Sánchez-Vázquez, 2010; Villamizar, Herlin, et al., 2012; Villamizar, Ribas, et al., 2012; Villamizar et al., 2013) (Fig. 1). These daily fluctuations rely on endogenous mechanisms (i.e., biological clocks) as shown in many species (e.g., *D. rerio,* see Blanco-Vives & Sánchez-Vázquez, 2009; *S. aurata,* see Meseguer et al., 2008). The so-called circadian clocks function autonomously on a 24 ± 4 h basis (*circa* = approximately; *dian* = day) and need to receive input from photoreceptors to synchronize their activity to the 24-h LD cycle. In turn, the clocks produce rhythmic output signals that inform the rest of the organisms on the environmental fluctuations. The photoreceptors (input), the endogenous oscillators (clocks), and the units that produce the overt rhythm (output) constitute the circadian system. Although less investigated, circannual clocks seem also to be at work along the seasonal cycle of reproduction as suggested from studies in the European minnow (Bullough, 1941); Asian stinging catfish, *Heteropneustes fossilis* (Vasal & Sundararaj, 1976); Atlantic salmon, *Salmo salar* (Duston & Bromage, 1986); rainbow trout *Oncorhynchus mykiss* (Randall et al., 1998); European sea bass (Prat et al., 1999); and mummichog, *Fundulus heteroclitus* (Shimizu, 2003) (Fig. 2). It is suspected that the circadian and circannual clocks cooperate in the timing and entrainment of the reproductive cycle in *S. salar* (Duston & Bromage, 1986). In brief, photoperiod, acting through the circadian and circannual systems, appears as a main synchronizer of internal biological clocks to determine at which time of the day and year spawning occurs (Blanco-Vives & Sánchez-Vázquez, 2009; Carrillo et al., 2009; Claydon et al., 2014; Falcón et al., 2010; Falcón & Zohar, 2018; Oliveira & Sánchez-Vázquez, 2010). It is therefore not surprising that in a process that requires such precise

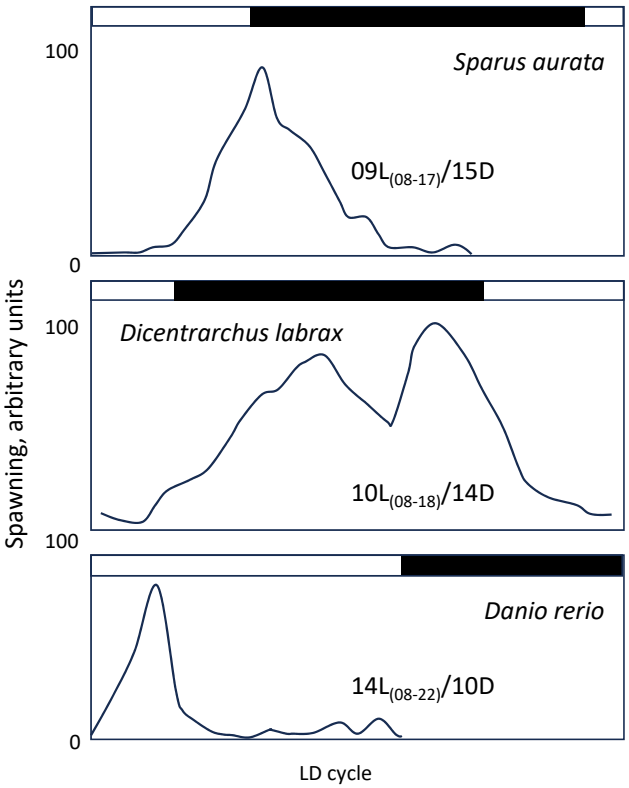

FIG. 1 Daily spawning rhythm. Spawning occurs at dusk in the Mediterranean seabream (*Sparus aurata*), at night in the European sea bass (*Dicentrarchus labrax*) and at dawn in the zebrafish (*Danio rerio*). The survival rates often follow the same pattern (see Blanco-Vives & Sánchez-Vázquez, 2009; Meseguer et al., 2008; Villamizar, Herlin, et al., 2012, for details). *(Modified and adapted from these same authors.)*

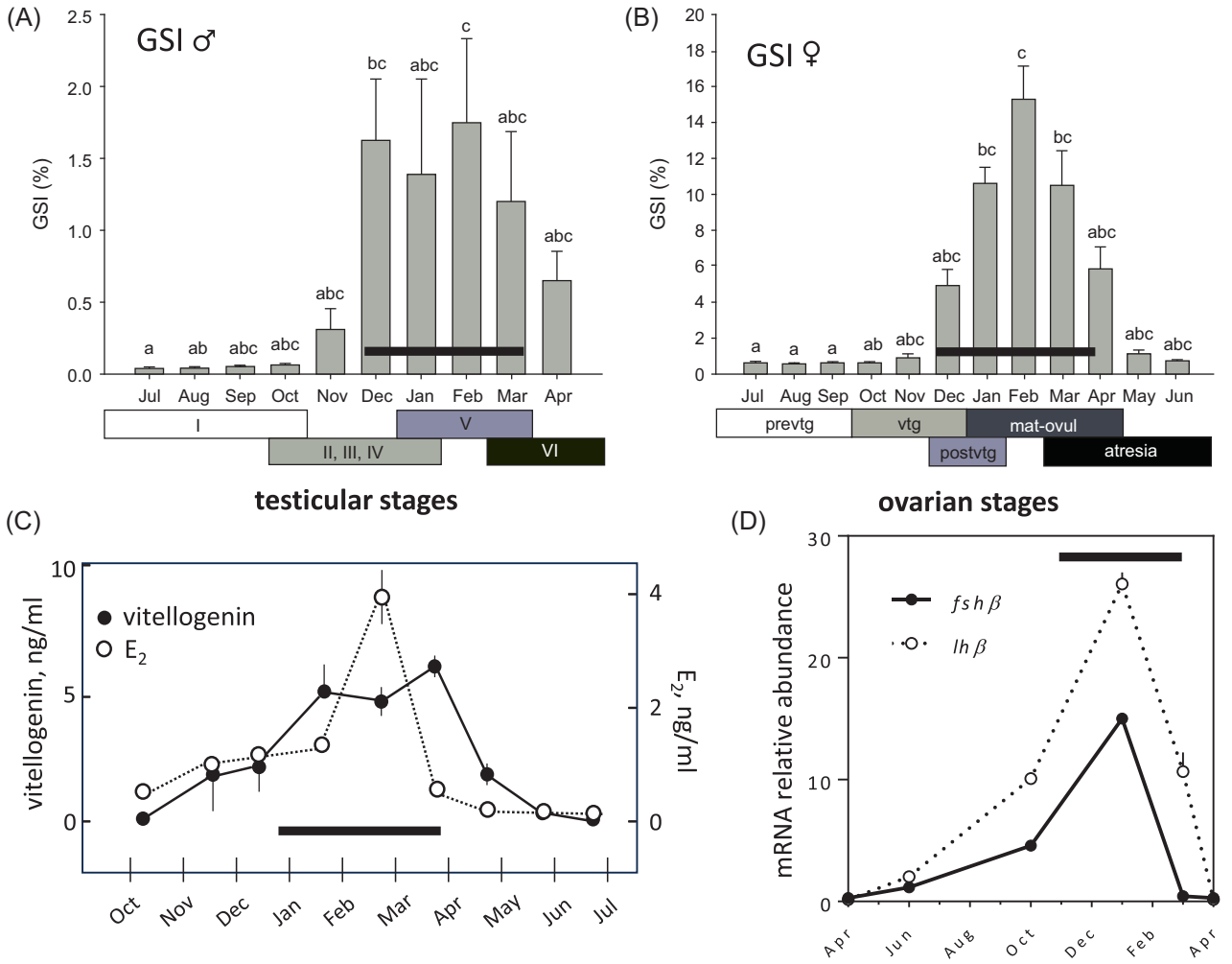

FIG. 2 Annual rhythm of reproduction in the European sea bass, *Dicentrarchus labrax*. The graph displays the seasonal variations of the gonadosomatic index (GSI) in males and females (A and B), plasma vitellogenin and 17β-estradiol (E_2) (C), and pituitary *fshβ* and *lhβ* mRNA abundance (D). The black bars correspond to the reproductive phase of the annual cycle. In (A), the stages are: I, immature; II, early recrudescence; III, mid-recrudescence; IV, late recrudescence; V, full spermiating; VI, postspawning. In (B), the stages are: Females: prevtg, previtellogenesis; evtg ($n = 10$), early vitellogenesis; lat-postvtg, late-post-vitellogenesis; mat-ovul, maturation-ovulation; atre, atresia. *((A, B) Rocha, A., Zanuy, S., Carrillo, M., & Gómez, A. (2009). Seasonal changes in gonadal expression of gonadotropin receptors, steroidogenic acute regulatory protein and steroidogenic enzymes in the European sea bass.* General and Comparative Endocrinology, 162*(3), 265–275. https://doi.org/10.1016/j.ygcen.2009.03.023.) (C) Navas, J. M., Mananos, E., Thrush, M., Ramos, J., Zanuy, S., Carrillo, M., Zohar, Y., & Bromage, N. (1998). Effect of dietary lipid composition on vitellogenin, 17β-estradiol and gonadotropin plasma levels and spawning performance in captive sea bass (*Dicentrarchus labrax *L.).* Aquaculture, 165*(1–2), 65–79. https://doi.org/10.1016/S0044-8486(98)00246-4. (D) Modified and adapted from Falcón, J., Herrero, M. J., Nisembaum, L. G., Isorna, E., Peyric, E., Beauchaud, M., Attia, J., Covès, D., Fuentès, M., Delgado, M. J., & Besseau, L. (2021). Pituitary hormones mRNA abundance in the Mediterranean sea bass* Dicentrarchus labrax*: Seasonal rhythms, effects of melatonin and water salinity.* Frontiers in Physiology, 12*, 774975. https://doi.org/10.3389/fphys.2021.774975.)*

timing, daily and annual fluctuations be observed at all stages of the brain-pituitary-gonadal (BPG) axis, which controls the reproduction of fish from molecules to physiological regulations and ending with the development and maturation of the gonads, courtship and mating behaviors, and spawning (Cowan, Azpeleta, & López-Olmeda, 2017; Falcón et al., 2010; Falcón & Zohar, 2018; Farley et al., 2013; Migaud et al., 2010; Pratt Jr. et al., 2022; Zohar et al., 2010).

Although the LD cycle is considered the strongest synchronizer of biological rhythms, temperature cycles are also able to entrain the circadian rhythms in most organisms. Temperature is an important factor that affects ectotherms, including fishes, the body temperature of which depends on the environmental water temperature (Wieser, 1973). Actually, previous research has shown that temperature has a profound effect on circadian clock function. Thus,

daily temperature cycles and drastic temperature variations can set the phase of the clock rhythm (Sweeney & Hastings, 1960). The effects of temperature on the circadian biology of fishes have been explored focusing mostly on locomotor activity rhythms (Lahiri et al., 2005; Reebs, 2002; Sánchez-Vázquez & López-Olmeda, 2018). Daily thermocycles are able to entrain locomotor activity rhythms of zebrafish in the absence of LD cycles (López-Olmeda et al., 2006). However, when imposing conflicting LD and temperature cycles, fishes are active mostly during the day, irrespective of the ambient temperature, suggesting light is a stronger *zeitgeber* than temperature, at least in this species (López-Olmeda et al., 2006; López-Olmeda & Sánchez-Vózquez, 2009). Regarding reproduction, the temperature change over the seasons appears also as a predictive cue. It contributes to triggering the onset and subsequent development of gametogenesis in fishes and to positioning spawning at specific times of the year. For example, in the European sea bass, natural spawning occurs providing the water temperature drops below 15°C (Carrillo et al., 1993). The alternation between day and night also causes a daily temperature cycle with water temperature increasing (thermophase) after sunrise and decreasing (cryophase) following sunset. Accordingly, the transition from cold to warm temperature is linked to dawn, whereas transition from warm to cold temperature is associated with dusk (Johnson et al., 2004). It is interesting that daily thermocycles are involved in the control of hatching rhythms, sex differentiation, gonad development, and sexual steroids production in several fish species (Blanco-Vives et al., 2011; Villamizar, Ribas, et al., 2012). Daily steroids rhythmicity is associated directly to daily rhythms of reproduction and spawning in fishes, which usually coincide with the phase of the LD cycle that displays the highest locomotor activity (Di Rosa et al., 2016; Oliveira, Dinis, et al., 2009; Oliveira, Vera, et al., 2009). Although photoperiod has a role in the control of these daily spawning rhythms (Meseguer et al., 2008), the involvement of daily thermocycles remains to be investigated in depth. The relationship between circadian/circannual rhythms and temperature is complex and not always easy to understand. On the one hand, a change in temperature can affect the rhythmic processes of organisms (Rensing & Ruoff, 2002), but on the other hand, biological rhythms are temperature-compensated, i.e., their period remains constant irrespective of the temperature changes (Pittendrigh & Caldarola, 1973).

The pineal organ (or pineal gland or *epiphysis cerebri*) occupies a central position in the circadian organization of vertebrates. In fishes, the organ contains photoreceptive cells, which are also thermoreceptors. In a majority of cases, these cells are true cellular circadian systems; i.e., they contain the input machinery to the clock (the phototransduction unit), the clock machinery itself, and an output machinery that delivers a rhythmic message. This message is the time-keeping hormone melatonin, the secretion of which reflects the ambient light and temperature conditions. Early studies investigating the impacts of pinealectomy and/or melatonin administration led us to suspect that the pineal organ of fishes was involved in the control of reproduction. The first investigations on this matter were performed in the goldfish, *Carassius auratus* (Fenwick, 1969, 1970). Intraperitoneal (*i.p.*) injections of melatonin inhibited the increase in gonads size observed during the increasing photoperiod and affected the size of the gonadotropes in the pituitary; the author concluded that pineal melatonin exerts an inhibitory effect upon gonad function, possibly by inhibiting the release of a gonadotropic factor. In the Japanese medaka, *Oryzias latipes*, pinealectomy, and/or eyectomy impacted the gonadosomatic index (GSI) in a manner, suggesting that during the breeding season, gonadal growth was stimulated by the pineal, whereas during the nonbreeding season, an antigonadal factor released by the pineal induced gonadal involution (Urasaki, 1972, 1976). In addition, the author suggested that the effects of photoperiod were exerted on the pineal through the eyes. The studies that followed, however, led to conflicting conclusions, i.e., some reporting no effect, while others describing either antigonadal or progonadal effects, or both, depending on the species or time of the year at which the experiments were performed (de Vlaming & Olcese, 1981; Joy & Agha, 1991; Mayer et al., 1997). In 1981, de Vlaming and Olcese concluded that, while not essential for reproduction, the fish pineal organ "*does modulate or 'fine tune' reproductive cycles in some ectothermic vertebrates*" (de Vlaming & Olcese, 1981). Here, we summarize our current knowledge on the functional organization of the fish pineal organ, the place it occupies in the fish circadian organization, and its role in setting the daily and seasonal rhythms of fish reproduction. "Fish" consists of three classes of vertebrates occupying very different positions on the evolutionary scale: The jawless fish are represented by myxines and lampreys; jawed fish include two clades, the cartilaginous fish (sharks, rays, and chimeras) and the bony fish (Actinopterygians [including teleosts and chondrostean] and Sarcopterygians [from which tetrapods emerged]). Actinopterygians represent the vast majority of the ~33,000 living species of fish. This chapter is mainly about teleosts, where most of the work has been done.

2 FUNCTIONAL ORGANIZATION OF THE FISH PINEAL ORGAN

The fish pineal organ is located just below the skull in the so-called "pineal window," where the bone is often thinner and translucent, and the skin covering it is less pigmented (Oksche, 1984) (Fig. 3). However, some fish species exhibit

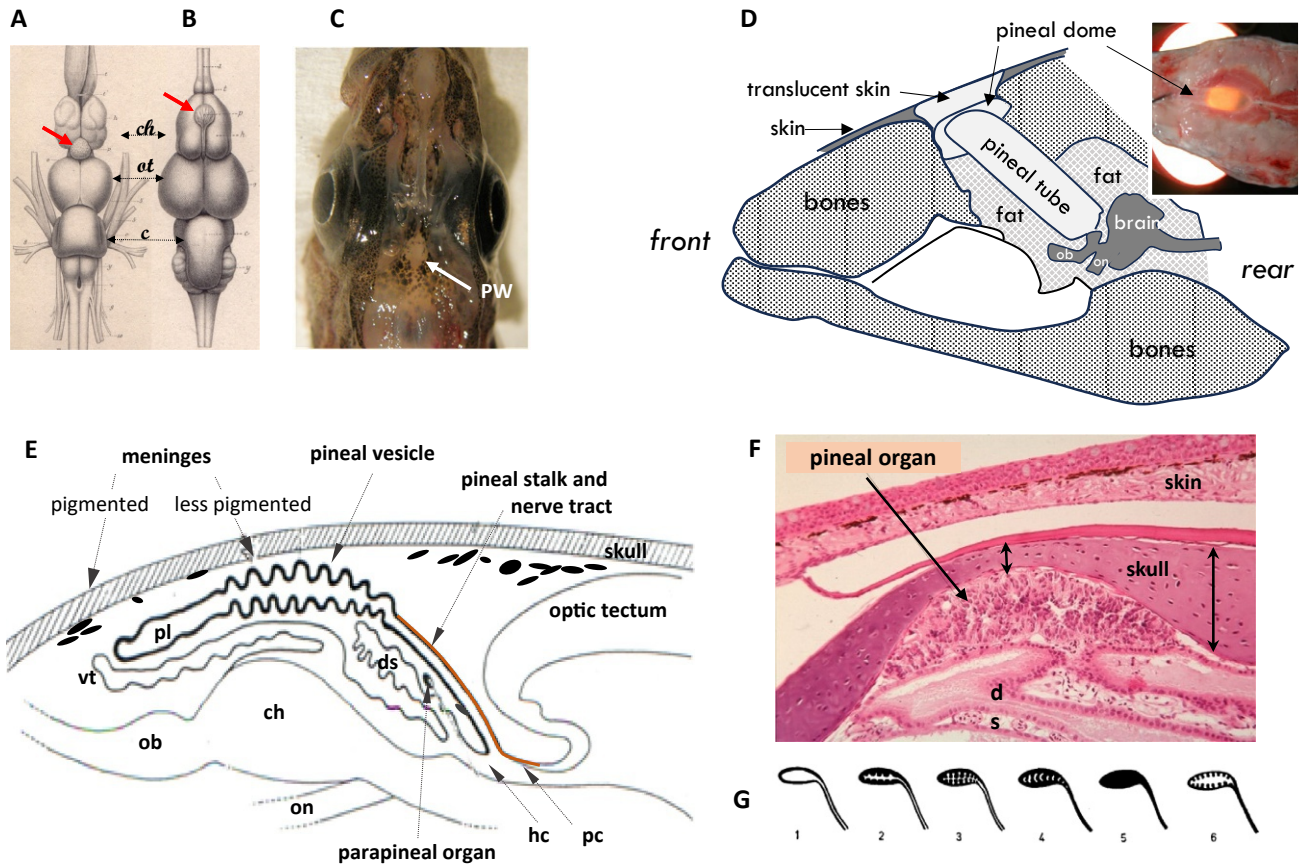

FIG. 3 Anatomy of the fish pineal organ. (Aand B) Dorsal view of the brains of the conger, *Conger vulgaris* (A) and stripped red mullet, *Mullus surmulletus* (B) showing the central location of the pineal organ (red arrows) above the cerebral hemispheres (*ch*). *ot*, olfactive bulb; *c*, cerebellum. (C) Dorsal view of the head of the Arctic cod (*Boreogadus saida*) showing the pineal window (PW), an area where the meninges are less pigmented, centrally located in between the two lateral eyes. (D) Schematic drawing of a sagittal section through the head of the bluefin tuna, *Thunnus thynnus*. In this species, the brain is located deep into the head, and a translucent cartilaginous structure (the pineal tube) allows light to reach the pineal gland. This pineal tube is covered by a translucent cartilage, the pineal dome, covered itself by thin translucent and less pigmented skin (drawing from personal observations). (E) Schematic drawing of a sagittal section through the brain of the northern pike *Esox lucius*. The pineal vesicle is connected to the brain between the habenula (hc) and posterior (pc) commissures by the pineal stalk. The large pineal vesicle covers the cerebral hemispheres (ch) and olfactory bulbs (ob). The pineal lumen (pl), filled with cerebrospinal fluid, opens into the 3rd ventricle; ds, dorsal sac; on, optic nerve; vt, *velum transversum*. (F) Eosin staining of a sagittal section through pineal area of the rainbow trout, *Oncorhynchus mykiss*. The pineal tissue is located in a pit, formed by the bone skull becoming substantially thinner in this area. (G) Diagrammatic presentation of the six types of pineal epithelia in teleosts: 1, flat; 2: folded; 3, convoluted; 4, small space; 5, compact; 6, intermediate. *((A) and (B) Modified from Baudelot, E. (1883).* Recherches sur le système nerveux des poissons. *Paris: Masson. (C) Modified from Rivas, L. R. (1953). The pineal apparatus of tunas and related scombrid fishes as a possible light receptor controlling phototactic movements.* Bulletin of Marine Science, 3*(3), 168–180. (D) Modified from Falcón, J., Besseau, L., Magnanou, E., Herrero, M.-J., Nagai, M., & Boeuf, G. (2011). Melatonin, the time keeper: Biosynthesis and effects in fish.* Cybium, 35*(1), 3–18. 10.26028/cybium/2011-351-001. (E) Modified from Falcón, J., Besseau, L., Magnanou, E., Herrero, M.-J., Nagai, M., & Boeuf, G. (2011). Melatonin, the time keeper: Biosynthesis and effects in fish.* Cybium, 35*(1), 3–18. 10.26028/cybium/2011-351-001. (F) Modified from Coppermine Photogallery Open Source. (G) Modified from Omura, Y., & Oguri, M. (1969). Histological studies on the pineal organ of 15 species of teleosts.* Bulletin of the Japanese Society of Scientific Fisheries, 35*, 991–1000.)*

no such specialization (Rüdeberg, 1969). In most of the fishes studied, the pineal organ is usually shaped as a vesicle that occupies a midline position and is connected to the epithalamus by a slender stalk (Falcón, 1999; Falcón, Besseau, & Boeuf, 2007; Oksche, 1984). However, in pleuronectiform species, such as the Senegal sole, which exhibits a real metamorphosis during early developmental stages that induces an asymmetry of the rostral forebrain areas, the pineal organ leaves its midline position and shifts its photosensitive pineal vesicle toward the upper-right pigmented side, where both eyes are also placed (Confente et al., 2008). The lumen of the fish pineal organ is opened to the third ventricle (3rd V) and thus filled with cerebrospinal fluid (CSF). However, it is worth mentioning that a range of anatomical situations are observed among fish, from a purely vesicular to a fully glandular (i.e., without lumen) organ (Omura & Oguri, 1969; Sastry & Sathyanesan, 1981) (Fig. 3F), highlighting the existence of a great diversity among the ~33,000 species of fishes. Such a diversity is reflected also at the level of the cellular

organization of the pineal epithelium, which appears in many respects as a simplified retina (Fig. 4); many analogies are found between the pineal and the retina at the tissular, cellular, and molecular levels (O'Brien & Klein, 1986). The early electron microscopy studies identified three main cell types in the pineal epithelium: photoreceptors, neurons, and glia (Collin, 1971; Ekström & Meissl, 1997; Falcón, 1999; Falcón, Besseau, & Boeuf, 2007; Oksche, 1984). However, a more complex situation appears to exist, as evidenced from electrophysiological recordings, detection of cell-specific molecules, or single-cell mRNA sequencing (mRNA-Seq), as detailed next (Fig. 4).

2.1 Photoreceptor cells

Photoreceptors usually distribute at the apical part of the epithelium, in contact with the CSF, and are generally isolated from the peripheral vasculature by the glia. Structurally, the fish pineal photoreceptor is analogous to the retinal cone displaying a typical bipolar organization (Fig. 4). At one side of the cell body is the inner segment, from which emerges the outer segment, the photoreceptive pole made of infoldings (30–150 stacks) of the plasma membrane that generally protrude into the pineal lumen. This outer segment contains the phototransduction machinery that

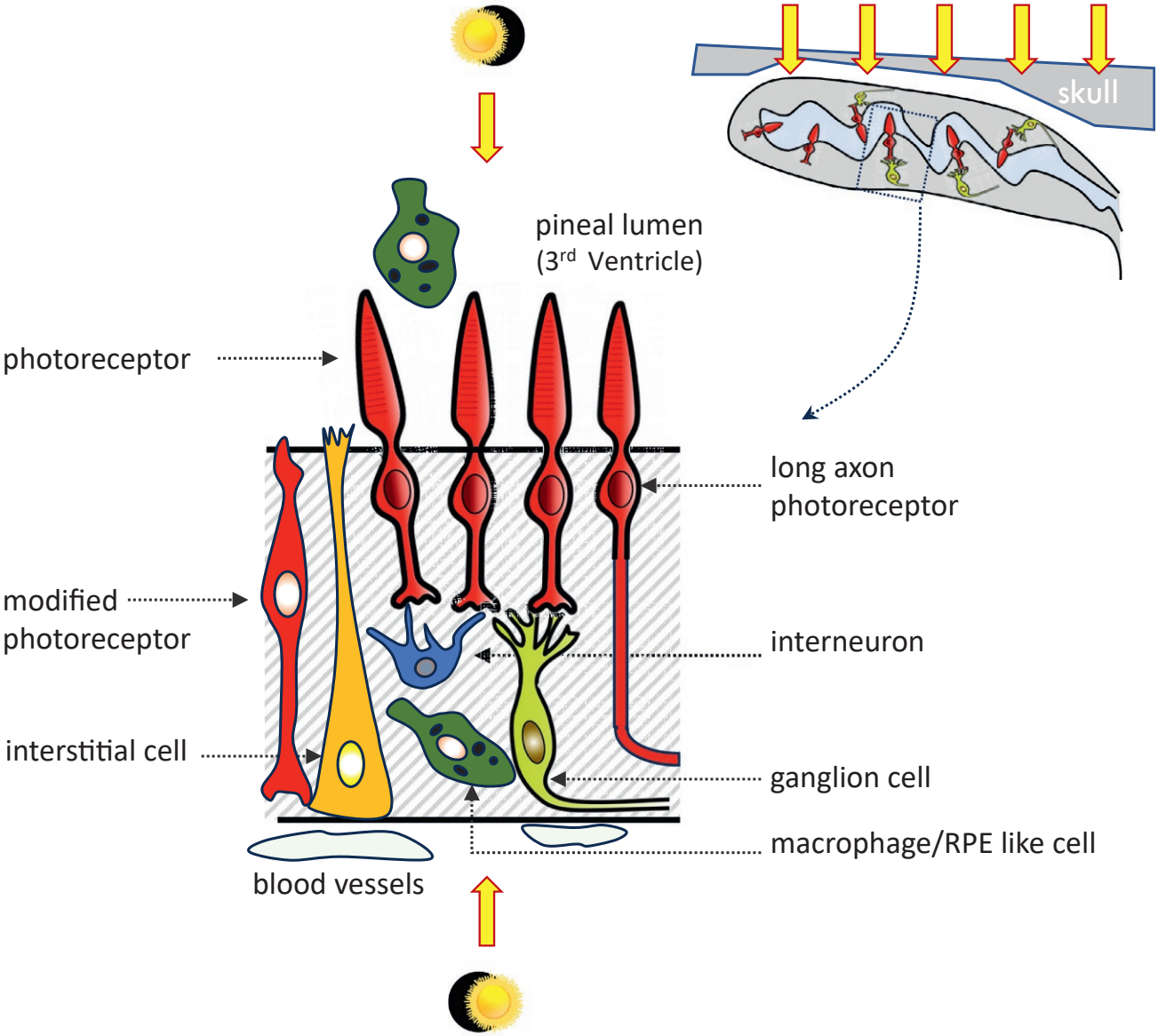

FIG. 4 The different cell types of the pineal epithelium. The arrows show the directions of the light input depending on the position in the epithelium as shown in the upper drawing (for details, cf. Section 2).

allows the conversion of light energy into an intracellular signal (references in Ekström & Meissl, 1997; Falcón, 1999; Falcón, Besseau, & Boeuf, 2007; Rüdeberg, 1969). At the other side of the cell body is the neurotransmitter pole, made of one or two synaptic pedicles, which accumulate numerous clear synaptic vesicles. The neurotransmitter pole establishes synaptic contacts with downstream neurons or with other photoreceptor cells by means of ribbon-type synapses as seen in the retina (Falcón, 1999; Falcón, Besseau, & Boeuf, 2007). In some species, part of the photoreceptor cell population shows atypical, more or less disorganized or even degenerated outer segments (Falcón, 1979a; Wagner & Mattheus, 2002). In the northern pike, *Esox lucius*, these photoreceptors do not establish contact with the second-order neurons, although they remain photosensitive (see next) (Falcón, 1979a) (Fig. 4).

The identification and localization of specific photoreceptor proteins (including opsins) by immunocytochemistry (ICC) or mRNA by in situ hybridization (ISH) and mRNA-Seq allowed the identification of several populations of photoreceptors, as earlier suspected from electrophysiological recordings (Dodt & Meissl, 1982; Ekström & Meissl, 1997; Falcón & Meissl, 1981; Morita, 1966; Shainer et al., 2019; Wada et al., 2021). The opsins found in the pineal organ of fishes belong to the nonvisual opsins family (pinopsin, parapineal opsin, exorhodopsin, vertebrate ancient opsins [VA and VAL], melanopsin) (Dekens et al., 2022; Eilertsen et al., 2014; Kawano-Yamashita et al., 2020; Porter et al., 2012; Vuilleumier et al., 2006). These opsins diversified after the teleost-specific whole-genome duplication (WGD) event (Jaillon et al., 2004). They localize in the same or in distinct cells (Wada et al., 2018, 2021). Although the pineal photoreceptors are all cone-shaped, the majority of them expresses rod-specific genes, whereas only a minority expresses cone specific genes, as shown by single-cell mRNA-Seq in the zebrafish (Shainer et al., 2019). In addition, a cell type-expressing melanopsin (*opn4xa*), but displaying a neuronal-like rather than a photoreceptor-like shape, has also been identified in the zebrafish; these cells send projections to the brain (Sapède et al., 2020). It is noteworthy that decades ago a subset of pineal cells expressing intracellular photoreceptor characteristics, but no outer segment was identified in the dogfish, *Scyliorhynus canicula* (Rüdeberg, 1969). Opsin-like proteins have been detected in pineal cells of rainbow trout and European minnow, which send their axons directly to the brain (Ekström, 1987; Ekström, Foster, et al., 1987). In lampreys, dye application to the optic tectum led to the labeling of a few photoreceptor-like shaped cells in the pineal vesicle in addition to the ganglion cells (Pombal et al., 1999). These cells might be analogous to the "intrinsic photoreceptive retinal ganglion cells" of the retina that express melanopsin and send their axons to the brain and project in the suprachiasmatic nuclei (SCN) of the hypothalamus (Díaz et al., 2016; Fu et al., 2005).

2.2 Neurons

The pineal neuronal population consists of a few interneurons and a larger number of ganglion cells (or second-order neurons) (Ekström & Meissl, 1988, 1997; Ekström, van Veen, et al., 1987). Interneurons connect photoreceptor cells to each other and to second-order neurons (Fig. 4). The vast majority of the pineal neurons are ganglion cells, which send their axons to the brain and establish synaptic contacts with photoreceptor cells or with other ganglion cells (Figs. 4 and 5). Their axons form bundles that converge dorsally at the level of the pineal stalk to form the pineal tract (or pineal nerve) (Ekström & Meissl, 1997; Falcón, 1999; Falcón, Besseau, & Boeuf, 2007) (Figs. 5 and 12). Most probably, some of the fibers of this tract belong to long-axon photoreceptor cells (Ekström & Meissl, 1997) (Fig. 4). Some axons of the pineal tract possess a myelin sheath and dense-cored vesicles, others do not.

2.3 Glia

Glial (interstitial) cells occupy the whole height of the pineal epithelium (Falcón, 1979b) (Fig. 4). Thin in their center, they enlarge at both their ends. A large base, containing the nucleus, allows glial cells to isolate photoreceptors and neurons from the extra-pineal spaces and peripheral vasculature. At the apex, the glia display a brush-like border bathed in CSF. The glial cells establish junctions (desmosomes, gap-, and tight-junctions) with their neighboring photoreceptors. The glial cells incorporate hemal elements released from the fenestrated blood vessels that surround the organ, allowing their distribution to other cell components of the pineal epithelium and their release into the pineal lumen (Omura et al., 1985). However, the passive intercellular transport of high-molecular-weight substances from the bloodstream to the CSF is prevented by the tight-junctions glia and photoreceptors establish at their very apical parts bordering the pineal lumen (Omura et al., 1985). Glial cells display all signs of an intense secretory activity (well-developed Golgi apparatus and endoplasmic reticulum, in which secretory-like material accumulates). They may also contain vortices of membranes, suggesting that in addition to a nutritive role, they also recycle photoreceptor outer segment material (Falcón, 1979b; Falcón, Besseau, & Boeuf, 2007). These cells are necessary to maintain the integrity and survival of photoreceptors. Indeed, in the northern pike and rainbow trout, isolated pineal photoreceptor cells in culture maintain their structural integrity and reconstitute 3D pineal-like vesicles, providing glial cells are present in the culture medium (Bolliet et al., 1996; Falcón et al., 1992). In the zebrafish, the

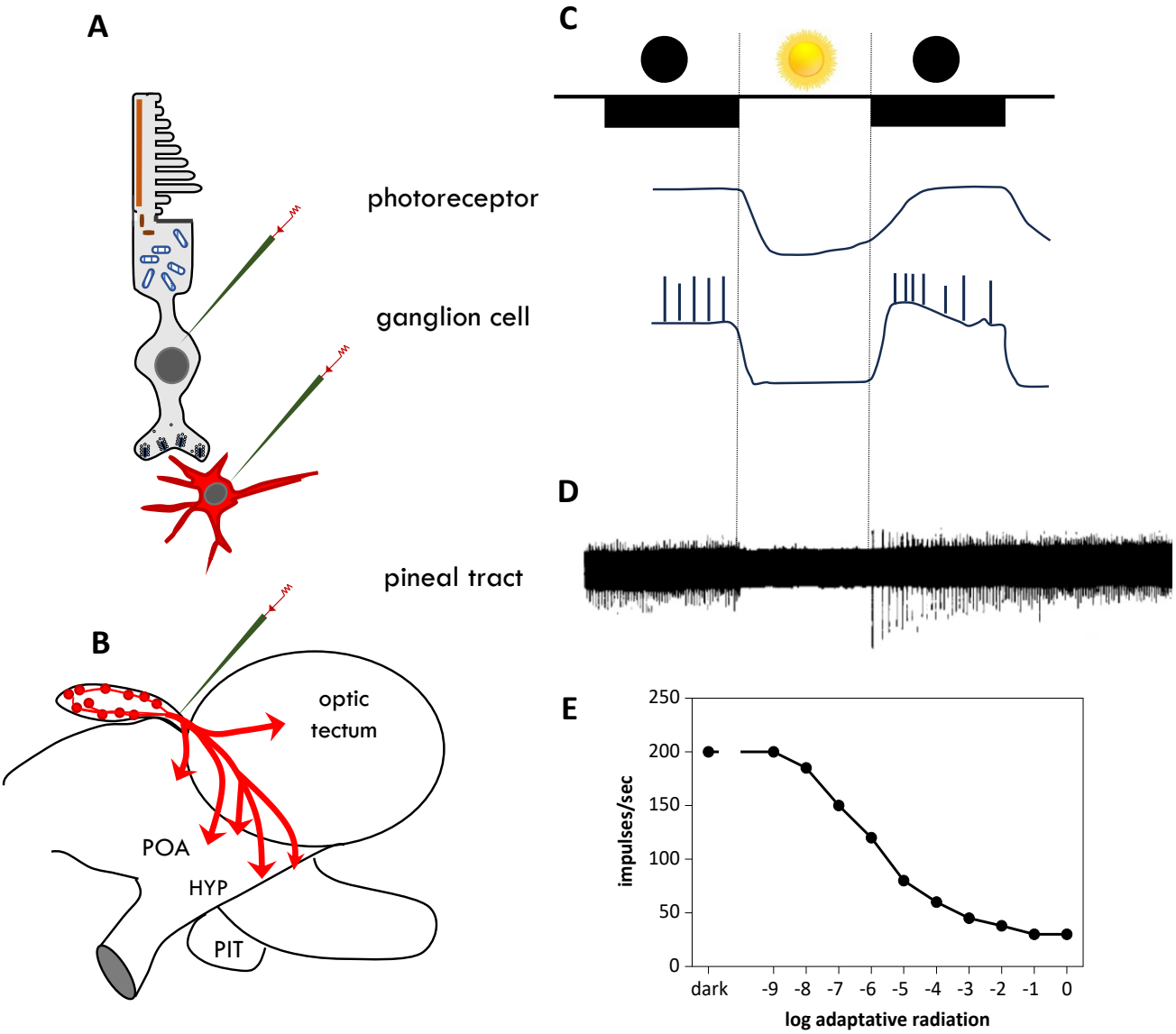

FIG. 5 Electrical activities recorded from the fish pineal organ. (A) Intracellular recordings may be obtained from the pineal photoreceptors and ganglion cells. (B) Extracellular recordings are obtained from the pineal tract (in red), made of the axons from the pinealofugal neurons. The nerve fibers innervate different brain areas. Hyp, hypothalamus; Pit, pituitary; POA, preoptic area. (C) In the dark (black bars and dark moons), the photoreceptors and ganglion cells are depolarized; illumination (sun) prompts hyperpolarization in both cell types; neurons also display spontaneous discharges in the dark. (D and E) Mass potentials recorded from the pineal tract of the northern pike, *Esox lucius* are inhibited by light. The frequency of the discharges decreases with the intensity of the light stimulus response over a range of several log units. *((C) Modified and adapted from Morita, Y., Tabata, M., & Tamotsu, S. (1985). Intracellular response and input resistance change of pineal photoreceptors and ganglion cells.* Neuroscience Research Supplements, *S79–S88. https://doi.org/10.1016/0921-8696(85)90008-8. (D and E) Modified from Falcón, J., & Meissl, H. (1981). The photosensory function of the pineal organ of the pike (*Esox lucius *L.). Correlation between structure and function.* Journal of Comparative Physiology, 144, *127–137. https://doi.org/10.1007/BF00612806.)*

knock down of a subpopulation of glial cells induces loss of the photoreceptor cells (Elazary et al., 2023).

2.4 Macrophages

Two populations of macrophages are found in the pineal end vesicle located: one in the lumen and the other within the pineal epithelium. Both accumulate lysosomes and membrane infoldings from detached photoreceptor outer segments (Falcón, 1979b; McNulty et al., 1988; Omura et al., 1986; Rüdeberg, 1969). However, the two populations display a different intracellular appearance (Falcón, 1979b). It is suspected that macrophages inhabiting the luminal space may be involved in scavenging and/or digesting outer segments that detach from photoreceptor cells. In addition, these macrophages can engulf particles and/or residual bodies released from the pineal epithelial elements as demonstrated in the rainbow trout (Omura et al., 1986).

2.5 Retinal-pigmented epithelium-like (RPE-like) cells

A small population of pineal cells, expressing the characteristic repertoire of genes of the retinal pigment epithelial cells (RPE) of the retina, has been identified in the zebrafish pineal (Shainer et al., 2019). In the retina, RPE cells contribute to many functions related to photoreceptor development and function, including retinomotor movements and visual cycle (Burnside, 2001; Strauss, 2005). These cells might correspond to the "unidentified macrophage-like cells" observed in the pineal epithelium of the northern pike (Falcón, 1979a, 1979b). According to Shainer et al. (2019), these cells participate in the pineal retinoid cycle (as is the case in the retina) and perhaps form a barrier that regulates transport of molecules between the pineal photoreceptors and the vasculature or the CSF or both; they also produce the Agouti-related peptide-2 (AgRP2) (cf. Section 5.3).

3 THE PINEAL INPUTS: DIRECT PHOTOSENSITIVITY

The first direct evidence that the fish pineal organ is photosensitive came from early studies in *O. mykiss* (Dodt, 1963). Spontaneous discharges recorded from the pineal nerve at night were inhibited by light. Since then, four types of electrical responses have been recorded in vivo or in vitro, as extensively detailed elsewhere (Ekström & Meissl, 2010; Falcón, Besseau, & Boeuf, 2007; Meissl & Dodt, 1981) (Fig. 5).

- The *early receptor potential* is a millisecond-fast electrical signal recorded from cone photoreceptors. It is generated by the light-induced charge transfer across the cell membrane resulting from the photoisomerization of opsins (Boyle et al., 2020). It is the earliest sign of photoreceptor activity. It has only been recorded from the pineal organ of the northern pike (Falcón & Meissl, 1981) and the bullfrog *Lithobates catesbeianus* (Morita & Dodt, 1975). In both species, the retinal and pineal early receptor potentials display very similar characteristics in latency and spectral sensitivity.
- The *electropinealogram* is analogous to the electroretinogram; it is a slow graded response believed to represent the sum of extracellular currents generated by the photoreceptors (Falcón & Meissl, 1981; Hanyu et al., 1969; Tabata et al., 1975).
- The *photoreceptor intracellular recordings* have been obtained in lampreys (species?) (Morita et al., 1984; Pu & Dowling, 1981; Uchida & Morita, 1990) and numerous teleosts (Meissl et al., 1986; Meissl & Ekström, 1988a, 1988b; Nakamura et al., 1986) (Fig. 5A). In response to light, the cells hyperpolarize with an amplitude proportional to the intensity and duration of the stimulus. The amplitude of the response is species-dependent (2.5–8 log units). Distinguishing features between retinal and pineal photoreceptor cells are the slow time courses of the rising and recovery phases of pineal cells, which are even slower than those of retinal rods. In addition, indication was provided that several receptor subtypes with rod- and/or cone-like characteristics exist in the teleostean pineal (Meissl & Ekström, 1988b; Shainer et al., 2019; Tabata et al., 1975). Intracellular recordings have also been obtained from the neuronal population (Fig. 5A). The data indicate that two populations exist, one consisting of interneurons and the other, more abundant, of efferent neurons (Meissl et al., 1986). The hyperpolarization of the photoreceptor cells is correlated to an hyperpolarization of the neuron and inhibition of its spontaneous discharges (Morita et al., 1985) (Fig. 5).
- The *extracellular recordings* are mass potentials recorded from the pineal nerve (Dodt, 1963, 1973; Meissl et al., 1986) (Fig. 5B). The great majority of the neuronal recordings are of the "*achromatic*" type, i.e., the neurons exhibit spontaneous firing in the dark, which is inhibited by light, either transiently under brief illumination, or in a manner that depends on intensity and duration of the stimulus under prolonged illumination (Ekström & Meissl, 1997; Falcón & Meissl, 1981; Meissl et al., 1986) (Fig. 5D). The relationship is linear over a range of 2 (*Lampetra japonica*) to 8 (*C. auratus, E. lucius*) log units (Fig. 5E), and the spectral sensitivity reflects that of the photoreceptors (Ekström & Meissl, 1997). In the rainbow trout, two types of ganglion cells have been distinguished according to their degree of spike inhibition by light displaying, one, a long-lasting suppression by light and the other a moderate inhibition (Tabata & Meissl, 1993). In some teleost species (e.g., *O. mykiss, E. lucius*), a "*chromatic*" response has also been recorded from some neurons, characterized by a long-lasting inhibition of the spike discharge by a UV light stimulation, whereas light of longer wavelengths causes excitation. Several explanations may account for this chromatic response, which may come from: (i) interneurons that could transfer information from one cone system to another (Meissl & Dodt, 1981); (ii) two different photoreceptor cell types, contributing to the generation of color opponency in the pineal ganglion cells (Wada et al., 2021); (iii) one single photoreceptor cell co-expressing two photopigments driving cell depolarization for one, and cell hyperpolarization for the other (Ekström & Meissl, 2010); (iv) or expressing a bistable opsin photopigment, each state displaying different signaling abilities (Wada et al., 2018); (v) the subpopulation of melanopsin projection neurons, which might be responsible for the light-on response (Sapède et al., 2020). It is of interest to mention that in addition to light, ambient temperature has also a modulatory influence on the

spontaneous spike discharges and their response to light in the pineal organ of *O. mykiss* (Tabata et al., 1993; Tabata & Meissl, 1993). In this species, the two types of ganglion cells mentioned previously responded to light between 10 and 20°C for one, and between 15 and 20°C for the other; the spike discharges were strongly diminished at higher temperatures and insensitive to light at lower temperatures (cf. Section 6.2 and Fig. 9).

4 THE PINEAL CLOCK

4.1 The circadian clock machinery

A circadian clock is characterized by a free-running rhythmic activity, which in the absence of external cues oscillates with a period (τ) of 24 ± 4 h. Circadian clocks are critical for the synchronization of biochemical, physiological, and behavioral processes to the external cues. In a large majority of cases, these processes display daily (e.g., feeding, locomotor activity, spawning) and seasonal (e.g., growth, migration, reproduction) rhythms. The clocks allow anticipating these variations of the environment. The 24-h LD cycle (photoperiod) is the most reliable and powerful synchronizer of the circadian clocks particularly in temperate and polar areas. Other external factors displaying also rhythmic fluctuations (e.g., rainfalls, temperature) may also play a role in tropical areas where the 12L/12D cycle is constant (Andrade & Braga, 2005; Ikegami et al., 2014). However, compared to photoperiod the daily and seasonal fluctuations of these other factors are less reliable, a fact worsened by the ongoing global changes (cf. Chapter 14, this volume).

A circadian clock machinery consists of core clock genes and proteins interconnected by a transcription/translation feedback loop, robustness, and stability of which is reinforced by auxiliary molecular mechanisms (Isorna et al., 2017; Ko & Takahashi, 2006; Pagano et al., 2017; Stanton et al., 2022; Vatine et al., 2011; Zhang & Kay, 2010). In mammals, four groups of genes encode the proteins that form the core oscillatory feedback loop system. A couple of positive elements, CLOCK and BMAL1, heterodimerize and initiate transcription of genes that contain E-box cis-regulatory enhancer sequences. This is the case of *period* (*per1, per2,* and *per3*) and *Cryptochrome* (*cry1* and *cry2*). In turn, the PER:CRY heterodimers repress the CLOCK:BMAL1 complex (Hurley et al., 2016). A similar process is observed in fishes. However, teleost fishes may display additional copies of these genes as a result of the teleost-specific and salmonids-specific WGDs mentioned previously (Gómez-Boronat et al., 2022; West et al., 2020). Investigations in the zebrafish and Atlantic salmon indicated that duplication resulted in functional diversification, and only some of the duplicates serve circadian function (Liu et al., 2015; West et al., 2020).

4.2 A clock in the fish pineal photoreceptor cells

The first studies indicating an intrapineal circadian activity were performed in the goldfish and Asian stinging catfish. In the photoreceptor cells of *C. auratus,* the number of synaptic vesicles, as well as the position and shape of the synaptic ribbons, displayed significant LD changes that persisted in fish exposed to constant darkness (DD); an internal autonomous control of these cellular movements was suggested (McNulty, 1981). In *H. fossilis*, the daily locomotor activity rhythm that free ran under DD, disappeared after pinealectomy (Garg & Sundararaj, 1986). The development of in vitro static and superfused cultures of isolated pineal glands and cells allowed the direct demonstration that the daily melatonin production rhythm observed in vivo was maintained in the absence of external cues in many species (cf. Section 5.2), indicating the existence of an endogenous circadian control (e.g., northern pike (Bolliet et al., 1995, 1996; Falcón et al., 1987); white sucker, *Catostomus commersoni* (Zachmann et al., 1992); *Policiliidae g.* (Okimoto & Stetson, 1999); and ayu, *Plecoglossus altivelis* (Iigo et al., 2003) (Fig. 8). Single-cell monitoring indicated this is a photoreceptor cell property (Bolliet et al., 1996; Wang et al., 2020). In addition, clock genes (three *clock*, three *bmal*, four *per* and seven *cry*) from the core clock loop have been identified in the pineal organ of several teleost species, as reviewed elsewhere (Lee et al., 2021; Saha et al., 2019; Saha et al., 2022a), and a clock gene of an accessory clock loop (*nr1d1* [also called *rev-erbα*], a repressor of *bmal*) has been localized in the pineal photoreceptors of the zebrafish (Wang et al., 2020). In the African sharptooth catfish, *Clarias gariepinus*, mRNA abundance of these genes oscillates in a daily and seasonal manner under LD and constant conditions, both in vivo and in vitro, speaking in favor of the existence of a functional circadian machinery in the pineal of this species (Saha et al., 2022b). The photoreceptor cells of the fish pineal thus constitute full cellular circadian systems that produce melatonin, which reflects the rhythmic function of the molecular clocks synchronized by photoperiod (Falcón, 1999; Falcón, Besseau, & Boeuf, 2007) (cf. Section 5.2). Virtually, all cells of the organism express clock genes and a functional clock machinery (Barclay et al., 2012). The question is what role does the pineal organ and its messenger melatonin play in the whole circadian organization of fishes.

4.3 The pineal gland in the fish circadian organization

In mammals, a master circadian clock synchronizing other brain and peripheral oscillators is located in the SCN (Barclay et al., 2012; Kolbe et al., 2019). The photoperiodic

information perceived through the retina is conveyed to the SCN via the retino-hypothalamic tract (RHT). From the SCN, the main output pathways reach the hypothalamus (subparaventricular zone and dorsomedial nucleus) and the thalamus (paraventricular nucleus, PVN) thus spreading the rhythmic information. From the PVN, a polysynaptic pathway involving the intermediolateral cell column of the thoracic spinal cord, and ultimately the superior cervical ganglion, ends with a sympathetic innervation of the pineal gland to control melatonin production (Barclay et al., 2012; Coomans et al., 2015; Klein et al., 1997). It seems that an interplay between the SCN and the other brain and peripheral clocks is necessary to maintain solid rhythmic regulations; this includes a feedback impact of melatonin on the SCN clocks (Arendt & Aulinas, 2000).

In fishes, the existence of such a system remains to be demonstrated. In most species, the photoperiod-dependent production of melatonin relies solely on the pineal, whether under circadian control (most species) or not (salmonids) (Falcón, 1999; Falcón et al., 2010; Migaud et al., 2010). It is interesting however that in some species, this production also depends partially (Nile tilapia, *Oreochromis niloticus*; *C. gariepinus*) or totally (*D. labrax*; Atlantic cod, *Gadus morhua*) on the lateral eyes (Bayarri et al., 2003; Martinez-Chàvez & Migaud, 2009; Migaud, Cowan, et al., 2007; Nikaido et al., 2009). Also, *per2* circadian expression has been detected in the SCN, as well as the pineal and pituitary glands of the flounder, *Paralichthys olivaceus,* and amberjack, *Seriola dumerili,* but not of the medaka (Watanabe et al., 2012). The authors concluded that some interspecific variation exists regarding the extent to which fish species depend on an SCN circadian activity. Although the pineal organ has received much attention, it is not the only site of extraretinal photoreception. Photopigment molecules of the opsin family have also been identified in the skin and brain areas, including olfactory bulb, thalamus, hypothalamus, habenula, preoptic area (POA), SCN, and optic tectum (Baker et al., 2015; Binder & McDonald, 2008; Chen et al., 2014; Eilertsen et al., 2021; Pérez et al., 2019). The roles these deep brain photoreceptors play remain to be explored in depth. It is interesting that some of these photoreceptive structures are found in areas that receive inputs from both the pineal gland and/or the retina (Eilertsen et al., 2021). Also, in vivo and in vitro studies in the zebrafish show that all the fish cells exhibit a light-dependent synchronization of circadian clocks. It was concluded that the circadian system exists as a decentralized collection of clocks in this species (Moore & Whitmore, 2014; Whitmore et al., 2000). Nevertheless, the zebrafish pineal clock seems necessary for the generation of daily behavioral rhythms, possibly as part of a multiple pacemaker system, as revealed by genetically modified zebrafish, in which the molecular clock is selectively blocked in the melatonin-producing cells (Ben-Moshe Livne et al., 2016). However, this situation may not apply to the thousands of known fish species as they display great morpho-functional diversity, and differences in habitats and responses to light stimuli (Watanabe et al., 2012). It is conceivable that the way light reaches the organism changes from one fish species to another, depending, for example, on the size of the fish and/or opacity of its tegument and internal tissues (Fig. 3). Species in which light does not penetrate deeply into the organism would need one or two "master clocks" to synchronize "weak oscillators," as suspected from studies on the locomotor activity of pinealectomized fishes. Indeed, the circadian free-running locomotor activity rhythm observed under DD was either lost (*H. fossilis*), or split into two components (*C. commersoni*), or maintained with a different period (burbot, *Lota lota*) (see Fig. 1 in Underwood, 1989). A total loss indicates a master role for the pineal gland, while the other two situations suggest other oscillators contribute to controlling the circadian activity rhythm, and the coupling strength between these oscillators determines the behavior of the system after pinealectomy. Thus, in some species, the pineal gland appears as a key element, occupying a top position in the hierarchy of oscillatory units, either alone or in conjunction with another organ or area (Underwood, 1989). Finally, whereas it is possible that no master clock is needed in a species like the zebrafish, it is noteworthy that time-lapse imaging of the promoter of the clock gene *nr1d1*. This indicates that its rhythmic expression initiates in the pineal photoreceptor cells before spreading to other brain regions (Wang et al., 2020), which would suggest a master role for the pineal in this species. This is a complex situation, and other factors add to the complexity. Aging is one such factor in the killifish, *Nothobranchius furzeri,* where the molecular clock elements are spatially confined to the pineal gland upon aging (Lee et al., 2021). The synchronizing cue is another factor. For example, in the goldfish and seabream, central oscillators are light-entrained (LEO) and peripheral oscillators (i.e., liver) are food-entrained (FEO) (Gómez-Boronat et al., 2022; Vera et al., 2013). In brief, the role the pineal organ plays in the fish circadian organization is not a simple question and Underwood (1989) concluded "*it is becoming increasingly apparent that the relative roles that these sites play between species can vary*" perhaps reflecting "*the different selection pressures operating on animals which occupy diverse ecological and temporal niches*." Watanabe et al. (2012) suggested that the function of the SCN as a circadian pacemaker arose in a common ancestor of teleosts and tetrapods that existed about 500 MYBP and that most teleost have retained this system although others have not.

5 PINEAL RHYTHMIC OUTPUTS

5.1 The nervous message: Glutamate

The photoreceptors' neurotransmitter is likely to be glutamate, as is the case in the retina (Debreceni et al., 1997; Meissl & George, 1984, 1985; Vigh & Debreceni, 1995; Wada et al., 2021), while the population of pineal interneurons uses gamma-aminobutyric acid (GABA) (Ekström, van Veen, et al., 1987; Meissl & Ekström, 1991). Glutamate is released from the photoreceptor synaptic vesicles at night, which stimulates the activity of the second-order neurons. The release of the neurotransmitter is proportional to the amount of light perceived over a variable range depending on the species, and this is at the basis of the "*achromatic*" response (cf. Section 2.2.4. and Figs. 4 and 5D and E). Thus, the organ functions as a perfect luminance detector and accordingly as a day-length indicator (Dodt, 1963, 1973; Ekström & Meissl, 1997, 2010; Falcón, 1999; Falcón, Besseau, & Boeuf, 2007; Falcón & Meissl, 1981). The evidence that the number of synaptic vesicles and ribbons displays daily and circadian variations in the goldfish (McNulty, 1981) might suggest that the sensitivity to light varies along the daily cycle, although there is no evidence that the production of the nervous message itself is under circadian control.

5.2 The hormonal message: Melatonin

A highly conserved feature of vertebrate physiology is the daily rhythm in melatonin production within the pineal gland (Klein et al., 1997). Melatonin is produced at night from tryptophan in four steps as detailed elsewhere (Falcón, 1999; Falcón, Besseau, & Boeuf, 2007; Klein et al., 1997) (Fig. 6). In brief, tryptophan hydroxylase

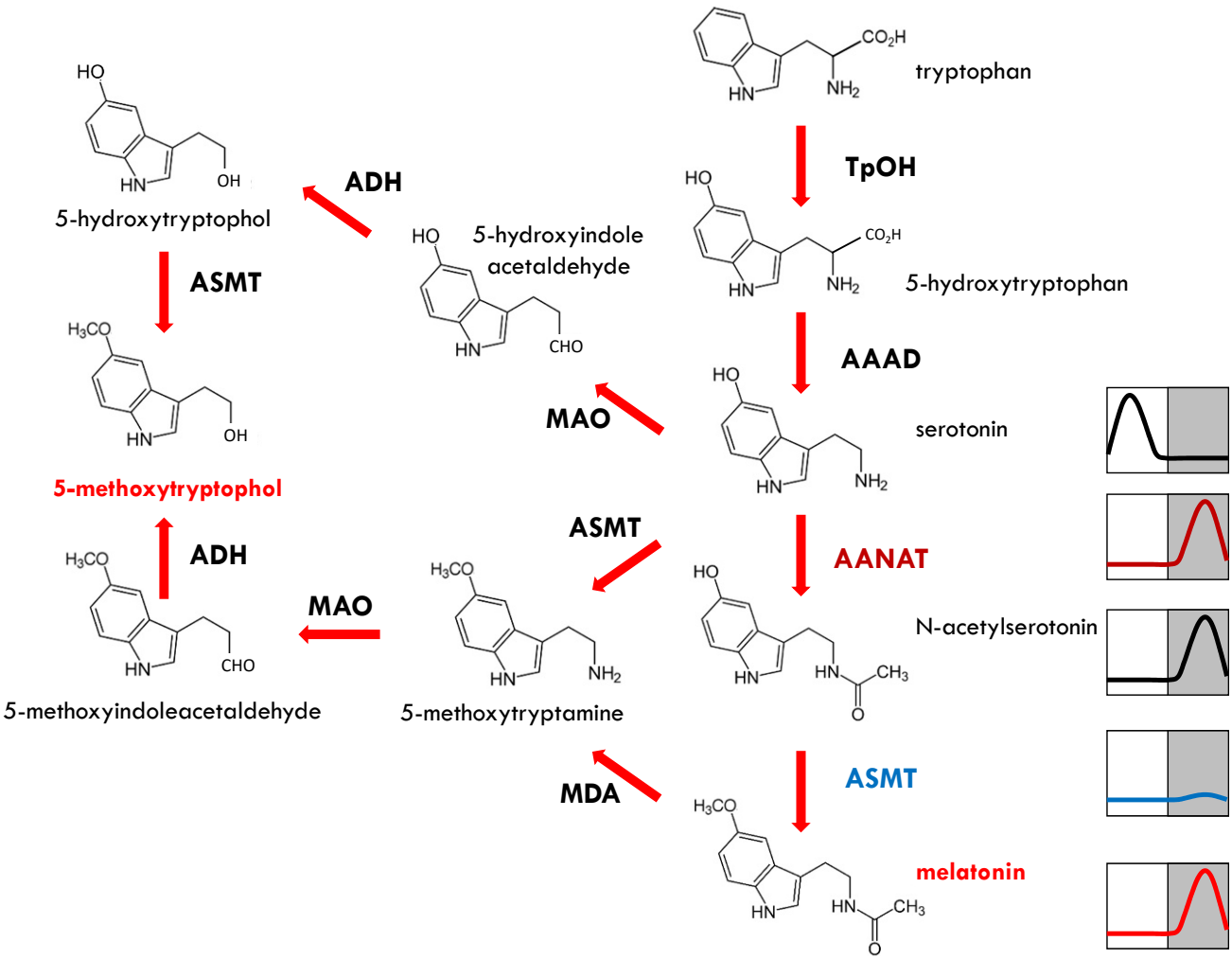

FIG. 6 Melatonin and 5-methoxytryptophol synthesis pathways. AAAD, aromatic amino acid decarboxylase; AANAT, arylalkylamine *N*-acetyltransferase; ADH, aldehyde dehydrogenase; ASMT, acetylserotonin *N*-methyltransferase; MAO, monoamine oxidase; MDA, melatonin deacetylase; TpOH, tryptophane hydroxylase. The graphs in the right represent the daily profiles of, from top to down, serotonin, AANAT, *N*-acetylserotonin, ASMT and melatonin. Day = white boxes; night = gray boxes. For details, see text.

(TpOH; EC 1.14.16.4) catalyzes the conversion of tryptophan into 5-hydroxytryptophan, which is then decarboxylated by the aromatic amino acid decarboxylase (EC 4.1.1.28) to produce serotonin. The arylalkylamine *N*-acetyltransferase (AANAT; EC 2.3.1.87) catalyzes the conversion of serotonin into *N*-acetylserotonin, which is then *O*-methylated by the action of the acetylserotonin *N*-methyltransferase (ASMT; EC 2.1.1.4; formerly HIOMT). Other indoles, including 5-methoxytryptamine, 5-hydroxyindole acetic acid, 5-hydroxytryptophol, and 5-methoxytryptophol, may also be produced after either serotonin oxidative deamination (by monoamine oxidase), or serotonin acetylation (by AANAT), or via melatonin deacetylation (Ceinos et al., 2005; Falcón et al., 1985; Pomianowski et al., 2020; Yáñez & Meissl, 1995) (Fig. 6).

Melatonin and other indoles are released into the blood stream and CSF (Ceinos et al., 2005). The variations in plasma melatonin levels reflect those of its production by the pineal gland; i.e., they are higher at night than during day (Falcón et al., 1987; Gern et al., 1978), and these variations are seasonally dependent (García-Allegue et al., 2001; Iigo & Aida, 1995; Kezuka et al., 1988; Masuda et al., 2003; Vera et al., 2007) (Fig. 7). In isolated pineal organs of the northern pike, in culture, addition of [^{3}H]-melatonin in the incubation medium results in an impressive accumulation of radioactivity in the surrounding blood vessels and fibroblasts, far higher in the evening than in the morning (Falcón et al., 1985). This suggests the possible existence of a yet unidentified melatonin (or metabolite) carrier displaying daily fluctuations.

All the elements of the phototransduction cascade and melatonin synthesis pathway have been identified within the photoreceptor cells of the fish pineal organ (Falcón et al., 1981, 1984; Falcón, Besseau, & Boeuf, 2007; Herrera-Pérez et al., 2011; Tamotsu et al., 1990). As mentioned previously (cf. Section 4.2), the pineal photoreceptor cells are photoneuroendocrine transducers with the full properties of a cellular circadian system (Bolliet et al., 1996).

Another well-characterized site of melatonin synthesis is the retina of vertebrates (Bubenik et al., 1978; O'Brien & Klein, 1986). In fishes, melatonin production occurs in vivo and in vitro from retinal extracts (Cahill, 1996; Iigo et al., 2006; Iigo, Furukawa, et al., 2007; Iigo, Hara, et al., 1997). *Aanat* and *asmt* mRNAs are detected in the tissue (Besseau et al., 2006; Mizusawa et al., 1998, 2000; Paulin et al., 2015; Pomianowski et al., 2020; Rajiv et al., 2016; Velarde et al., 2010; Zilberman-Peled et al., 2006), and the corresponding enzyme activities are measured from retinal homogenates (Benyassi et al., 2000; Falcón, Bolliet, & Collin, 1996; Falcón & Collin, 1991). AANAT and ASMT enzymes colocalize in the photoreceptor cell layer, basal part of the inner nuclear layer, and in ganglion cell layer (Besseau et al., 2006; Paulin et al., 2015; Zilberman-Peled et al., 2006). These areas also display melatonin-like immunoreactivity (Falcón & Collin, 1991). It must be noted that the pineal and retinal AANAT enzymes differ remarkably in amino acid sequence and kinetics (i.e., substrate preferences, temperature dependence of activity and stability) (Benyassi et al., 2000; Coon et al., 1999; Falcón, Bolliet, & Collin, 1996). Actually, the retinal and pineal AANAT are paralogs, respectively, named AANAT1 and AANAT2 that appeared after several WGD (two at the origin of the vertebrates and one specific to teleost fishes) (Cazaméa-Catalan et al., 2014; Falcón et al., 2014; Huang et al., 2022). AANAT2 has been conserved in all fish species and only one form is found, preferentially expressed in the pineal gland. In contrast, two isoforms of retinal AANAT1 exist, AANAT1a and AANAT1b, and fishes may express either form or both (Cazaméa-Catalan et al., 2014). In some groups (salmonids, sturgeons, carps), more paralogs of AANAT1a and 1b may be found as these species have experienced a fourth round of WGD (Huang et al., 2022). Although less studied, there is evidence that at least 2 *asmt* genes may be expressed, as is the case in the goldfish (Velarde et al., 2010) and stickleback, *Gasterosteus aculeatus* (Pomianowski et al., 2020). Although different cell types of the retina may produce melatonin, it seems likely that the photoreceptor cells are the main producers; indeed, quantitative ISH studies showed the abundance of *aanat* and *asmt* mRNAs is far higher in the photoreceptor cell layer than in the other retinal cell layers (Besseau et al., 2006). Furthermore, teleost ocular melatonin rhythms exhibit species-specific variations, with some species showing higher melatonin levels during the dark phase of the LD cycle, others during the light phase, and still others display no daily variation in melatonin levels (Iigo, Furukawa, et al., 2007). Whatever it might be, melatonin produced within the retina is most probably an autocrine/paracrine effector (Behrens et al., 2000; Huang et al., 2013; Ping et al., 2008; Ribelayga et al., 2004), which is catabolized in situ (Grace et al., 1991); i.e., it is not released into the blood stream.

Melatonin might also be synthetized in brain areas other than the pineal and in peripheral tissues. Indeed, *aanat* mRNA is detected and localized in several brain areas and/or peripheral tissues (Fernández-Durán et al., 2007; Kulczykowska et al., 2017; Maitra et al., 2015; Muñoz-Pérez et al., 2016; Paulin et al., 2015; Takahashi & Ogiwara, 2021; Velarde et al., 2010). However, AANAT-like immunoreactivity was detected (Western blots) only from gut extracts of the tropical carp (Yasmin et al., 2021), and enzymatic activity occurs in homogenates from goldfish liver and gut (Nisembaum et al., 2013) and from *G. aculeatus* skin (Pomianowski et al., 2020), while ASMT activity has never been measured to date (cf. Section 7).

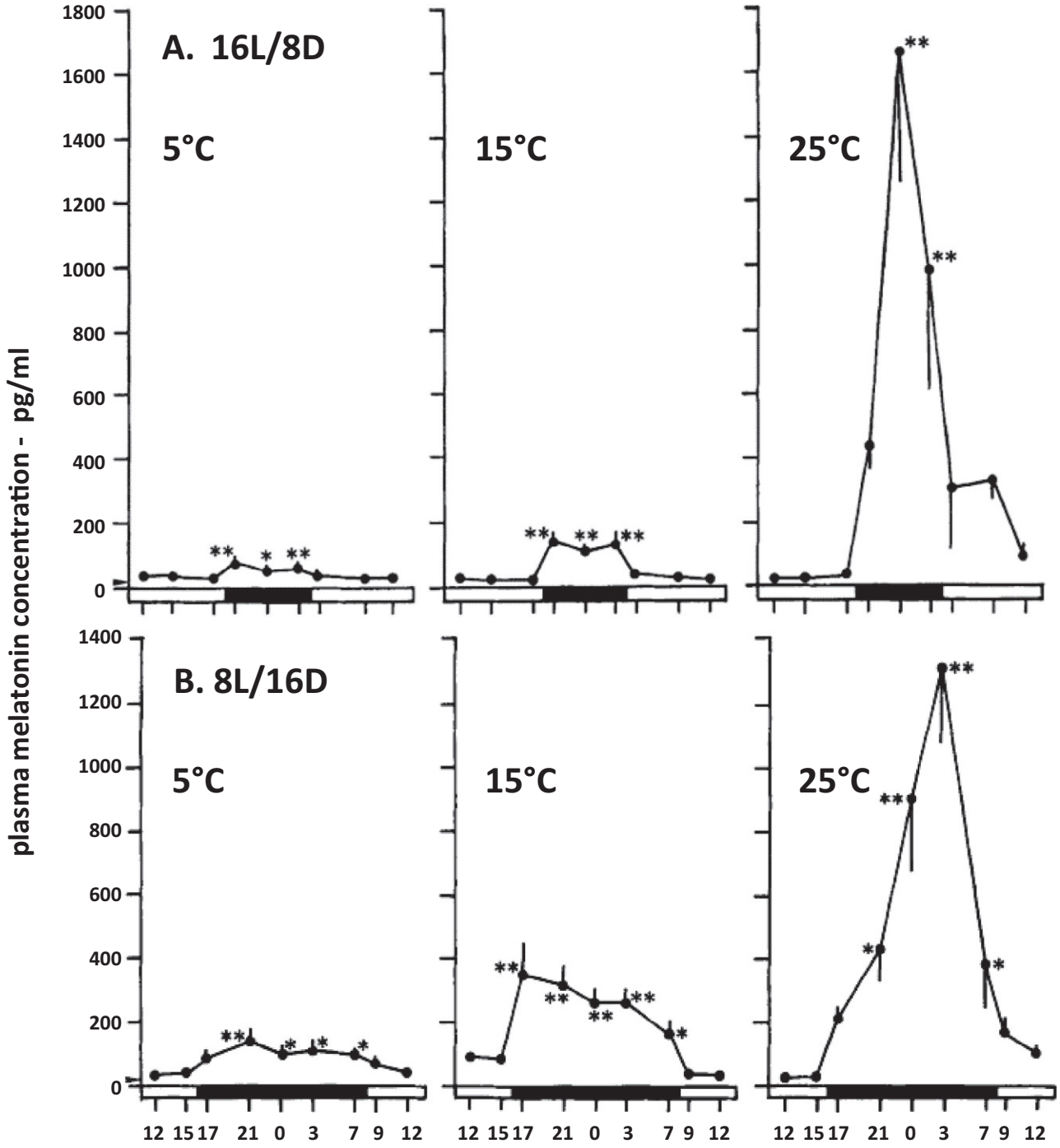

FIG. 7 Plasma melatonin content reflects ambient photoperiod and temperature. In the goldfish, *Carassius auratus*, plasma melatonin content is higher during the night (black bars) than during the day (white bars) hours. The amplitude of the signal depends on the ambient temperature under the summer (A) and the winter (B) photoperiodic conditions. *(Modified from Iigo, M., & Aida, K. (1995). Effects of season, temperature, and photoperiod on plasma melatonin rhythms in the goldfish,* Carassius auratus. The Journal of Pineal Research, 18*(2), 62–68. https://doi.org/10.1111/j.1600-079X.1995.tb00141.x.)*

Thus, the existence of extra-pineal and extraretinal sites of melatonin production awaits further experimental evidence. Also, the AANAT activity found in these tissues may serve other functions than melatonin synthesis, e.g., dopamine acetylation (Nisembaum et al., 2013), as this may occur in some retinal layers (Zilberman-Peled et al., 2006).

5.3 The neurohormonal peptidergic message(s)

5.3.1 *Agouti-related peptide (AgRP)*

Two AgRP paralogs have been identified in fishes, AgRP1 and AgRP2, which are endogenous antagonists at the melanocortin receptors. AgRP2 is specific to fishes and is present in cells of the pineal organ and POA of zebrafish (Shainer et al., 2019; Zhang et al., 2010), turbot and Senegal sole (Guillot et al., 2012), and sea bass (Agulleiro et al., 2014). Single-cell sequencing of zebrafish pineal cells identified AgRP2 is produced by the RPE-like cells (cf. Section 2.5), from where it is released into the CSF (Shainer et al., 2019). It is hypothesized that AgRP2 is made constitutively, while its release is controlled by the LD cycle (Zhang et al., 2010).

5.3.2 *Growth hormone (GH) releasing hormone*

GH-releasing hormone immunoreactivity is detected in the goldfish pineal parenchyma, possibly reflecting a production by photoreceptor cells (Rao et al., 1996). The function of this pineal peptide, so far detected only in this species, is not known but deserves attention since GH production by the pituitary is modulated by melatonin in rainbow trout and European sea bass (Falcón et al., 2003, 2021).

5.3.3 *Arginine vasotocin (AVT)*

Radioimmunoassay and bioassays have suggested the presence of AVT in fish pineal glands of *O. mykiss*, brown trout (*Salmo trutta*), brook trout (*Salvelinus fontinalis*), and Atlantic eel, *Anguilla anguilla* (Holder et al., 1979). Moreover, AVT immunoreactive cells were localized in the stalk of the pineal organ of the plainfin midshipman *Porichthys notatus*. The projections and functions of pineal AVT-positive cells have not yet been deciphered, but this neuropeptide has been correlated with reproductive behavior and tactics in fish (Foran & Bass, 1998).

6 THE CONTROL OF THE RHYTHMIC PINEAL PRODUCTIONS

6.1 Photoperiod and circadian clock control

Melatonin secretion increases at night and is inhibited during day (Fig. 8). This is achieved through controlling a rhythm in AANAT2 activity, while ASMT activity remains rather constant (Falcón, 1999; Falcón, Besseau, & Boeuf, 2007) (Fig. 6).

AANAT2 synthesis and activity are under both direct and indirect light control (Fig. 9). The direct control results from a cascade of events driven by the photoreceptive pole, which controls cell membrane polarization (cf. Section 3 and (Falcón, Besseau, & Boeuf, 2007)). In brief, the current idea is that: (1) cell depolarization in the dark promotes opening of cell membrane voltage-gated calcium channels (VGCC) and calcium (Ca^{2+}) entry into the cell; (2) $[Ca^{2+}]_i$ then binds to a calmodulin-like Ca^{2+}-binding protein that activates the adenylyl cyclase and thus the production of cyclic-3′,5′-adenosine monophosphate (cAMP); (3) cAMP activates protein kinase A (PKA), which (4) catalyzes AANAT2 phosphorylation; (5) phosphorylated AANAT2 binds to the chaperone protein 14-3-3, which protects the enzyme from degradation (Falcón, 1999; Falcón, Besseau, & Boeuf, 2007) (Fig. 10). Based on indirect facts, it has been hypothesized that PKA activation at night might phosphorylate the cAMP response element-binding protein, thus inducing *aanat2* gene expression. When the phototransduction is activated by light, the photoreceptor hyperpolarizes, and the VGCC close; AANAT2 is no more phosphorylated as a consequence of a $[Ca^{2+}]_i$ depletion, and unphosphorylated AANAT2 cannot bind the chaperone protein 14-3-3 anymore, which leads to its degradation through the proteasome (Fig. 10).

The indirect control operates via the circadian clock. Indeed, pineal *aanat2* transcription exhibits a robust daily and circadian rhythm in many fish species (Bégay et al., 1998; Coon et al., 1999; Gothilf et al., 1999; McStay et al., 2014; Rajiv et al., 2016; Velarde et al., 2010; Zilberman-Peled et al., 2007). There is compelling evidence that *aanat2* is a clock-controlled gene and that the rhythmic transcription of *aanat2* results from the direct action of circadian clock genes acting on E-box enhancers present in its promoter. E-box sequences are targeted by the CLOCK/BMAL dimers. They are present in *aanat2* from zebrafish (Appelbaum et al., 2005, 2006), European sea bass (McStay et al., 2014), and northern pike and Mediterranean seabream (Zilberman-Peled et al., 2007). In the zebrafish, one such E-box together with three other photoreceptor conserved elements mediates the synergistic effect of the photoreceptor-specific homeobox OTX5 and the rhythmically expressed clock protein heterodimer—BMAL/CLOCK—on *aanat2* expression. In addition, the profiles of the *bmal*/*clock* oscillations described in fish (displaying peaks around dusk in zebrafish (Cahill, 2002), European sea bass (McStay et al., 2014), and turquoise killifish (Lee et al., 2021)) are consistent with the observed increases in *aanat2* mRNA abundance observed between noon and midnight (previous refs), and genetically blocking zebrafish

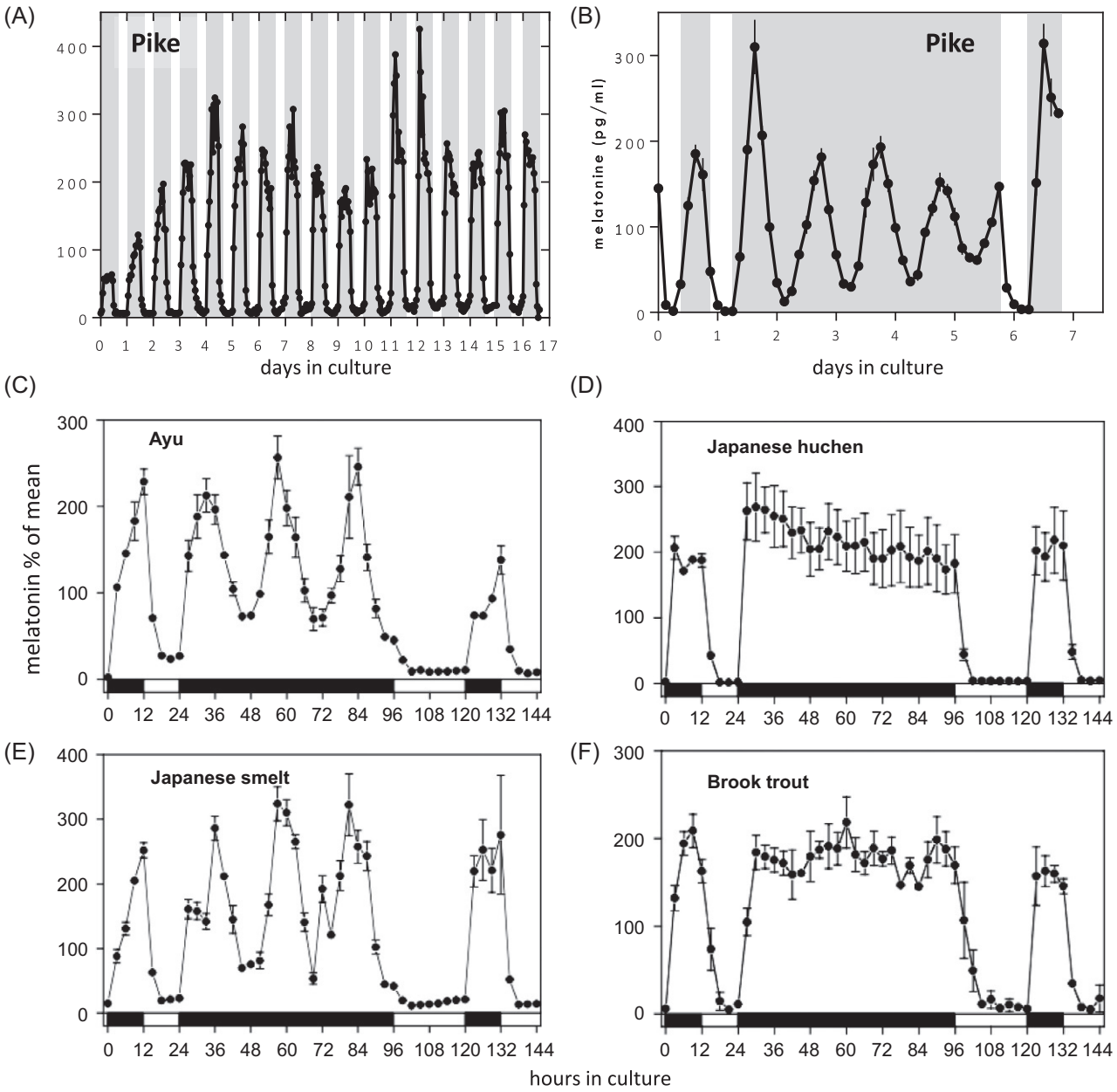

FIG. 8 Photoperiodic and circadian control of melatonin secretion. In all species investigated, isolated superfused fish pineal glands produce melatonin rhythmically in a high at night (DD) low during day pattern, as observed in vivo in the plasma (Fig. 7). (A) The rhythm is sustained for several weeks (northern pike, *Esox lucius*). (B, C, and E) In culture, pineal photoreceptor cells (B, pike), or pineal glands (C, Ayu, *Plecoglossus altivelis*, and E, Japanese smelt, *Hypomesus nipponensis*) maintain the rhythmic pattern under DD, indicating a circadian clock control. The dampening of the rhythm in (B) suggests desynchronization of the individual cellular oscillators, which resynchronize again upon restoring the LD condition. (D and F) No such circadian clock operates in salmonids (here Japanese huchen, *Hucho perryi*, and brook trout, *Salvelinus fontinalis*) so that the melatonin response to the LD is an on/off type of response. *((A) Adapted and modified from Bolliet, V., Bégay, V., Taragnat, C., Ravault, J. P., Collin, J. P., & Falcón, J. (1996). Photoreceptor cells of the pike pineal organ as cellular circadian oscillators.* European Journal of Neuroscience, *9(4), 643–653. https://doi.org/10.1111/j.1460-9568.1997.tb01413.x. (C–F) Iigo, M., Abe, T., Kambayashi, S., Oikawa, K., Masuda, T., Mizusawa, K., Kitamura, S., Azuma, T., Takagi, Y., & Aida, K. (2007). Lack of circadian regulation of in vitro melatonin release from the pineal organ of salmonid teleosts.* General and Comparative Endocrinology, *154(1), 91–97. https://doi.org/10.1016/j.ygcen.2007.06.013.)*

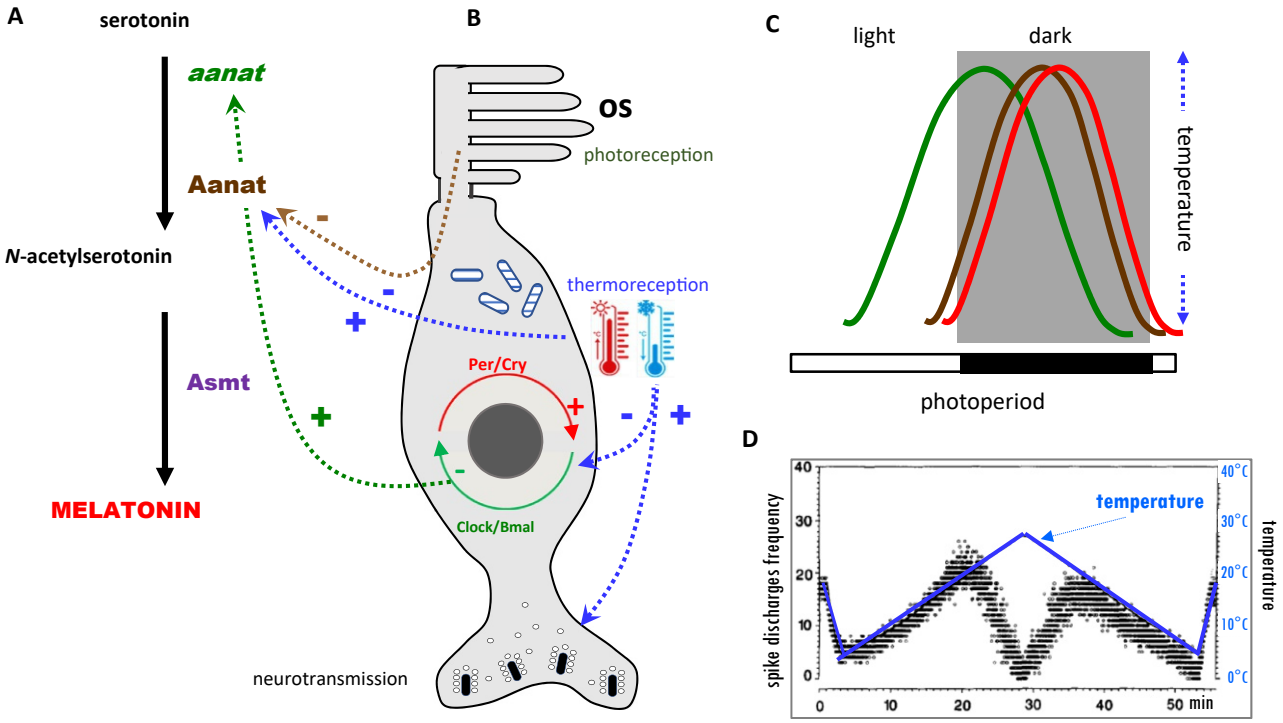

FIG. 9 Photoperiod and temperature control of the pineal photoreceptor cell productions. (A) Melatonin synthesis from serotonin involves two enzymatic steps (cf. Section 5.2 and Fig. 6). The arylalkylamine *N*-acetyltransferase protein (AANAT in brown) is stable only in the dark and thus catalyzes the acetylation of serotonin at night; *N*-acetylserotonin is then converted to melatonin by the acetylserotonin *N*-methyltransferase (Asmt). (B) Upon illumination, the phototransduction process, within the photoreceptor outer segment (os), induces degradation (brown dotted line) of the AANAT protein. Photoperiod also synchronizes the molecular clock (if present), represented here by its core clock components Per/Cry (positive loop) and Clock/Bmal (negative loop). Clock activates *aanat* expression and thus accumulation of *aanat* mRNA (green dotted line), which ceased progressively as the clock runs. The blue dotted arrows indicate that temperature impacts on AANAT protein directly or indirectly, as detailed in the text (cf. Section 6.2). Temperature also affects neurotransmission. (C) Schematic presentation of the daily profiles of *aanat* mRNA (green), AANAT protein (brown), and melatonin production (red). Photoperiod dictates the duration of the melatonin secretion rhythm and temperature controls its amplitude. (D) Frequency of the neuronal firing rate (Y left axis) in the rainbow trout *Oncorhynchus mykiss* as a function of temperature (blue line and Y right axis). *((D) Modified and adapted from Tabata, M., & Meissl, H. (1993). Effect of temperature on ganglion cell activity in the photoreceptive pineal organ of rainbow trout* Oncorhynchus mykiss. Comparative Biochemistry and Physiology A: Physiology, 105*(3), 449–452. https://doi.org/10.1016/0300-9629(93)90417-3.)*

clock affects AANAT2 activity and the circadian production of melatonin (Ben-Moshe Livne et al., 2016) (Fig. 11). In addition to this, (i) miR-183, a microRNA that displays pineal-enhanced and light-induced expression, downregulates *aanat2* mRNA levels through binding a target site in the *aanat2* 3′UTR (Ben-Moshe et al., 2014), and (ii) the clock gene *per2* mediates the effects of light on the onset of the rhythmic expression of *aanat2* in the developing zebrafish (Vuilleumier et al., 2006; Ziv et al., 2005). Not all fish species exhibit such a clock-controlled expression of *aanat2*. In sea lamprey, *Petromyzon marinus* (Bolliet et al., 1993), and salmonids (Gern & Greenhouse, 1988; Iigo, Abe, et al., 2007; Iigo, Hara, et al., 1997), the increase or decrease in melatonin production reflects exclusively ambient illumination (Fig. 8C–F). In the rainbow trout (Coon et al., 1998) and Atlantic salmon (McStay et al., 2014), pineal *aanat2* mRNA levels remain constant under LD, LL, or DD and unaffected whatever the condition. Clock genes are indeed present in the Atlantic salmon pineal, but their rhythmic expression seems to depend on an extra-pineal master oscillator; and, no E-box regulatory elements has been identified in Atlantic salmon *aanat2* promoter (McStay et al., 2014). Thus, melatonin secretion in salmonids and lampreys depends exclusively on the LD control of AANAT2 protein production and stability (Falcón, Besseau, & Boeuf, 2007).

6.2 Temperature

Temperature modulates the production of melatonin (cf. Section 3). Whereas photoperiod controls the duration of the nocturnal melatonin surge, temperature may modulates its amplitude (Benyassi et al., 2000; Bolliet et al., 1993; Falcón et al., 1994; Falcón, Bolliet, & Collin, 1996; Iigo & Aida, 1995; Masuda et al., 2003; Max & Menaker, 1992; Porter et al., 2001; Samejima et al., 2000; Thibault, Falcón, et al., 1993; Vera et al., 2007; Zachmann et al., 1991, 1992) (Fig. 9A–C). The melatonin response to temperature is not (or not only) a passive response to changes in molecular kinetics. From the very few studies available,

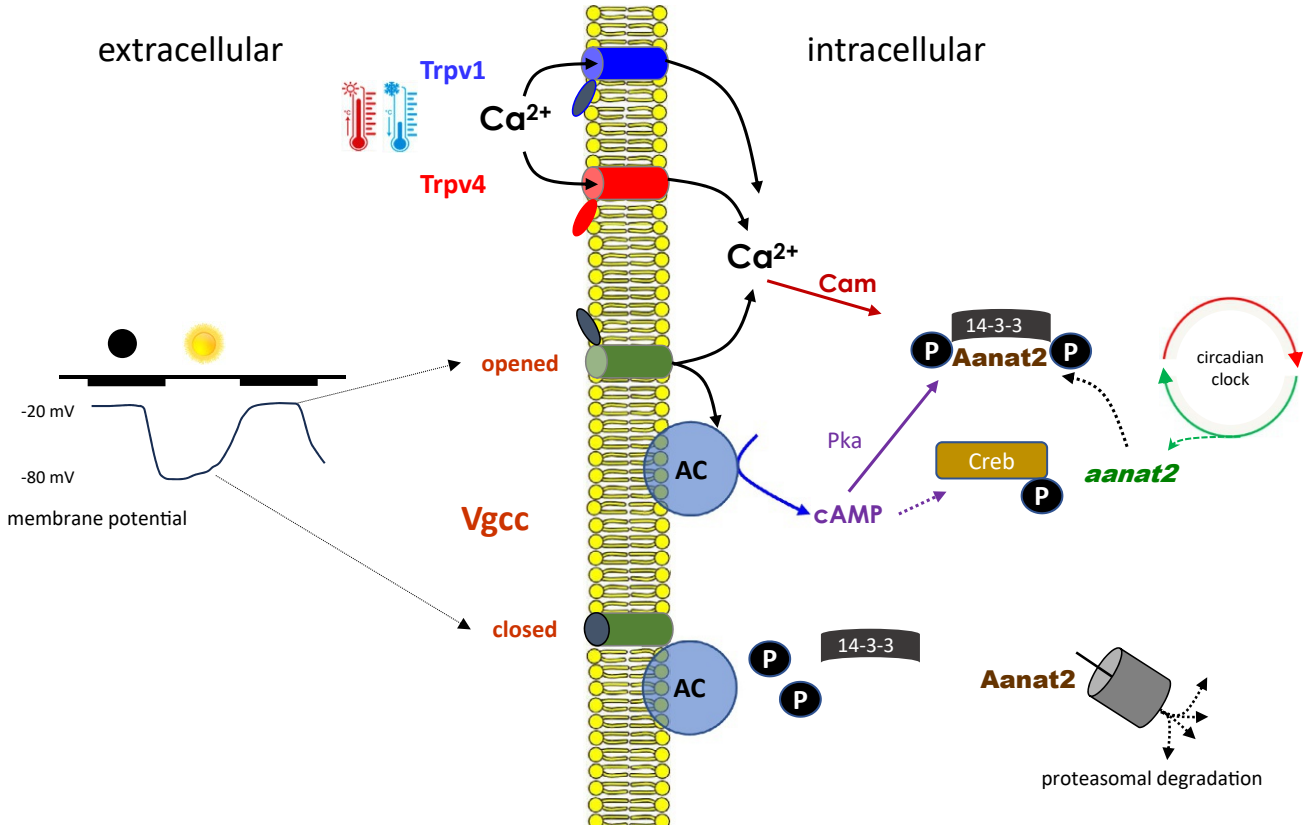

FIG. 10 Intracellular control of arylalkylamine *N*-acetyltransferase (AANAT) activity. Both light and temperature are involved in the control of calcium entry into the cell. Phototransduction controls membrane voltage, which in turn controls the gating of voltage-gated calcium channels (VGCC). VGCC are opened in the dark, when the photoreceptor is depolarized and are closed upon a light-induced cell hyperpolarization (see also Fig. 5). Temperature acts through channels of the transient-receptor-potential vanilloid family (TRPV), which activate at specific temperature ranges, thus contributing to controlling $[Ca^{2+}]_i$. In the cell, $[Ca^{2+}]_i$ binds to a Ca^{2+}-binding protein (CAM) to phosphorylate (P) AANAT; it also activates the adenylyl cyclase (AC)/cAMP pathway, which contributes to AANAT phosphorylation, via the protein kinase A (PKA). Once phosphorylated AANAT binds to, and is thus protected by, the 14-3-3, a chaperone protein. A cAMP/PKA activation of *aanat* transcription via the cAMP-responsive element-binding protein (Creb), as observed in mammals, remains to be investigated in depth in fish. Low $[Ca^{2+}]_i$ reverses the process; the dephosphorylated AANAT dissociates from the 14-3-3, which results in its degradation through the proteasome. It is noteworthy that internal effectors, such as melatonin, catecholamines, and adenosine, are likely to act through the AC/cAMP/PKA pathway.

the melatonin response curve to temperature reflects more or less the aerobic scope of a fish (Cazaméa-Catalan et al., 2013; Max & Menaker, 1992; Nisembaum et al., 2015, 2022; Thibault, Collin, & Falcón, 1993; Thibault, Falcón et al., 1993), as is the case for the spike frequency response curve of the pineal neurons (Tabata & Meissl, 1993) (Fig. 9D). Each species may have its own "fingerprint." For example, isolated white sucker and northern pike pineal glands cultured under a similar photo-thermo-cycle respond in an opposite manner: the former releases more melatonin at night under warm-days/cold-nights ($12L_{20°C}/12D_{10°C}$) than under cold-days/warm-nights ($12L_{10°C}/12D_{20°C}$), while the opposite holds true for the latter species (Falcón et al., 1994; Zachmann et al., 1991). In addition, the response to temperature changes depends on the fish's previous temperature acclimation history (Nisembaum et al., 2022). The state of the art supports previous hypothesis that the effects of temperature are mediated directly in pineal organs lacking an autonomous clock, whereas the effects are due partly to entrainment and partly to direct impact (masking) in pineal organs possessing a circadian clock (López-Olmeda, 2017; Rensing & Ruoff, 2002).

6.2.1 *Direct effects*

The direct effects target the AANAT2 enzyme activity in two ways. The first way is mediated by temperature-sensitive Ca^{2+} channels of the transient-receptor-potential vanilloid (TRPV) family (Fig. 10):

- **(i)** *trpv1* and *trpv4* mRNA have been identified (ISH) within rainbow trout and Atlantic salmon pineal photoreceptor cells, whereas the corresponding proteins are immunodetected (ICC) in their plasma membrane (Nisembaum et al., 2015, 2022);
- **(ii)** TRPV1 and TRPV4 agonists and antagonists modulate melatonin production in vitro, and in a temperature-dependent manner;

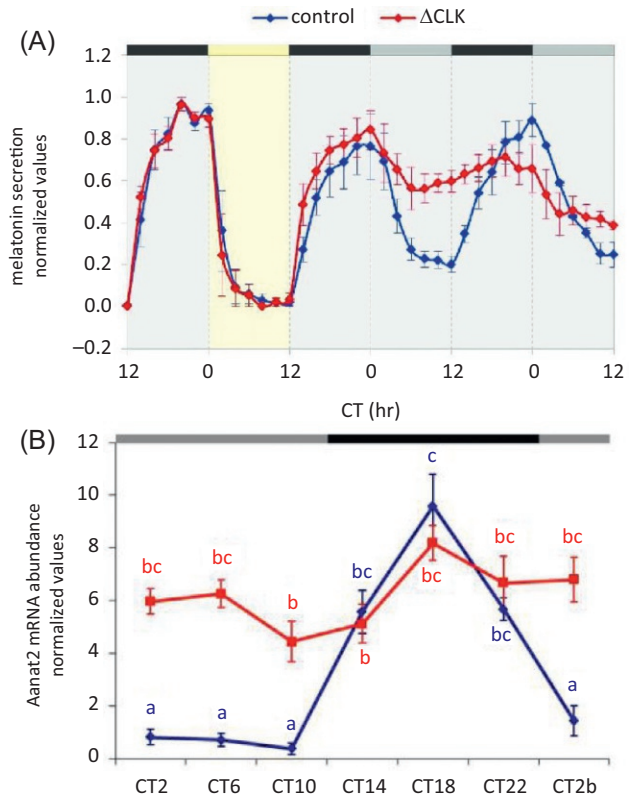

FIG. 11 Clock is essential for the rhythmic production of melatonin. (A) In transgenic *clock* knockdown zebrafish, *Danio rerio,* the circadian rhythms of melatonin release in vitro (A) and of *aanat2* mRNA abundance in vivo (B) are disrupted in the dark (DD). Yellow background corresponds to light, black bars represent dark, and gray bars represent dark during the subjective day. *(Modified from Ben-Moshe Livne, Z., Alon, S., Vallone, D., Bayleyen, Y., Tovin, A., Shainer, I., Nisembaum, L. G., Aviram, I., Smadja-Storz, S., Fuentès, M., Falcón, J., Eisenberg, E., Klein, D. C., Burgess, H. A., Foulkes, N. S., & Gothilf, Y. (2016). Genetically blocking the zebrafish pineal clock affects circadian behavior*. PLoS Genetics, 12*(11), e1006445. https://doi.org/10.1371/journal.pgen.1006445.)*

(iii) in vitro, the temperature-induced changes in cAMP content, AANAT2 activity and melatonin secretion display superimposed profiles in a species-dependent manner (Falcón, 1999; Thibault et al., 1993,b).

Thus, it appears that photoperiod and temperature modulate melatonin production by using the same intracellular messengers (Ca^{2+}, cAMP), and corresponding cascade of events (cf. Section 5.2) (Fig. 10).

The second way is the AANAT2 protein itself. The characterization of AANAT2 activity from pineal homogenates and from recombinant enzymes indicated marked differences between fish AANAT1 and AANAT2 with regard to temperature impacts (Benyassi et al., 2000; Cazaméa-Catalan et al., 2013; Falcón, Bolliet, & Collin, 1996; Zilberman-Peled et al., 2004). Thus, AANAT1 displays classical kinetics, i.e., activity increases linearly with increasing temperature and drops abruptly above 37°C. Conversely, AANAT2 activity peaks at temperatures closer to the fish thermal preferences. In salmonids, two amino acid positions of the AANAT sequence play a crucial role in determining the enzyme thermal stability and catalytic efficiency of AANAT2 (Cazaméa-Catalan et al., 2012).

6.2.2 *Indirect effects*

The indirect effects are observed in species in which *aanat2* expression is clock-controlled. Temperature affects the molecular circadian clock (Lahiri et al., 2005; Rensing & Ruoff, 2002; Sua-Cespedes et al., 2021). In fishes, the free-running rhythm in melatonin secretion by pineal glands cultured under DD is synchronized, but not entrained, by temperature cycles, and its amplitude depends on the ambient temperature (Falcón et al., 1994; Zachmann et al., 1992). Similarly, temperature cycles synchronize the circadian clock in zebrafish, acting on the core loop in a gene-specific manner and modulating the amplitude of the oscillations without affecting their period (temperature compensation) (Lahiri et al., 2005). There is a strong correlation between in vivo and in vitro effects of temperature on the molecular clock genes and the *aanat2* gene in the zebrafish, and air-breathing African sharptooth catfish (Saha et al., 2022b; Singh et al., 2017; Sua-Cespedes et al., 2021). It is hypothesized that temperature determines the amplitude of E-box-directed rhythmic expression, via changes in CLOCK protein levels, phosphorylation, and E-box binding (Lahiri et al., 2005) and, the *aanat2* gene promoter possesses BMAL/CLOCK E-box responsive elements, required for expression in the pineal gland (Appelbaum et al., 2004, 2006) (Fig. 11).

In brief, it is the combination of the photoperiod and temperature that shapes the melatonin secretion rhythm, the former affecting the duration and the latter the amplitude of the melatonin signal. This provides a strong internal indication of both daily and calendar time, and the pineal melatonin-producing cells appear to be "photo-thermo-receptors" (Fig. 9).

6.3 Other (internal) modulators of pineal productions

As part of a neuroendocrine loop, the pineal organ of fishes receives information from a variety of sources, which contributes to modulating the production of its nervous and hormonal messengers. The modulators may be produced locally (melatonin, adenosine), or routed via the circulation (steroids, catecholamines) or afferent fibers (catecholamines, peptides).

6.3.1 *Autocrine and paracrine regulators*

The existence of endogenous pineal factors modulating melatonin secretion is inferred from studies on isolated pineal

cells in culture, where the rate of medium renewal and cell density affected the amount of melatonin secretion (rainbow trout, northern pike), as well as the expression of the melatonin circadian rhythm under DD (northern pike) (Bégay et al., 1992; Bolliet et al., 1996). Melatonin is such a factor. In isolated, light- or dark-adapted, rainbow trout pineal glands, 2-iodomelatonin inhibits (i) the release of melatonin, as well as of 5-methoxytryptamine and 5-methoxytryptophol (Yáñez & Meissl, 1995), and (ii) the spike discharges of the ganglion cells in rainbow trout (Meissl et al., 1990). Thus, the hormone is an autocrine and paracrine regulator of both the nervous and hormonal pineal messengers, respectively.

GABA, the neurotransmitter of the pineal interneurons (cf. Sections 2.2 and 5.1 and Ekström & Meissl, 1997) also modulates the production of the electric and hormonal signals. GABA receptors have been identified in the Atlantic salmon pineal gland (Anzelius et al., 1995). In *S. salar* and *O. mykiss*, GABA binds a discrete population of neurons and glial cells (Meissl et al., 1993). In *O. mykiss*, the ganglion cells spike discharges were either inhibited (a majority of cases) or stimulated (a minority of cases) or both (depending on the light or dark adaptation state of the organs), after application of GABA; and, the responses were modulated by melatonin (Meissl & Ekström, 1991) in agreement with the observation that the binding of a benzodiazepine GABA receptor ligand was decreased in the presence of the hormone (Meissl et al., 1993). It was suggested that GABA allows extending the operating range of pineal ganglion cells under conditions when the system would otherwise saturate (Ekström & Meissl, 1997). GABA also slightly inhibits melatonin secretion in vitro in glands maintained in the mesopic and photopic ranges of illumination, with no clear-cut effect in the dark-adapted glands (Meissl et al., 1994; Meissl & Yañez, 1996). Benzodiazepines, which usually potentiated the effects of GABA through GABA-A receptors, are stimulatory.

Another candidate is adenosine, which contributes to inhibiting nocturnal AANAT2 activity and melatonin secretion in isolated *E. Lucius* and *O. mykiss*, pineal glands in culture (Falcón et al., 1991). The effects involve adenosine receptors coupled to the adenylyl cyclase. Adenosine is produced extracellularly from extracellular ATP, and intracellularly from cAMP and *S*-adenosyl-methionine, the cofactor of ASMT. It is degraded by the adenosine deaminase, which is found associated with the plasma membranes of all the pineal cells, and with the synaptic vesicles within the photoreceptor cells (Falcón et al., 1988). It is not known whether adenosine also modulates the release of the excitatory neurotransmitter, as is the case for the retinal rods and cones (Stella Jr. et al., 2009).

6.3.2 Catecholamines

In *E. Lucius*, norepinephrine modulates melatonin secretion as is the case in Sauropsida and mammals (Collin et al., 1989; Klein et al., 1997): β-adrenergic agonists stimulate, whereas α-adrenergic agonists inhibit AANAT2 activity and melatonin secretion (Falcón et al., 1991). Dopamine had no effect in the species investigated (*E. Lucius*; *O. mykiss*; *D. rerio*) (Cahill, 1997; Falcón et al., 1991). Regarding the nervous response, both norepinephrine (via β-adrenergic receptors) and dopamine (via D1- and D2-dopaminergic receptors) increase the firing rate of the pineal neurons in *O. mykiss* (Brandstätter & Hermann, 1996; Ekström & Meissl, 1997; Martin & Meissl, 1992; Samejima et al., 1994).

How do catecholamines reach the pineal gland. In mammals, norepinephrine from the sympathetic nerve endings that innervate the pineal parenchyma triggers the nocturnal rise in melatonin production, under control by light perceived through the eyes (cf. Section 4.3) (Collin et al., 1989; Klein et al., 1997). In some fish species, the eyes contribute to controlling pineal melatonin secretion (partially in the European sea bass and Atlantic cod; totally in the African sharptooth catfish and Nile tilapia (Bayarri et al., 2003; Martinez-Chàvez & Migaud, 2009; Migaud, Davie, et al., 2007). This suggests the existence of a neural pathway connecting the retina to the pineal, as in the case of lizards, birds, and mammals (Klein et al., 1997). The existence of such a pathway remains to be demonstrated in fishes. Autonomous nerve endings are found surrounding the pineal parenchyma in lampreys, chondrichthyans, and teleosts (Frank et al., 2005), including catecholaminergic fibers in northern pike (Owman & Rüdeberg, 1970). However, they do not enter the pineal epithelium. Rather, they appear in close contact with the vasculature. The possibility that catecholamines reach the pineal cells through the circulation has been discussed elsewhere (Falcón et al., 1991; Martin & Meissl, 1992). Catecholamines might also be synthetized in situ. Indeed, a quite small population of tyrosine hydroxylase immunoreactive neurons, perhaps interneurons, has been observed in the pineal parenchyma of adult rainbow trout (Brandstätter et al., 1995), and developing three-spined stickleback, although absent in adult stickleback (Ekström et al., 1992).

6.3.3 Steroids

Sexual steroids modulate melatonin production. 17β-estradiol (E_2) receptors (ER) have been detected in the pineal gland of rainbow trout (ERα, Bégay et al., 1994) and midshipman fish, *P. notatus* (ERβ, Forlano et al., 2005). Messenger RNA abundance of *erβ* displayed

seasonal variations in *P. notatus*, being higher during the prespawning phase than at other phases of the reproductive cycle in females. E_2 has complex effects:

(i) In rainbow trout pineal cells in culture, a 12-h incubation in the presence of E_2 inhibited in the nanomolar range, and stimulated in the micromolar range, melatonin secretion; but after several LD cycles, E_2 applied every night increased the amplitude of the melatonin rhythm whatever the concentration.

(ii) In cultured pineal glands of the African sharptooth catfish, a 6-h incubation with micromolar concentrations of E_2, estriol, estrone (E_1), and testosterone (T) resulted in inhibition of AANAT2 activity (Yanthan & Gupta, 2007). Inhibition was stronger during the regressive, than during the quiescent phase of the reproductive cycle.

The fish pineal gland also responds to glucocorticoids (Benyassi et al., 2001; López-Patiño et al., 2014; Nikaido et al., 2010; Yanthan & Gupta, 2007). Glucocorticoid receptors (GRs) and their mRNA are present in pineal glands of rainbow trout and Mozambique tilapia (Benyassi et al., 2001; Nikaido et al., 2010). In vivo, rainbow trout displayed higher levels of serotonin and lower levels of *aanat2* mRNA and AANAT2 enzyme activity 5 and 48 h after receiving a cortisol implant, mimicking the effects of a stressful situation (López-Patiño et al., 2014). In isolated rainbow and African sharptooth catfish, pineal glands in culture a 6-h treatment with cortisol, corticosterone or the agonist dexamethazone, inhibited AANAT2 activity dose-dependently over a wide range of concentrations (from the nanomolar to the micromolar range), without affecting ASMT activity (Benyassi et al., 2001; Yanthan & Gupta, 2007). The effects of corticosteroids were more pronounced during breeding than during the quiescent reproductive phase in *C. gariepinus*.

Overall, the data are consistent with the observation that plasma melatonin and cortisol levels display an inverse relationship in fishes (Larson et al., 2004; Nikaido et al., 2010). How steroids affect melatonin secretion remains an opened question. They may act through (i) glucocorticoid-responsive elements present in the *aanat* promoter; (ii) cell surface receptors modifying Ca^{2+} and cAMP levels; or (iii) stimulation of AANAT proteasomal proteolysis (Benyassi et al., 2001; Nikaido et al., 2010; Yanthan & Gupta, 2007).

6.3.4 Peptides

The occurrence of fibers innervating the fish pineal is suspected from studies in the brook and rainbow trout, where axon terminals establish synaptic contacts with photoreceptor cells (Omura & Ali, 1980). More recently, afferent fibers carrying peptidergic information have been evidenced in the pineal of several fish representatives (*P. marinus, S. canicula,* and spotted ray, *Raja montagui* (Mandado et al., 2001); *Acipenser baerii* (Yáñez & Anadón, 1998); *D. labrax* (Muñoz-Cueto et al., 2020; Paullada-Salmerón, Cowan, Aliaga-Guerrero, Gómez et al., 2016; Servili et al., 2011); *O. mykiss* (Yáñez & Anadón, 1996); *F. heteroclitus* (Subhedar et al., 1996); *G. aculeatus* (Ekström et al., 1988); *D. rerio* (Alba-González et al., 2022); Mrigal carp, *Cirrhinus mrigala* (Sakharkar et al., 2005)) (cf. Section 8 for those involved in the control of reproduction).

Neuropeptide Y (NPY) fibers have been found in Gulf killifish (Subhedar et al., 1996) and rainbow trout (Blank et al., 1997). In the latter species, they display predominantly a perivascular location, suggesting that they represent autonomic nerve fibers. Fibers containing the tetrapeptide FMRFamide (Phe-Met-Arg-Phe-NH2) have been identified in the pineal of the three-spine stickleback (Ekström et al., 1988), but it is possible that these fibers actually represent gonadotropin-inhibitory hormone (GnIH)-immunoreactive axons, which share C-terminal amino acids with FMRFamide (see next). In the three-spine stickleback, they enter the pineal parenchyma, but their function remains unknown. The retina of goldfish also receives fibers containing both FRMFamide and gonadotropin-releasing hormone (GnRH), which in the dark can cause increased spontaneous activity of ganglion cells and loss of light-induced inhibition in a season-dependent manner (Stell et al., 1984).

GnRH and GnIH are two hypothalamic neuropeptides involved in the control of fish reproduction (cf. Section 8). GnRH-immunoreactive fibers are present in the pineal gland of the European sea bass (Servili et al., 2010), dogfish shark, and spotted ray fish (Mandado et al., 2001). Among the three GnRH isoforms found in the European sea bass, only GnRH2 fibers reach the pineal gland; they originate from cell bodies located in the dorsal mesencephalic tegmentum (Servili et al., 2010). *D. labrax* pineal also expresses Gnrh receptors (*gnrhr*) mainly *gnrhr2b* and, to a lesser extent, *gnrhr1a*. An in vitro or an in vivo treatment with GnRH2 resulted in an increase of the nocturnal release of melatonin (Servili et al., 2010). Immunoreactive GnIH fibers occur in pineals of several fish species, including the European sea bass (Muñoz-Cueto et al., 2020; Paullada-Salmerón, Cowan, Aliaga-Guerrero, Morano, et al., 2016, Paullada-Salmerón et al., 2019); tropical gar, *Atractosteus tropicus* (Di Yorio et al., 2019); Senegal sole (Aliaga-Guerrero et al., 2018); and pejerrey, *Odontesthes bonariensis* (Pahí-Rosero et al., 2018).

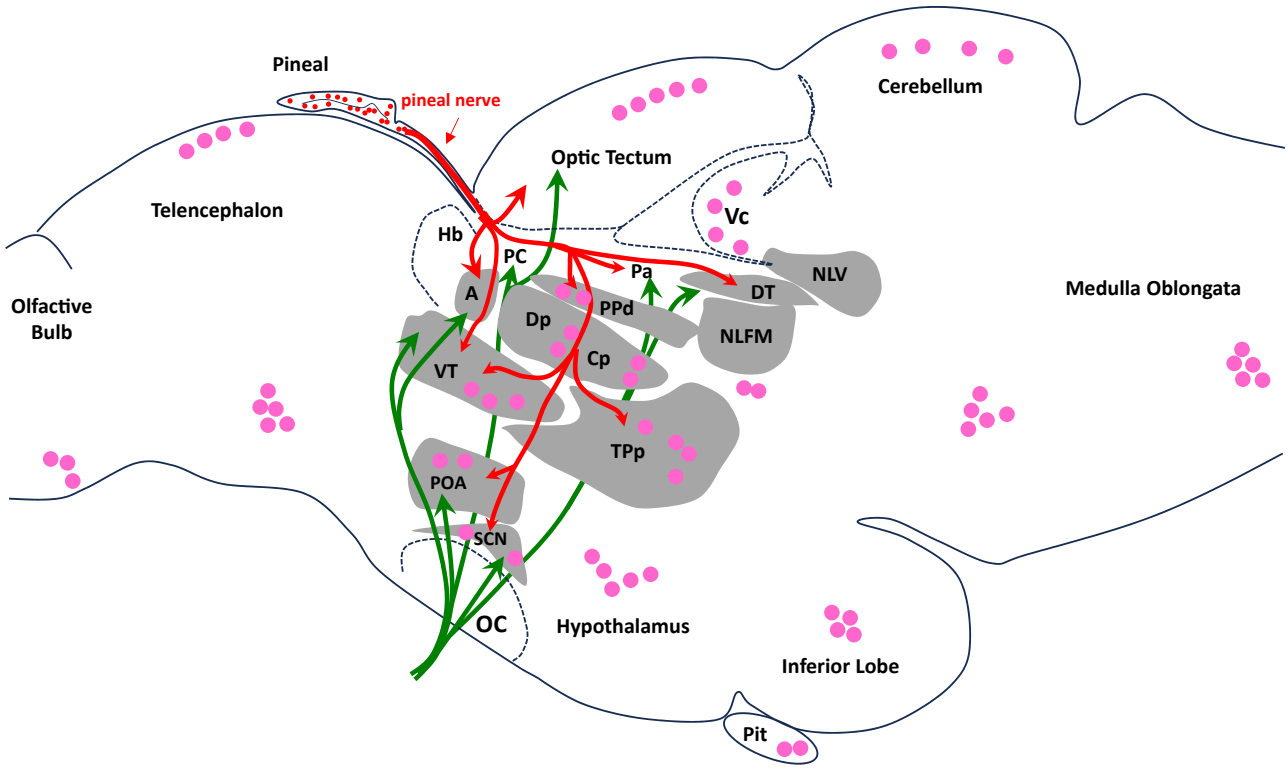

FIG. 12 Pineal and retinal targets in the fish brain. The drawing is a schematic presentation of the pineal (red arrows) and optic (green arrows) nerve projections, together with the areas where the melatonin receptors have been identified (pink dots). A, anterior prethalamic nucleus; Cp, central posterior thalamic nucleus; Dp, dorsal posterior thalamic nucleus; DT, dorsal tegmental nucleus; Hb, habenula; NFLM, nucleus of the medial longitudinal fascicle; NG, *nucleus glomerulosus*; NLV, lateral nucleus of the valvula; OC, optic chiasm; OT, optic tectum; Pa, paracommissural pretectal nucleus; PC, posterior commissure; PPd, dorsal periventricular pretectal nucleus; POA, preoptic nucleus; RF, reticular formation; SCN, suprachiasmatic nucleus; TPp, periventricular nucleus of the posterior tubercle; Vm, trigeminal motor nucleus; TS, *torus semicircularis*; VT, ventral prethalamus. *(Data from Yáñez, J., Busch, J., Anadón, R., & Meissl, H. (2009). Pineal projections in the zebrafish (*Danio rerio*): Overlap with retinal and cerebellar projections.* Neuroscience, 164*(4), 1712–1720. https://doi.org/10.1016/j.neuroscience.2009.09.043 and Servili, A., Herrera-Perez, P., Yanez, J., & Munoz-Cueto, J. A. (2011). Afferent and efferent connections of the pineal organ in the European sea bass* Dicentrarchus labrax*: A carbocyanine dye tract-tracing study.* Brain Behavior and Evolution, 78*(4), 272–285. https://doi.org/10.1159/000330824 for the pineal projections, and from Herrera-Pérez, P., Del Carmen Rendon, M., Besseau, L., Sauzet, S., Falcón, J., & Muñoz-Cueto, J. A. (2010). Melatonin receptors in the brain of the European sea bass: An in situ hybridization and autoradiographic study.* Journal of Comparative Neurology, 518*(17), 3495-3511. https://doi.org/10.1002/cne.22408, Mazurais, D., Brierley, I., Anglade, I., Drew, J., Randall, C., Bromage, N., Michel, D., Kah, O., & Williams, L. M. (1999). Central melatonin receptors in the rainbow trout: Comparative distribution of ligand binding and gene expression.* Journal of Comparative Neurology, 409*(2), 313–324. https://doi.org/10.1002/(SICI)1096-9861(19990628)409:2<313::AID-CNE11>3.0.CO;2-1, and Feng, N. Y., Marchaterre, M. A., & Bass, A. H. (2019). Melatonin receptor expression in vocal, auditory, and neuroendocrine centers of a highly vocal fish, the plainfin midshipman (Porichthys notatus).* Journal of Comparative Neurology, 527*(8), 1362–1377. https://doi.org/10.1002/cne.24629, for the melatonin receptors.)*

Another peptide involved in reproduction, kisspeptin (Kp), has been localized in the pineal gland of the Chinese sucker *Myxocyprinus asiaticus* (Su et al., 2020). The role that GnIH and Kp play in the pineal is not known.

7 THE TARGETS OF THE PINEAL MESSAGES

7.1 The pineal nerve and its projections

The pineal organ is bidirectionally connected with the brain through pinealofugal and pinealopetal (afferent) projections. The axons from the pineal second-order neurons and from central projecting photoreceptor cells constitute the pineal tract that innervates specific central areas (Fig. 12). The fish pineal organ also receives axon terminals originating from neurons located in different central cell masses (Ekström et al., 1994; Ekström & Meissl, 2003; Jimenez et al., 1995; Mandado et al., 2001; Pombal et al., 1999; Servili et al., 2011; Yáñez & Anadón, 1994, 1996; Yáñez et al., 1999). Pioneer works by Holmgren (Holmgren, 1918) and later by Hafeez (Hafeez, 1971; Hafeez & Zerihun, 1974) studied the pineal efferent tract using methylene blue staining and silver impregnation techniques. Subsequently, the pineal nerve projections have been identified using in vivo or in vitro anterograde or retrograde labeling and dyes (e.g., horseradish-peroxidase and 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine

perchlorate [DiI]) injected into pineal cells or applied to different brain areas (lampreys: *L. fluviatilis, Ichthyomyzon unicuspis, P. marinus* (Pombal et al., 1999); rainbow trout (Hafeez & Zerihun, 1974; Yáñez & Anadón, 1996); Siberian sturgeon *A. baerii* (Yáñez & Anadón, 1998); three-spined stickleback (Ekström, 1984; Ekström & van Veen, 1983); Atlantic eel and European carp, *Cyprinus carpio* (Ekström & van Veen, 1984); goldfish (Jimenez et al., 1995); zebrafish (Yáñez et al., 2009); and European sea bass (Servili et al., 2011). The areas innervated are substantial similar among the different fish species investigated (Servili et al., 2011).

The main target areas of the pineal organ are reported for lampreys (Pombal et al., 1999; Puzdrowski & Northcutt, 1989; Yáñez et al., 1993), Siberian sturgeon (Yáñez & Anadón, 1998), elasmobranchs (Mandado et al., 2001), and teleosts (Ekström & van Veen, 1983, 1984; Hafeez & Zerihun, 1974; Herrera-Pérez et al., 2014; Muñoz-Cueto et al., 2019; Servili et al., 2011; Yáñez et al., 2009), as summarized in Fig. 12. In all of these fishes, the pinealofugal fibers from the pineal stalk enter the brain through the habenular commissure, and the rostral and caudal parts of the posterior commissure (PC) and extend bilaterally, innervating the habenula, POA, prethalamus, thalamus, periventricular hypothalamus, periventricular, central and superficial pretectal regions, posterior tuberculum, and medial and dorsal mesencephalic tegmentum and optic tectum (Mandado et al., 2001; Servili et al., 2011; Yáñez & Anadón, 1998; Yáñez et al., 1993, 2009). In the teleost fishes investigated, most of these areas also receive retinal projections (Ekström, 1984; Servili et al., 2011; Yáñez et al., 2009), which also express melatonin receptors (Herrera-Pérez et al., 2010) (Fig. 12). Furthermore, some of these pinealo- and/or retino-recipient areas also contain hypophysiotropic cells (Anglade et al., 1993; Holmqvist & Ekström, 1995), and belong to neuroendocrine centers, including (i) the habenula, which contain Kp1 neurons (Escobar et al., 2013; Kitahashi et al., 2009); (ii) the POA, which shows GnRH1/3 and GnIH neurons; (iii) the prethalamus/thalamus, which exhibit catecholaminergic (Batten et al., 1993) and NPY (Cerdá-Reverter et al., 2000) cells; (iv) the periventricular hypothalamus, showing galanin neurons (Rodríguez-Gomez et al., 2000); (v) the posterior tuberculum, containing serotonin- and dopamine-immunoreactive cells (Batten et al., 1993); (vi) the dorsal mesencephalic tegmentum, displaying both GnRH2 (Muñoz-Cueto et al., 2020) and GnIH (Muñoz-Cueto et al., 2017) neurons. In fishes, these aminergic and neuropeptidergic systems are responsible for the modulation of reproduction, food intake, feeding behavior, and/or metabolism (Delgado et al., 2017; Lin et al., 2000; Volkoff, 2016; Zohar et al., 2010). All these different processes exhibit daily and/or seasonal variations. It is thus conceivable that the pineal fibers reaching these brain areas represent one pathway through which the photic information captured by the pineal organ reaches the neuroendocrine centers, thus contributing to the daily and/or seasonal synchronization of reproduction and other hormonally controlled rhythmic processes.

The pineal organ is the target of afferent projections arising from distinct brain areas as reported in lamprey (Yáñez et al., 1993), Siberian sturgeon (Yáñez & Anadón, 1998), elasmobranchs (*R. montagui* and *S. canicula* (Mandado et al., 2001)), or teleosts (*D. labrax, S. senegalensis* and *D. rerio*; Muñoz-Cueto et al., 2019; Servili et al., 2011; Yáñez et al., 2009). The cell bodies of the pinealopetal fibers have been detected in most of the areas that already displayed pineal and/or retinal efferent projections (prethalamic eminence, habenula, prethalamus and thalamus, periventricular pretectum, posterior tuberculum, and dorsal/medial tegmental area), which suggests their relevant role in the integration of photic inputs (Ekström et al., 1994; Holmqvist et al., 1994; Yáñez et al., 1993). These cell masses could represent the source of neuro-peptidergic fibers containing GnRH, NPY, FMRFamide, Kp1, and GnIH previously detected in the pineal organ of different teleost species (cf. Section 6.3.4). No afferent projections are present in the brain of the three-spined stickleback, crucian carp, European eel, goldfish, and rainbow trout (Ekström & van Veen, 1983, 1984; Hafeez & Zerihun, 1974; Jimenez et al., 1995), but their presence is suspected in the latter (Omura & Ali, 1980). Thus, the existence of central neurons projecting to the fish pineal might represent a conserved feature in these teleosts.

7.2 The melatonin receptors

7.2.1 Characterization

In vertebrates, melatonin receptors were cloned first the frog, *Xenopus laevis*, sheep, *Ovis aries,* and human, *Homo sapiens* (Ebisawa et al., 1994; Reppert et al., 1994). Since then, an impressive number of receptor sequences were obtained. Teleost fishes possess four melatonin receptor subtypes: MT1 (Mel1a), MT2 (Mel1b), MT3 (Mel1c), and Mel1d (Denker et al., 2019; Li et al., 2021; Maugars et al., 2020a, 2020b; Sakai et al., 2019). These receptors probably appeared at the origin of vertebrates, 2-[^{125}I] iodo-melatonin (^{125}I-MEL) binding occurs in larval and adult lampreys (*P. marinus*), but is absent in the cephalochordate amphioxus (*Branchiostoma lanceolatum*) and Atlantic hagfish (*Myxine glutinosa*) (Maugars et al., 2020b; Vernadakis et al., 1998). Strong similarities are found between MT1 and Mel1d on the one hand, and MT2 and MT3 on the other hand. Multiple paralogs of MT1 and MT2 were retained after the teleost-specific and salmonids-specific WGDs; in contrast, MT3 and Mel1d

always appear as a single copy. MT3 has been lost in the Atlantic salmon (Ciani et al., 2019), while MT3 and Mel1d have been lost in birds and mammals (Denker et al., 2019; Maugars et al., 2020b). The melatonin receptors arose possibly from the duplication of a common ancestor of the melatonin receptor and the opsin genes in a eumetazoan (Feuda et al., 2012), and melatonin receptor-like sequences have been identified in the genome of invertebrates (Maugars et al., 2020b). The melatonin receptors belong to the G protein-coupled receptors (GPCR) family (Denker et al., 2019; Gao et al., 2022). The molecular signaling of the receptors has been studied mainly for the mammalian MT1 and MT2. One main difference between MT1 and MT2 is their affinity for melatonin, in the picomolar range for the former and the nanomolar range for the later. Both interact mainly with Gi proteins; they prompt inhibition of the cAMP/PKA pathway. Modulation of the phospholipase C pathway and mobilization of diacylglycerol, inositol trisphosphate, and $[Ca^{2+}]_i$ has also been reported for MT1, whereas MT2 may also activate the protein kinase C/cGMP pathway (for extensive details, see Cecon et al., 2019; Gao et al., 2022; Nikolaev et al., 2021). In teleost fishes, inhibition of the cAMP pathway occurs in rainbow trout, northern pike, spotted snakehead, *Chana punctatus*, and medaka (Falcón et al., 2003; Gaildrat et al., 2002; Gaildrat & Falcón, 2000; Ogiwara & Takahashi, 2016; Roy et al., 2008; Sakai et al., 2019). Stimulation, perhaps via a G_s protein, has been reported in Atlantic salmon (Ciani et al., 2019). The receptors may form homodimers or heterodimers with themselves or other GPCRs (Cecon et al., 2019; Gao et al., 2022; Nikolaev et al., 2021). This situation is likely to vary from species to species and within the same species from one tissue to another, which may have profound impacts on the responses to a melatonin challenge.

7.2.2 Sites of expression

Several approaches have been used to localize the melatonin receptors, including PCR from tissue extracts, ISH, and binding of radiolabeled ^{125}I-MEL to membrane preparations or tissue sections (Ekström & Vanecek, 1992; Herrera-Pérez et al., 2010; López-Patiño et al., 2008; Martinoli et al., 1991; Mazurais et al., 1999). Whatever the method, the prominent characteristic is the ubiquitous distribution of the receptors both in the central and peripheral tissues. The subtypes expressed and their relative abundance depends on the species and tissue considered (Herrera-Pérez et al., 2010; Mazurais et al., 1999). The mapping of the melatonin receptors was first performed using ^{125}I-MEL binding on membrane preparations and tissue sections (radioautography) and later on using riboprobes (ISH; PCR).

(1) Melatonin receptors are found in the pineal gland and the retina. The pineal gland of the golden rabbitfish, *Siganus guttatus*, expresses MT1 and MT3 receptors (Park et al., 2006, 2014), which supports previous information indicating pineal melatonin modulates its own production, as well as the firing rate of the pinealofugal neurons (cf. Section 6.3.1). In the European sea bass, MT1 and MT2 receptors are localized in all three nuclear layers of the nervous retina, as well as in the RPE (López-Patiño et al., 2008; Sauzet et al., 2008). This is consistent with retinal melatonin being an internal autocrine/paracrine modulator of retinal function (cf. Section 5.2 and Huang et al., 2013).

(2) The telencephalon, diencephalon, mesencephalon, metencephalon, and myelencephalon express melatonin receptors (Ekström & Vanecek, 1992; Feng & Bass, 2016; Feng et al., 2019; Herrera-Pérez et al., 2010; Iigo et al., 1994; López-Patiño et al., 2008; Martinoli et al., 1991; Mazurais et al., 1999). Only three studies have provided a precise localization of different melatonin receptor mRNAs in the teleost brain: MT1 in the European sea bass (Herrera-Pérez et al., 2010), MT1 and MT2 in the rainbow trout (Mazurais et al., 1999), and MT2 in the plainfin midshipman, *P. notatus* (Feng et al., 2019). The sites of expression are generally found in areas involved in:

- **(i)** the processing of sensory information, including visual (cf. Section 7.1 and Falcón et al., 2010; Herrera-Pérez et al., 2010; Servili et al., 2011), and vocal-acoustic (Feng & Bass, 2016) and auditory (Feng et al., 2019) networks;
- **(ii)** eye-body motor/sensorimotor coordination and behavioral activities (Feng et al., 2019; Herrera-Pérez et al., 2010); (ii) neuroendocrine and hypophysiotropic regulation (Choi et al., 2016; Falcón et al., 2010; Falcón & Zohar, 2018; Feng et al., 2019; Herrera-Pérez et al., 2010).

Melatonin receptor-expressing cells are in the olfactory bulb, dorsal and ventral telencephalon, parvocellular POA, SCN, anterior, ventral, lateral, and posterior tuberal hypothalamus, lateral recess, and inferior lobes of the hypothalamus, periventricular nucleus, and lateral/medial preglomerular and glomerular nuclei of the posterior tuberculum, ventral prethalamus and dorsal thalamus, periventricular gray zone of the optic tectum, periventricular, central and superficial pretectum, *torus longitudinalis*, *torus semicircularis*, rostral/dorsal, medial and lateral midbrain tegmentum, interpeduncular nucleus, isthmus, corpus and valvula of the cerebellum, oculomotor and trigeminal motor nuclei, vagal sensory and motor areas, vocal pacemaker column of the hindbrain, and medial reticular formation (Fig. 12) (Feng et al., 2019; Herrera-Pérez et al., 2010; Mazurais et al., 1999).

(3) The pituitary gland, which provides a link between the neuroendocrine brain and the peripheral endocrine

organs, also possesses melatonin binding sites and melatonin receptors mRNA, although at much lower levels than in the brain, perhaps explaining that conflicting results have been obtained regarding this matter. Binding of ^{125}I-MEL to pituitary membrane preparations and sections was first mentioned in the goldfish (Iigo et al., 1994), rainbow trout, and northern pike (Gaildrat & Falcón, 2000, 2002). In the latter two species, melatonin modulates pituitary cAMP content and production (cf. Section 8). Binding occurred in the antero-ventral part of the pituitary and PCR studies later extended these observations (e.g., European sea bass (Sauzet et al., 2008); Senegal sole (Confente et al., 2010); mudskipper, *Boleophthalmus pectinirostris* (Hong et al., 2014); cinnamon clownfish, *Amphiprion melanopus* (Kim et al., 2015); and Atlantic salmon (Ciani et al., 2019)). However, it is unclear which pituitary cells represent a direct target for melatonin in fishes.

(4) Finally, melatonin receptors are found in peripheral tissues, including the gills, heart, spleen and blood cells (macrophages), adipose tissue, skin, kidney, liver, intestine, muscle, testis, and ovary in salmonids (*S. salar*, Arctic charr, *Salvelinus alpinus,* and *O. mykiss*; Pang et al., 1994b); European sea bass (López-Olmeda et al., 2009; Sauzet et al., 2008); golden rabbit fish (Park et al., 2006, 2007,b); tench, *Tinca tinca* (López-Patiño et al., 2008, 2012); spotted snakehead (Roy et al., 2008); Nile tilapia (Jin et al., 2013); orange-spotted grouper, *Epinephelus coioides* (Chai et al., 2013); medaka (Maugars et al., 2020b).

7.2.3 Characterization and regulation

A number of parameters must be taken into account when investigating the melatonin receptors and their regulation: (1) the species and tissues investigated; (2) the sex, age, developmental, and reproductive status of the fish; (3) the method used (mRNA, ^{125}I-MEL binding); (4) the subtype investigated; (5) the time at which the experiments are conducted; (6) the number of sampling points along the day or year. With so many factors to consider, making comparisons between species and tissues is extremely difficult. The first studies on the matter investigated the binding of ^{125}I-MEL. In a general manner, this binding is GTP-dependent (indicating its dependency to a GTP binding protein) and it displays affinities in the picomolar range of concentrations in both nervous and non-nervous structures (Bayarri et al., 2004; Falcón, Molina Borja, et al., 1996; Iigo, Sánchez-Vázquez, et al., 1997; Kulczykowska et al., 2006; López-Patiño et al., 2012; Pang et al., 1994a, 1994b; Vernadakis et al., 1998). The displacement curves usually indicate the presence of one, sometimes two, binding sites.

Daily variations in the maximal number (B_{max}) and/or affinity ($1/k_D$) of the binding sites have been reported to occur in some, but not all, species (Amano et al., 2003b, 2006; Falcón, Molina Borja, et al., 1996; Gaildrat et al., 1998; Iigo et al., 1995; Iigo, Sánchez-Vázquez, et al., 1997; Pang et al., 1994b) (Fig. 13). Thus, no clear-cut daily rhythm was found in heart and whole-brain preparations from salmonids (Atlantic salmon, Arctic charr, rainbow trout, coho salmon, *Oncorhynchus kisutch;* Ekström & Vanecek, 1992; Pang et al., 1994a, 1994b), while studies on *S. salar* brain sections indicated the existence of a daily rhythm in the POA and *corpus cerebelli* only (Ekström & Vanecek, 1992). The B_{max} of ^{125}I-MEL binding displayed clear LD variations in the brain of the goldfish (Iigo et al., 1994), seabream (Falcón, Molina Borja, et al., 1996), northern pike (Gaildrat et al., 1998), and masu salmon, O*ncorhynchus masou* (Amano et al., 2003b). The affinity also varied in the latter three species. LD variations of mRNA abundance have been reported in the brain, retina, pineal gland, or pituitary (Fig. 13) (Chai et al., 2013; Ciani et al., 2019; Falcón et al., 2021; Ikegami, Motohashi, et al., 2009; Maugars et al., 2020b; Nisembaum et al., 2021; Park et al., 2006; Park, Park, Hiyakawa et al., 2007; Park, Park, Jeong, et al., 2007; Shi et al., 2004). In the species investigated, the B_{max} is usually high during the day and low at night, but the oscillations in mRNA abundance may peak at different times of the LD cycle in a species-dependent manner. These discrepancies between the profiles of mRNA and their corresponding proteins in the regulation of melatonin receptors highlight the fact that both must be taken into account, and in the end, only the quantity of receptors reflects their functionality.

In addition to their daily variations, the ^{125}I-MEL binding characteristics or receptors mRNA abundance may also display lunar (Hong et al., 2014; Ikegami et al., 2014; Park et al., 2014) and annual cycle (Amano et al., 2003a; Bayarri et al., 2010; Chai et al., 2013; Ciani et al., 2019; Confente et al., 2010; Falcón et al., 2021) variations (Fig. 13). Thus, in the mudskipper, the levels of transcripts of two isoforms of the MT1, expressed in the diencephalon and ovary, displayed two cycles within one lunar month (Hong et al., 2014). It is hypothesized that a close relationship exists between the transcript levels of melatonin receptors and the lunar synchronized cycle of oocyte maturation and spawning in the golden-lined spinefoot (Ikegami et al., 2014). Similarly, the annual variations have sometimes been correlated to the developmental and reproductive status of the fish. For example, daily fluctuations in mRNA abundance in the Atlantic salmon pituitary for three melatonin receptors vary between seasons (Fig. 13). Levels remained low and stable during the 24-hour cycle in the autumn, but showed strong fluctuation in the spring when gonad maturation starts (Ciani et al., 2019). In the

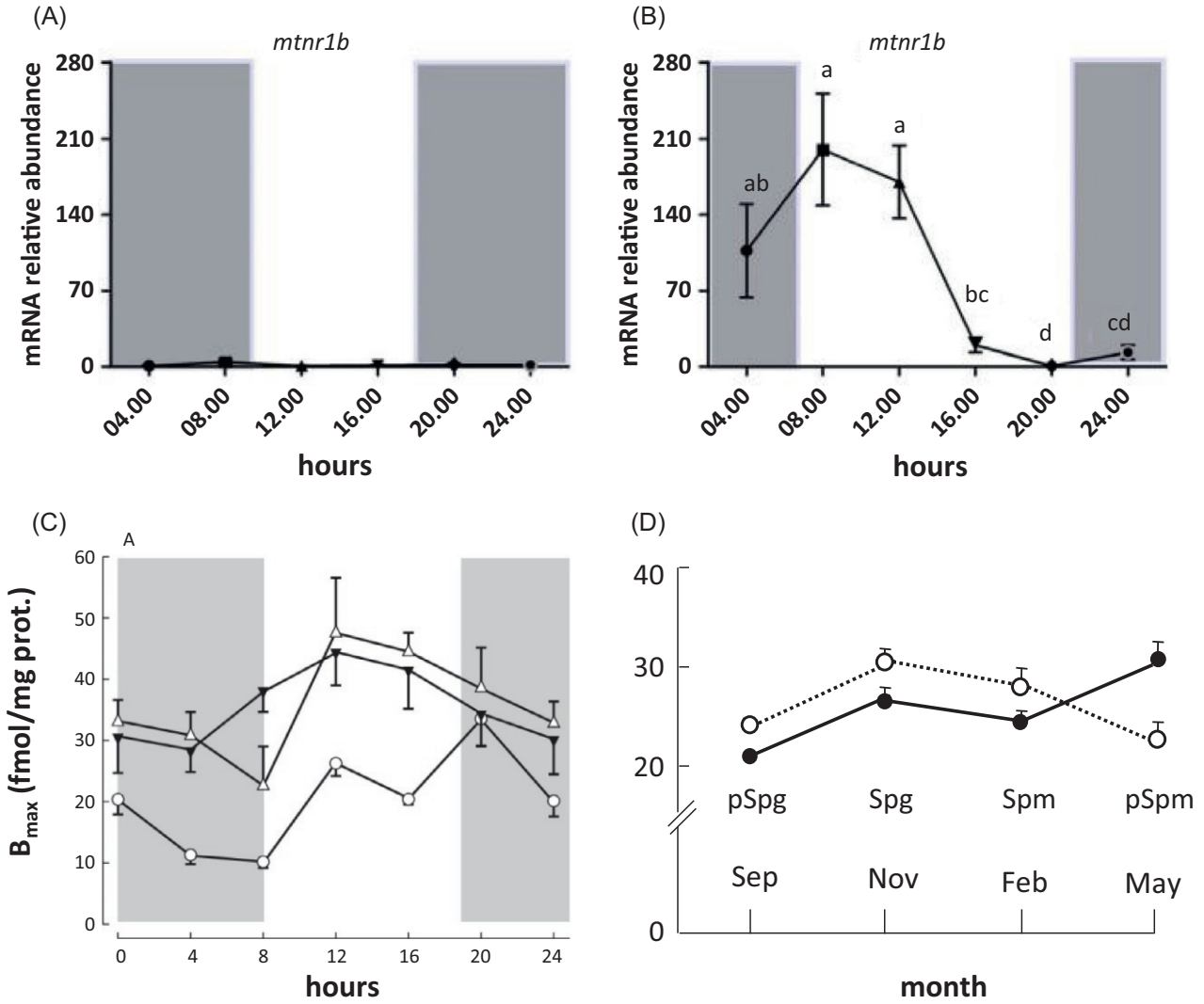

FIG. 13 Daily and seasonal profiles of melatonin receptors. (A and B) Daily pituitary variations of the melatonin receptor subtype *mtnr1b* abundance in male Atlantic salmon, *Salmo salar*, in spring (A) and autumn (B). (C) Daily variations of the maximal number of binding sites (B_{max}) of 2-[^{125}I]iodo-melatonin (^{125}I-MEL) to brain membrane homogenates from northern pike, *Esox Lucius*, maintained under a 11$L_{(08,00–19:00)}$/13D (gray boxes = darkness) cycle (opened circles), constant light (opened triangles), or constant darkness (filled triangles). (D) Annual variations of ^{125}I-MEL binding to hypothalamus membrane preparations from male European sea bass, *Dicentrarchus labrax*, maintained for 2 years under a natural LD cycle (filled circles) or constant light (opened circles) and sampled at different times of their reproductive cycle: pSpg, pre-spermatogenesis; Spg, spermatogenesis; Spm, spermiation; pSpm, postspermiation. *((A, B) Ciani, E., Fontaine, R., Maugars, G., Mizrahi, N., Mayer, I., Levavi-Sivan, B., & Weltzien, F. A. (2019). Melatonin receptors in Atlantic salmon stimulate cAMP levels in heterologous cell lines and show season-dependent daily variations in pituitary expression levels.* The Journal of Pineal Research, 67*(3), e12590. https://doi.org/10.1111/jpi.12590. (C) Gaildrat, P., Ron, B., & Falcón, J. (1998). Daily and circadian variations in 2-^{125}I-iodomelatonin binding sites in the pike brain (*Esox lucius*).* Journal of Neuroendocrinology, 10*(7), 511–517. https://doi.org/10.1046/j.1365-2826.1998.00240.x. ((D) Modified and adapted from Bayarri, M., Falcón, J., Zanuy, S., & Carrillo, M. (2010). Continuous light and melatonin: Daily and seasonal variations of brain binding sites and plasma concentration during the first reproductive cycle of sea bass.* General and Comparative Endocrinology, 169*(1), 58–64. https://doi.org/10.1016/j.ygcen.2010.07.007.)*

European sea bass, significant variations in the B_{max} and/or affinity were found in the hypothalamus and optic tectum, with peak values observed during spermatogenesis (Bayarri et al., 2010) (Fig. 13).

The daily and seasonal variations (mRNA abundance and B_{max}) might be under circadian and circannual control in some tissues, because they persist in fishes maintained under LL and DD (Gaildrat et al., 1998; Ikegami, Azuma, et al., 2009; Park et al., 2006; Park, Park, Hiyakawa et al., 2007; Park, Park, Jeong, et al., 2007) (Fig. 13). Melatonin from the pineal gland contributes to controlling the rhythm in the amount of receptors available because their diel changes observed in the goldfish brain were abolished after pinealectomy or constant LL exposure (Iigo et al.,

1995). However, it is probably not the only factor because the daily variations in B_{max} persisted in northern pike maintained under LL, a situation that drastically abolishes plasma melatonin levels and rhythm (Gaildrat et al., 1998). Similarly, European sea bass maintained for 2 years under LL exhibited persistent variations of the binding parameters typically observed under normal LD conditions (Bayarri et al., 2003) (Fig. 13).

As is the case for melatonin production, temperature and salinity may also modulate the number of melatonin receptors available (Davies et al., 1994; López-Olmeda et al., 2009; López-Patiño et al., 2008). Studies in the tench indicated that temperature affects the kinetics of ^{125}I-MEL binding (association and dissociation constants) without modify the B_{max} and K_d (López-Patiño et al., 2008), although it did affected the B_{max} in rainbow trout (Davies et al., 1994). In the zebrafish, a high temperature (37°C vs. 25°C) for 3 days induced higher brain melatonin levels, but resulted in a drastic reduction of MT1, MT2, and MT3 mRNA levels, in most of the brain areas studied (Loganathan et al., 2018). In the same species, a low temperature (23°C vs. 28°C) for 5 days also resulted in lower mRNA abundance of two MT1 isoforms in the morning, but not in the evening (Sua-Cespedes et al., 2021). This might suggest that the variations in melatonin receptor mRNA reflect the thermal preferences of the zebrafish, as is the case for melatonin secretion (cf. Section 6.2).

Sex, development, and aging are also factors to consider when investigating the regulation of melatonin receptors (Amano et al., 2003a; Falcón, Molina Borja, et al., 1996; Jin et al., 2013; Lan-Chow-Wing et al., 2014; Shi et al., 2004). In the seabream, ^{125}I-MEL B_{max} was 20-fold lower in 1-year-old males compared to brain membranes of 3-year-old female (seabream are males for the first 2 years and turn to females thereafter) (Falcón, Molina Borja, et al., 1996). In the chum salmon, *Oncorhynchus keta,* MT1 and MT2 mRNA are detected in the brain and retina before hatching, and remain low until day 50 posthatching followed by a dramatic increase on day 100 posthatching for MT2 only, but a daily rhythm is not apparent until day 180 posthatching (Shi et al., 2004). Similarly in the developing Nile tilapia, MT1 mRNA abundance started to increase on day 90 posthatching, peaked day ∼day 100 and then decreased again (Jin et al., 2013). The authors concluded this profile paralleled the developmental profile of sexual maturity and that MT1 receptors might be involved in the process of maturity. In the Senegal sole, MT1, MT2, and MT3 mRNA display peak levels, respectively, on 6, 4, and 4 days postfertilization (dpf) and decrease thereafter until metamorphosis (dpf 12). After metamorphosis, MT1 and MT2 mRNA levels continue to decrease (up to 21 dpf), while those of MT3 increase dramatically at least up to dpf 21 (Lan-Chow-Wing et al., 2014).

8 THE PINEAL GLAND AND REPRODUCTION

The components of the BPG axis (cf. see Chapter 2, this volume) generally display daily and annual variations (Cowan, Azpeleta, & López-Olmeda, 2017; Falcón et al., 2010; Juntti & Fernald, 2016; Mateos et al., 2003; Wang et al., 2023). The effects of the pineal gland on fish reproduction have been investigated in vivo and in vitro. The role of the nervous message, conveyed by the pinealofugal innervation, in modulating the activity of the BPG axis remains obscure and can only be speculated from the areas this innervation reaches in the brain (cf. Section 7.1). More information is available regarding melatonin. Pinealectomy and/or melatonin administration (*i.c.v., i.p., i.m.*, implants, water) provided the first indication of a pineal impact on the neuroendocrine reproductive system.

8.1 The effects of melatonin depend on season and species

The first investigations dealing with the effects of the pineal gland and melatonin on reproduction often led to inconsistent or even contradictory results, indicating pro- or antigonadal effects or no effect at all, as reviewed earlier (Borg & Ekström, 1981). Effects depended on a series of factors, including the species investigated, gender, time of the day and year, modes, and amounts of melatonin administered (Falcón et al., 2011; Falcón, Besseau, Sauzet, & Boeuf, 2007; Migaud et al., 2010). Examples of in vivo experiments follow:

(1) *Three-spined stickleback*. Melatonin injections (*i.p.*) resulted in antigonadal effects in November and January and progonadal effects in July, depending on the sex and photoperiodic conditions (Borg & Ekström, 1981).

(2) *The Asian stinging catfish*. Melatonin administration (*i.p.* administration every other day) reduced the GSI, inhibited vitellogenesis, and glycogen content in the ovary only during the preparatory and prespawning seasons, in the oocytes, atresia occurred during the prespawning spawning and postspawning seasons together with a reduction in ascorbic acid levels in all seasons (Joy & Agha, 1991). 5-Methoxytryptophol (cf. Section 5.2) also induced season-dependent inhibitory effects. GSI was reduced in spotted snakeheads receiving melatonin injections, but GSI increased or remained unaltered if melatonin was administered through the water (Renuka & Joshi, 2010). They concluded that the effects of melatonin on reproduction in this species depended on the photoperiod and duration of exposure to melatonin.

(3) *Pacific salmon*. Melatonin given through food pellets diminished GSI, growth and pituitary FSH content from August to October, pituitary GnRH and LH levels in August and September, respectively, and plasma T levels all year long (Amano et al., 2004).
(4) *Walking catfish*, *Clarias batrachus*. Melatonin administration (*i.m.*) during the prespawning period reduced plasma levels of E_1, E_2, and 17α-hydroxyprogesterone (17αHP) in a dose-dependent manner, while the effects on T and thyroid hormones (triiodothyronine T_3 and thyroxine T_4) were biphasic, inhibitory at the low doses and stimulatory at the higher ones (Nayak & Singh, 1987a). In the same species, pinealectomy increased T_3 and T_4 levels in the thyroid during the gonadal development and maturation periods only; in the plasma of the same individuals, T_3 was increased, while T_4 was decreased (Nayak & Singh, 1987b).
(5) *European sea bass*. 150 days after males received a melatonin implants in October and December, GSI and locomotor activity (as observed during spermatogenesis and full spermiation stages) were diminished and blood levels of T, 11-ketotestosterone (11-KT), FSH and LH were decreased (Alvarado et al., 2015). Body weight and condition factor, as well as the hepatosomatic and mesenteric fat indexes, were also reduced suggesting a concomitant impact of melatonin on food intake.
(6) *Zebrafish*. Administration of melatonin through the water increased GSI and egg production in females, as well as synthesis and plasma level of vitellogenin, and E_2 receptors in the liver (Carnevali et al., 2011), a contrasting situation compared to the other case studies listed previously. In zebrafish, melatonin promotes reproduction by acting both in the brain/pituitary and in the gonads (cf. Section 8.2.2).

Thus, it appears from the examples taken previously that in most, but not all, cases studied melatonin has antigonadic properties, and this occurs at specific times of the year. Considering the melatonin targets identified previously (cf. Section 7.2.2), how are the of melatonin effects mediated?

8.2 Melatonin acts at all stages of the BPG axis

Melatonin receptors are found at all stages of the neuroendocrine reproductive axis. It is therefore not surprising that melatonin impacts processes linked to reproduction in these areas.

8.2.1 Melatonin effects in the brain

The brain centers that control the pituitary function are mainly located in the POA and hypothalamus in fishes (cf. Chapter 2 and Zohar et al., 2010). A few studies, performed mostly in vivo, indicate that melatonin administration impacts the main brain factors known to control pituitary gonadotropes, i.e., GnRH, Kp, GnIH, and dopamine (Ciani et al., 2021). Khan and Thomas (1996) showed that administration of melatonin into the 3rd ventricle, close to the POA and hypothalamus, decreased GnRH-induced LH release from the pituitary of Atlantic croaker, *Micropogonias undulatus*. Later studies indicated that melatonin inhibits *gnrh* transcript or GnRH protein amounts. Thus, in the European sea bass, the transcripts levels of *gnrh1* and *gnrh3*, and of three GnRH receptor genes (*gnrhr* subtypes), are greater during day than at night, and *i.p.* injection of melatonin reduced these transcripts levels (Servili et al., 2013). These effects were probably indirect because GnRH neurons and melatonin receptors expressing cells did not overlap. In this same species, *kp1* and *kp2* were also reduced 1 and 3 months, respectively, after the fish received a melatonin implant, and this treatment also affected testicular maturity (Alvarado et al., 2015). These data agree with the observation that pinealectomy affected mRNA levels of *kp2* (increased in August) and *gnih* (decreased in March) in distinct brain regions of the sea bass (Cowan, Paullada-Salmerón, et al., 2017). In the damselfish, *Chrysiptera cyanea,* fed melatonin pellets, short- and long-term reductions of *gnrh1* and *kp2* mRNA abundance were accompanied by reduced *fshβ* and *lhβ* transcript levels, lower GSI, and an increased oocyte atresia (Imamura et al., 2022). In masu salmon fed melatonin pellets, pituitary GnRH and LH levels were diminished as was the case of plasma T and GSI (Amano et al., 2004). In female *H. fossilis*, *i.p.* administration of melatonin reduced *gnrh2* and *kp2* mRNA (Chaube et al., 2020). In contrast, in the zebrafish, melatonin administration increased transcripts levels of *kp1*, *kp2,* and *gnrh3* in the brain and of *lhβ* in the pituitary (Carnevali et al., 2011; Loganathan et al., 2018). Parallel to the inhibition of the GnRH/Kp system, melatonin stimulates *gnih* mRNA levels, as shown in the Nile tilapia, resulting in a decrease of *fshβ* and *lhβ* mRNA levels in the pituitary, and of E_2 and 11-KT in the plasma (Kim et al., 2018). Again, the data obtained in the zebrafish were in the opposite direction because in vitro treatment of whole zebrafish brains by melatonin reduced *gnih* mRNA (Yumnamcha et al., 2017).

Melatonin may also act on gonadotropins release by modulating the activity of the dopamine system (Badruzzaman et al., 2013; Dufour et al., 2010; Popek, Drag-Kozak, & Luszczek-Trojnar, 2010). Dopamine is inhibitory to gonadotropin secretion, thus providing fish with a dual "dopamine$^{(-)}$/GnRH$^{(+)}$" control of reproduction in the brain. Brain dopamine displays daily and annual rhythms in fish that are 180° out of phase with the melatonin rhythm (Badruzzaman et al., 2013, 2021; Le Bras, 1984), as is the case in the retina where melatonin controls the circadian rhythm of dopamine production (Ribelayga et al., 2004).

Melatonin inhibits the hypothalamic-pituitary dopaminergic metabolism in rainbow trout (Hernandez-Rauda et al., 2000). In female Atlantic eels that received a melatonin implant, tyrosine hydroxylase (*th*) transcript levels were increased in specific brain areas, including the POA (from where dopamine axons are sent to the pituitary) (Sebert et al., 2008). Implantation also resulted in lower FSH, LH, and 11-KT productions, without affecting E_2 plasma levels. In vivo and in vitro studies in the European carp suggest dual effects of melatonin on hypothalamic dopamine production, with melatonin being stimulatory in immature fish but inhibitory during the spawning period of mature fish (Popek, Drag-Kozak, & Luszczek-Trojnar, 2010; Popek, Natanek, & Luszczek-Trojnar, 2010).

8.2.2 Melatonin effects in the pituitary

In addition to its actions on the brain neuroendocrine centers that control the pituitary function, melatonin may exert direct effects on the pituitary, in agreement with the evidence that melatonin receptors are expressed in the pituitary of some fish species (cf. Section 7.2.2, for references and discussion, see Ciani et al., 2021). However, in vitro studies in goldfish found no effect of melatonin on adenylyl cyclase activity (Deery, 1975) or release of gonadotropins (Somoza & Peter, 1991). Similar observations were made in European carp (Popek, Drag-Kozak, & Luszczek-Trojnar, 2010; Popek, Natanek, & Luszczek-Trojnar, 2010). In contrast, a stimulation of LH release was detected in the Atlantic croaker pituitaries following challenge with melatonin; the effects were time-dependent (1–12 h) and concentration-dependent (1 nM to 10 μM) (Khan & Thomas, 1996). Interestingly, GnRH also stimulated LH release in *M. undulatus*, but the melatonin and GnRH effects were not additive; instead, LH release was diminished in the presence of both factors compared to the effects of either factor alone. This reveals the existence of complex regulatory mechanisms. In the medaka, 10 μM melatonin had no effect on *lhβ* mRNA abundance, but it reduced *fshβ*, *tshβ,* and somatolactin (*sl*) transcript levels (Kawabata-Sakata et al., 2020). The effect on *tshβ* mRNA was later confirmed in the same species using a similar melatonin concentration (Royan et al., 2023). In the European sea bass, the mRNA of all pituitary hormone genes were affected by a 12-h melatonin challenge at physiologically relevant melatonin concentrations (10^{-12} to 10^{-8} M) (Falcón et al., 2021; Herrero et al., 2010). However, the effects varied depending on the time of the year and reproductive status of the fish, as well as on previous adaptation to low or high salinity water (Falcón et al., 2021), thus in seawater adapted fish:

(i) in February (spawning phase), mRNA levels of *fshβ* and *gh* (*gh*) were inhibited, while those of proopiomelanocortin (*pomc*) were stimulated; *tshβ* mRNA abundance displayed a complex response, increasing at the picomolar, and decreasing at the nanomolar, range of concentrations; *sl* and prolactin (*prl*) remained unaffected;

(ii) in August (arrest phase) and, the effects where less pronounced for *fshβ*, *tshβ,* and *gh*, but were inhibitory on *pomc, prl,* and *sl*; *lhβ* mRNA levels were increased at the picomolar concentration of melatonin.

Altogether, it appears that melatonin may act directly on the pituitary to modulate the production of hormones directly involved in the control of reproduction, namely, FSH, LH, and TSH, or in other neuroendocrine processes, including growth, food intake, stress, skin pigmentation, and salinity adaptation. However, the responses appear complex as they vary from species to species and from study to study. In addition, a few species have been investigated and most studies used a single and nonphysiological concentration of melatonin. A clearer and coherent view needs the use of standardized protocols that take into account the species (and within the species the specific strain and previous history), age and gender, the time of day and year, the concentration of melatonin, and the type of melatonin receptors expressed, among other factors. The identification of the cell types responsive to melatonin may also provide useful information.

8.2.3 Melatonin effects in the gonads

Melatonin and melatonin-synthesizing enzymes are present in the in the gonads (Félix et al., 2023; Takahashi & Ogiwara, 2021), as well as melatonin receptors mRNA and ^{125}I-MEL binding sites (cf. Section 7.2.2) in the gonads (Chai et al., 2013; Chattoraj et al., 2009; Confente et al., 2010; Hong et al., 2014; Jin et al., 2013; López-Patiño et al., 2012; Molina-Borja et al., 1994; Moniruzzaman & Maitra, 2012; Ogawa et al., 2012; Sauzet et al., 2008).

Melatonin is present in seminal plasma of European sea bass, gilthead seabream, and Senegal sole (Félix et al., 2023). In all three species, blood levels of the hormone were much higher at night than during daytime; seminal levels were detected at night only in the seabream and Senegal sole, and at significantly lower levels than in the blood. A recent study reported seasonality of intratesticular melatonin concentration in relation to the dynamics of spermatogenesis in male walking catfish, where GSI and mature stages of germ cells (spermatids and spermatozoa) were positively associated with testicular melatonin levels (Acharyya et al., 2023). However, it remains to be determined whether seminal plasma melatonin detected in these studies comes from the circulation or local synthesis (Félix et al., 2023). In sea bass, all three *aanats* (*1a*, *1b,* and *2*) mRNA, but not *asmt* mRNA, have been identified in the ovary (Paulin et al., 2015), while both *aanat2* and *asmt* amplicons were obtained from goldfish gonadal extracts

(Velarde et al., 2010). In the medaka, local synthesis was suspected to occur in the preovulatory follicles of the ovary, which express *aanat1a* and *asmt* mRNA and the corresponding proteins were immunodetected on Western blots (Ogiwara & Takahashi, 2016). While *aanat1a* mRNA increased in the ovary 3–5 h prior to ovulation during the 24-h spawning cycle, the levels of *asmt2* mRNA remained constant. Ovarian melatonin levels displayed no LD rhythm and were equivalent to those measured during daytime in the blood. Only the addition of serotonin to granulosa cells (GC) in culture led to the detection of melatonin in the medium. PCR amplification of *tpoh*, *aanat1*, *aanat2,* and *asmt* was also obtained from zebrafish ovary and testis extracts, and AANAT and ASMT immunoreactivity were localized in frozen testis sections (Devi et al., 2022; Khan et al., 2016). In the testes, the amount of *tpoh*, *aanat1*, and *aanat2* transcripts had a rhythmic pattern, whereas that of *asmt* was arrhythmic, while in the ovary, *tpoh*, *aanat1,* and *asmt* mRNA abundance varied with the LD cycle (Devi et al., 2022). Altogether, these data strongly support the idea that melatonin is produced locally in the gonad where it could exert autocrine effects. In the medaka, the machinery for melatonin synthesis and Mel1c receptors colocalize in the GC of the ovary (Ogiwara & Takahashi, 2016). However, a clearer picture should be provided once the activity of the melatonin-synthesizing enzymes is measured from tissue extracts. It is worth mentioning that the kinetics of the different isoforms of AANATs differ significantly in terms of substrate affinity or temperature preferences. Thus, AANAT1 catalyzes the acetylation of catecholamines, as well as indolamines, and the latter induce inhibition of AANAT1 activity at high substrate concentrations (Benyassi et al., 2000; Falcón, Bolliet, & Collin, 1996). It has been proposed that the main substrate for AANAT1 in brain and peripheral tissues is dopamine (Nisembaum et al., 2013; Zilberman-Peled et al., 2006).

Melatonin action in the gonads seems to depend on the dose, species, reproductive status, and photoperiod condition. It seems to play different roles in the regulation of reproductive hormones in long-day (inhibitory) and short-day (stimulatory) breeders (Zhang et al., 2022). Melatonin effects in the ovary have been reviewed in depth recently, reflecting its modulatory actions on steroidogenesis, folliculogenesis, oocyte maturation, and ovulation (Takahashi & Ogiwara, 2021). Although a direct effect of melatonin on E_2 synthesis in teleost ovaries has not been reported (Takahashi & Ogiwara, 2021), a significant decrease in the androgenic 11-KT plasma levels was observed in female Atlantic eels treated with melatonin (Sebert et al., 2008). Moreover, melatonin treatment significantly induced the 17α,20b-dihydroxy-4-pregnen-3-one (DHP; a maturation-inducing hormone in teleost fishes) both in vivo and in vitro in the mudskipper (Hong et al., 2014). Although melatonin affects vitellogenin synthesis and ovarian vitellogenesis in fishes, these effects seem to be exerted through the BPG axis and not directly at the ovarian level. However, both the direct action of melatonin on the ovary and its indirect effects via the BPG axis seem to operate to promoting oocyte maturation and ovulation in teleost (Takahashi & Ogiwara, 2021). An influence of melatonin on the process of oocyte growth and maturation was reported in the tropical carp (Chattoraj et al., 2005, 2008; Maitra et al., 2005) and zebrafish (Carnevali et al., 2011). Oocyte growth of tropical carp was accelerated in the preparatory phase and retarded in the prespawning and spawning phases of the annual cycle by melatonin treatment (Mondal et al., 2017). Cooperative actions of melatonin (via MT1 receptors) and prostaglandin E2 (PGE_2) (via its Ptger4b receptor) appear necessary for follicle rupture and successful ovulation in medaka. Specifically, melatonin produced by the GC of preovulatory follicles ensures PGE_2 synthesis throughout the spawning cycle and induces actin cytoskeleton rearrangement in the follicular cells at ovulation (Ogiwara & Takahashi, 2016).

Melatonin affects testicular function, gametogenesis, and/or steroidogenesis in a number of teleost fishes. Melatonin is a progonadal key factor in the marine four-eyed sleeper, *Bostrychus sinensis*, promoting proliferation and differentiation of spermatogonia and functional sperm production, mainly by acting on MT1 receptor and through extracellular signal-regulated kinase 1/2 (Erk1/2) signaling (Zhang et al., 2022). In contrast, melatonin is inhibitory on testicular function in the longnose killifish, *Fundulus similis,* where it induced a decrease in GSI, but these effects varied with season and photoperiod (de Vlaming et al., 1974). In the tropical carp, the influence of melatonin on seasonal activity of the testis also varies in relation to reproductive status, inducing testicular maturation during the preparatory phase and inhibiting testicular functions during prespawning and spawning phases, although the testes did not respond to melatonin during the postspawning phase (Bhattacharya et al., 2007). Melatonin administration to mimic a short photoperiod stimulated testicular development in precocious masu salmon, increasing GSI and plasma T levels (Amano et al., 2000). However, high doses of orally administered melatonin had the opposite effect; i.e., it inhibited testicular maturation (Amano et al., 2004). A similar response was observed in the three-spined stickleback in which *i.p.* administration of a high melatonin dose-induced antigonadal effects in males maintained under long photoperiod conditions (Borg & Ekström, 1981).

9 CONCLUSIONS

With over 33,000 species, distributed in three classes, fishes represent by far the largest group of vertebrates, with a long

evolutionary history and a great diversity in habitats (i.e., pelagic, estuarine, shallow water, benthic, from tropics to polar regions). Accordingly, fish have been exposed to a variety of environmental conditions, including light intensity and spectral composition, photoperiod, temperature, salinity, water turbidity, food availability, pressure, and more. Thus, fishes have developed a great variability of sensory, physiological, and behavioral adaptations to meet different ecological challenges. They also exhibit the most diverse modes of reproduction among vertebrates, displaying differences in reproductive strategies (gonochorism, hermaphroditism [either protandrous, protogynous, bidirectional, or simultaneous]), modes of fertilization (external, internal, self-fertilization), mating systems (monogamy, polygyny, polyandry, promiscuity), parental care (no care, nest building, mouth cavity, brood pouches, protective horny egg capsules, viviparity) or in secondary sexual characteristics (size, tubercles, fat pad, fins shape [caudal, pelvic, pectoral, and/or anal], bony hooks on fin rays, ovipositor, coloration, etc.), among others. In order to ensure the best survival of progeny, reproduction must occur at the most favorable time of the day and year, which vary from a species to another. Accordingly, the timing of reproduction also differs among fish species with differences in daily (diurnal, crepuscular, and nocturnal) and seasonal (short-days, long-days) spawning times. Controlling these cyclic processes is better achieved with a timekeeper that allows synchronization to, and anticipation of, the cyclic changes in the environment. The pineal organ occupies a key position at the interface between the environment and the organism. By converting light and temperature information into a rhythmic neurohormonal message, the pineal keeps the body informed of the external daily and seasonal fluctuations.

The great fish diversity is also reflected at the level of the anatomy, cellular, and functional organization of the pineal gland. Tremendous progress has been made in our understanding of the fish pineal functional organization. The abundant in-depth investigations not only reinforce the already long list of analogies between this gland and the retina (O'Brien & Klein, 1986), they also provide indication of a more complex molecular, cellular, and functional diversity and organization than initially believed. This diversity results, at least in part, from the successive rounds of WGDs. The resulting duplication of genes, and subsequent neofunctionalization or loss of the duplicates, ultimately enriched the repertoire of genes, including those encoding opsins and components of the phototransduction cascade, circadian clock machinery, and the melatonin synthesis pathway. Thus, the role of the pineal gland in the fish circadian organization appears to differ significantly among species, from being a master clock sustaining all rhythmic processes and behaviors (e.g., locomotor activity) in some species, to being one among the organized central and/or peripheral pacemakers in other species. Similarly, the photoperiodic and circadian control of melatonin secretion varies greatly and the involvement of a circadian clock is not a general rule (lampreys and salmonids are well-known exceptions). In addition, the photoperiodic synchronization of the rhythm in melatonin production depends solely on the pineal in some species and solely on the eyes in others, while intermediate situations also exist. Altogether, there are reasons to believe there is as much diversity between early and distant fish, as there is between early and distant vertebrates (Collin, 1969, 1971).

Importantly, it appears that in addition to being light sensors, the photoreceptor cells of the fish pineal gland also sense temperature, i.e., they are "photo-thermo-receptors." The response to temperature seems to reflect, at least in part, specific constraints and adaptation to the fish habitat (Cazaméa-Catalan et al., 2012). The integration of the photo- and thermo-periodic information is reflected in the daily and seasonal rhythm of melatonin secretion, in a stronger and more accurate manner than with either factor alone. This information must be considered in future studies investigating the impact of the ongoing climate and temperature changes on timed neuroendocrine processes as is the case of reproduction ((Servili et al., 2020); cf. see Chapter 14, this volume). More investigation is certainly needed and on a larger number of species than those investigated so far, to further elucidate how the fish pineal gland transduces the temperature information and how it impacts the production of the nervous and neurohormonal messages and its relationship to thermosensitive regulatory centers found in other brain areas and the lateral line of fishes. Similarly, more information is needed on the internal factors known or suspected to modulate the production of melatonin (neuropeptides, neurotransmitters, neuromodulators, and steroids). These factors may represent elements of regulatory loops as is the case of, e.g., steroids or Kp for reproduction. There is suspicion that melatonin might also be produced in extra-pineal and extraretinal tissues, including brain, gut, liver, skin, and gonads, where it might act in an autocrine/paracrine manner. So far, information remains fragmentary and contradictory. Future investigations need to include the full characterization and localization of both AANAT and ASMT enzymatic activities, and their localization in the tissues of interest.

The effects of melatonin are mediated by a variety of receptors belonging to the GPCR family. Melatonin receptors are widely distributed in both central and peripheral tissues. In many brain areas, their sites of distribution overlap with those receiving pineal and/or retinal projections (POA, prethalamus/thalamus, pretectum, posterior tuberculum, optic tectum), suggesting their important role in integrating the periodic photo-thermic information.

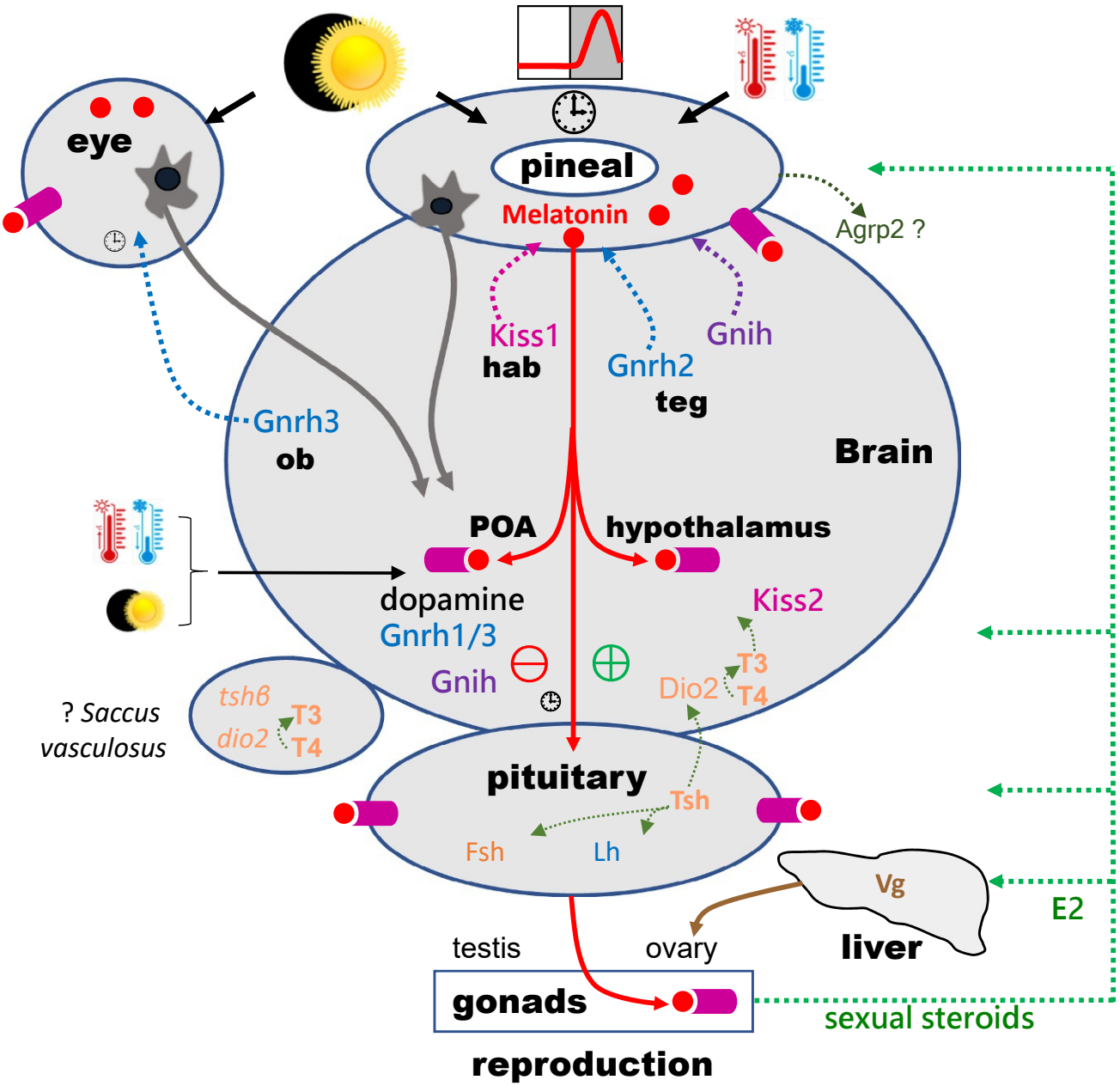

FIG. 14 Schematic presentation of the photo- and thermo-periodic regulation of the brain-pituitary-gonadal (BPG) axis. The photoperiodic (retina and pineal) and photo-thermo-periodic (pineal) information reach the neuroendocrine axis through nonvisual retinal and pineal nerve fibers (brown arrows) and pineal melatonin (red circles) released into the cerebrospinal fluid and circulation. Melatonin acts through specific receptors (purple boxes) found at all stages of the BPG axis. Deep brain thermoreceptors and photoreceptors might also operate in the basal telencephalon. Melatonin effects have been reported on the main preoptic (POA) and hypothalamic stimulatory (GnRH1/3, Kp2, ⊕) and inhibitory (GnIH, dopamine, ⊖) factors known to control fish pituitary gonadotropes (FSH and LH cells). At the pituitary level, melatonin also modulates the production of adenohypophysial hormones, including those involved in the control of reproduction, FSH, LH, and TSH. TSH from the pituitary may regulate FSH and LH productions via the pituitary folliculostellate cells and/or the brain deiodinase-2 (Dio2), which allows production of T3 (triiodothyronine) from T4 (thyroxine). FSH and LH act on the gonads (ovary and testis) to control the progress of gametogenesis and steroidogenesis. A feedback of gonadal steroids operates on the pineal gland, reproductive brain, and pituitary (green dotted lines). Estradiol (E_2) also acts on the liver of female fish to promote the synthesis and release of vitellogenin (Vg), which reaches the ovary through the vascular system and contributes to the progression of vitellogenesis. Moreover, nerve projections (colored dotted lines) from the habenula (hab), containing Kp1-producing cells, and mesencephalic tegmentum (teg), containing Gnrh2 and Gnih neurons, reach the fish pineal gland, whereas the retina receives Gnrh3 fibers originating from cells in the olfactory bulbs (ob). The *saccus vasculosus* (SV), present in some fish species, contains opsin proteins, Tsh and Dio2; it might also act as a sensor of seasonal changes in day length in some fish species. The pineal gland also produces AgRP2 (agouti-related peptide-2), although its function remains unknown. ◷: circadian clock machinery. For details and references, see text.

As fish move in a 3D environment, information from the horizontal plane is provided preferentially by the retina and that from the above preferentially by the pineal gland. The pineal provides two types of responses: a fast (milliseconds) response via the pineal nerve and a slow (hours and days) response via melatonin release. In contrast to melatonin, clear information regarding a potential role for the pinealofugal nerve on reproduction is lacking. The presence of melatonin binding sites and/or receptors in the photoreceptive organs (pineal and retina), and along the entire BPG axis brings strong support to the role of melatonin as a modulator of reproduction in fishes. The WGDs have also led to a diversification of these receptors, which display species-specific expression, distribution, and properties, as well as age or sex-dependent variations within the same species. This, together with the observation that the receptors display daily and annual variations in abundance and affinity, highlights the complexity of the system. Thus, understanding the effects of melatonin requires that investigations be carried out not only on the daily and seasonal profiles of its secretion, but also on those of its receptors in each tissue where these receptors are expressed, and perhaps also on the mechanism of melatonin clearance, which have never been considered to date.

It is necessary to identify the cell types that express melatonin receptors along the BPG axis, which ultimately control FSH, LH, and TSH synthesis and secretion. A recent investigation in the Atlantic croaker led to the hypothesis that melatonin modulation of gonadotropin production is indirect, and mediated by TSH cells responsive to the hormone (Royan et al., 2023). Finally, better knowledge is necessary concerning transduction pathways activated by melatonin receptors, considering also the possibility that these receptors may form homo and/or heterodimers with other GPCRs in a given cell type.

Finally, studies suggest that a TSH/deiodinase/thyroid hormone mechanism in the pituitary and brain acts as a photoperiodic signaling system controlling seasonal reproduction in birds and mammals (Nakane & Yoshimura, 2014). A TSH/Dio2 system may also operate in fishes. Nakane and Yoshimura (2014) suggest this is achieved through the *saccus vasculosus*, which contains opsins, TSH, and Dio2. Experimental evidence for this pathway is lacking, and many fishes do not possess a *saccus vasculosus* (Tsuneki, 1992). In Atlantic salmon, TSH from the pituitary did activate on Dio2 in midbrain, optic tectum and hypothalamus, to convert T_4 to T_3 but not in the *saccus vasculosus* (Irachi et al., 2021). In the medaka, there TSH may act locally on gonadotropes via the folliculostellate cells of the pituitary (Royan et al., 2023). These two examples suggest that the TSH/Dio2/T3 axis may be a common feature of photoperiodic regulation of seasonality in vertebrates, but the mechanisms of this proposed control seems to vary greatly among vertebrate species. The observation that melatonin modulates pituitary TSH production in the medaka and European sea bass (Falcón et al., 2021; Kawabata-Sakata et al., 2020; Royan et al., 2023) suggests a pineal/melatonin control of pituitary TSH exists in fishes. This does not exclude the possible involvement of deep brain photoreceptors, as well as direct actions of pineal melatonin at other levels of the BPG axis, as summarized Fig. 14. It can be assumed that different modalities of this control exist among the representatives of the largest group of vertebrates. The complexity of the melatonin impact on neuroendocrine regulations is part of the reasons why contrasting results have so often been obtained regarding its effects. It is becoming clear now that the effects of the pineal and melatonin on fish reproduction depend on the species and, within the same species, on a number of factors, such as previous history of the fish, development and aging, gender, time of day or year, concentration of melatonin, type of melatonin receptor(s) expressed, and more. In brief, we believe that for now, generalizations should be made with caution, and conclusions provided on a case-by-case basis.

ACKNOWLEDGMENTS

This contribution is in memory of Professor Jean-Pierre Collin (1936–2022), Endocrinologist at the University of Poitiers, France.

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Hormones and Reproduction of Vertebrates, Volume 1
Fishes

Second Edition

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An imprint of Elsevier

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125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

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ISBN: 978-0-443-16009-7

Publisher: Mara Conner
Acquisitions Editor: Simonetta Harrison
Editorial Project Manager: Andrea Dulberger
Production Project Manager: Fahmida Sultana
Cover Designer: Vicky Pearson Esser
Cover Art: Photo from Shutterstock. A male and female sockeye salmon, *Oncorhynchus nerka*, in full breeding dress.

Typeset by STRAIVE, India