Chapter 13
Molecular Mechanisms of the Function of Pineal Organs

Daisuke Kojima and Yoshitaka Fukada

Abstract The pineal organ in nonmammalian species is a light-sensitive brain structure mediating photosensory and photoendocrine functions. This chapter reviews the photopigments and the phototransduction pathways in the pineal organs of chicken, teleosts, and lamprey and those in the pineal-related organ, the parietal eye, of lizard. Chicken pinealocytes contain a rhodopsin-like molecules, pinopsin, which activates a G protein, transducin, in a light-dependent manner resulting in acute suppression of melatonin synthesis within the cells. Pinopsin is dominantly expressed in the avian and reptilian pineal organs, whereas teleost pineal organs have another rhodopsin-like molecule, exo-rhodopsin, instead of pinopsin. The pineal organs of lampreys exhibit antagonistic responses to green and UV light at the interneuron level: This UV response is mediated by parapinopsin in the photo-receptor cells. In lizards, the parietal eye photoreceptor cells show antagonistic responses to green and blue light at the photoreceptor cell level: parietopsin and pinopsin are likely to antagonistically regulate a cGMP pathway to elicit the responses. This chapter also introduces a more recent topic on a new pineal function as producing a neurosteroid, 7α-hydroxypregnenolone, that regulates behavioral activities in some species.

Keywords 7α-Hydroxypregnenolone • Exo-rhodopsin • Parapinopsin • Parietopsin • Pinopsin

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13.1   Introduction

The pineal organ is an isolated brain structure and, in most non-mammalian vertebrate species, it is present in the dorsal brain just under the skull (Oksche 1965). The pineal organ of many nonmammalian vertebrates is sensitive to light because the pineal organ contains photoreceptor cells that respond to changes in ambient light condition, sending light information via neural connections to other neurons and secreting melatonin into circulating blood. In avian and mammalian species, the pineal organ functions as a neuroendocrine and/or photoendocrine gland. The mammalian pineal gland is not sensitive to light directly but its activity is indirectly regulated by the ambient light–dark information, which is transmitted from the retina via several neural connections (Klein 1985; Simonneaux and Ribelayga 2003).

The pineal organs of nonmammalian vertebrates generally consist of three basic cell types: photoreceptor cells (pinealocytes), projection neurons, and glial cells (Ekstrom and Meissl 2003). In lamprey, teleosts, and amphibians, the pineal photoreceptor cells have a well-developed lamellar outer segment that closely resembles those of retinal rod and cone photoreceptor cells. The photoreceptor cells transmit the light signals to the secondary afferent neurons (projection neurons) through synaptic contacts within the pineal organ. The projection neurons innervate several areas of the central brain, and in this sense they are similar to the retinal ganglion cells. The pinealocytes of reptiles and birds have a regressed outer segment with degenerated lammellar structure, and they are thus refered as "modified" photoreceptor cells. Most of the modified photoreceptor cells act as neuroendocrine cells specialized for secreting melatonin, rather than primary sensory cells. Note that mammalian pinealocytes, having no direct light sensitivity, lack any pronounced outer segment-like structure and instead function as specialized neuroendocrine cells (Ekstrom and Meissl 2003).

Physiological functions for the pineal organs have been reported mainly in circadian biologies. For example, surgical removal of the pineal gland from oscine passerine birds, such as the house sparrow (*Passer domestics*), abolishes the expression of circadian locomotor rhythms when birds are placed in constant darkness (Gaston and Menaker 1968), although the effects of pinealectomy are variable in other avians (Cassone et al. 2009). The pineal gland also plays a role in keeping a circadian rhythm of body temperature (Refinetti and Menaker 1992).

In some vertebrate species, such as lampreys and teleosts, the pineal organ constitutes a structural unit of a pineal complex with an accessory organ called the parapineal organ, which is also photosensitive. Some lizards have an extracranial photosensory organ, called the parietal eye or parietal organ, which is considered as a parapineal organ homologue (Ekstrom and Meissl 2003). Another example of extracranial photosensory organs is the frontal organ in frogs, but in this case it is likely to to be a specialization of the distal part of the pineal organ (Ekstrom and Meissl 2003).

In this chapter, we review the photopigments and the phototransduction pathways of chicken and teleost pineal organs. We then discuss the photopigments

in the lamprey pineal complex, in which light signals sent from multiple photoreceptor cells having different spectral sensitivities are likely to be converged at the level of interneurons exhibiting "chromatic" photoresponses. We also review the antagonistic phototransduction pathway of lizard parietal eye photoreceptor cells, where light signals from multiple photopigments are converged within the photoreceptor cells. Finally, a more recent topic is introduced on a new pineal function as producing a neurosteroid, 7α-hydroxypregnenolone, that regulates behavioral activities in some species.

13.2 Photopigments and Phototransduction Pathways in Pineal and Related Organs

13.2.1 Avian Pineal Gland

The intrinsic photosensitivity in the chicken pineal gland was reported in the late 1970s (Binkley et al. 1978; Deguchi 1979a,b,c; Kasal et al. 1979), and the presence of rhodopsin-like molecule(s) in the pineal gland was predicted by immunohistochemical and physiological studies in the 1980s. In 1994, a rhodopsin-like photoreceptive molecule, pinopsin, was identified in the chicken pineal gland (Okano et al. 1994) as the first example of a "nonvisual" opsin expressed in a tissue outside the retina. Pinopsin is closely related to vertebrate visual pigments in the primary structure (Fig. 13.1), and binds 11-*cis*-retinal as the chromophore to form a blue-sensitive pigment having the absorption maximum at 468 nm (Okano et al. 1994; Nakamura et al. 1999).

The absorption maximum of pinopsin is ~30 nm blue-shifted from the peak of the physiological action spectrum (500 nm) for light-induced inhibition of chicken pineal arylalkylamine *N*-acetyltransferase (Deguchi 1981), a rate-determining enzyme in the melatonin synthesis pathway. This difference suggested that the chicken pineal gland contains at least one additional photoreceptive molecule having longer wavelength sensitivity, such as red cone opsin, and it is indeed expressed in the pineal gland (Okano et al. 1994).

Chicken pinopsin is expressed only in the pineal gland (Okano et al. 1994; Max et al. 1995). Pinopsin protein is localized in the outer segment of pinealocytes (Hirunagi et al. 1997; Matsushita et al. 2000), which is considered as the primary photosensitive structure and likely to contain phototransduction proteins just as in the outer segments of retinal rods and cones (see following).

The chicken pineal gland has intermediate properties between a neuroendocrine and photoendocrine organ, producing and secreting melatonin in a manner dependent on both the efferent input signal and the light signal captured by intrinsic photoreceptors. Melatonin is a nighttime hormone involved in a variety of physiological aspects such as sleep–wake regulation. Melatonin production shows a
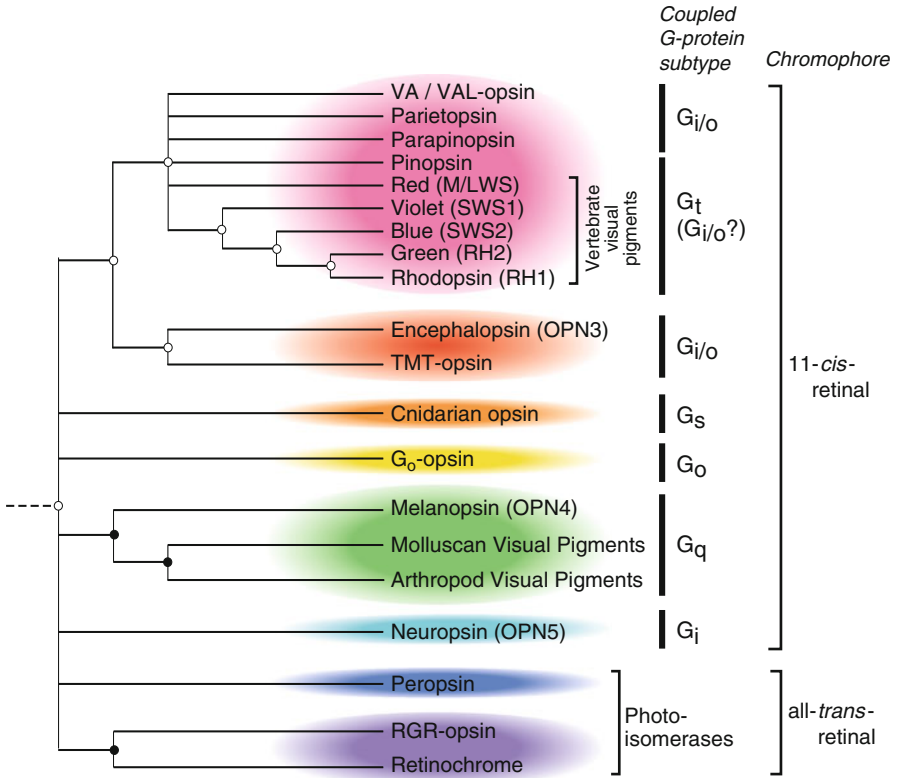
Fig. 13.1 Phylogenetic relationship among subfamilies in the opsin family. Nomemclatures for vertebrate visual pigments (M/LWS, SWS1, SWS2, RH2 and RH1) are indicated in parentheses according to Ebrey and Koutalos (2001)). Each node with a *closed circle* represents species divergence; *open circle* represents gene duplication. (Modified from Kojima et al. 2008)

nocturnal rhythm, which is controlled by the endogenous circadian clock in individual cells (pinealocytes) of the pineal gland. The phase of the circadian rhythm is shifted by light given at subjective night (phase-shifting effect; see Fig. 13.2). On the other hand, the chicken pinealocytes contain another phototransduction pathway mediating acute suppression of melatonin production by light (acute suppression effect; see Fig. 13.2). These two effects of light on chicken pineal cells can be discriminated by an administration of pertussis toxin (PTX). The PTX treatment does not influence the phase-shifting effect of cellular clocks but blocks the acute suppression effect on melatonin production (Zatz and Mullen 1988), indicating the the latter effect is mediated by PTX-sensitive molecules, most probably by a PTX-sensitive heterotrimeric GTP-binding protein (G protein). Consistently, the chicken pineal gland shows mRNA expression of α-subunits of PTX-sensitive G proteins, such as $G\alpha_{t1}$ (rod transducin-α), $G\alpha_{i2}$, $G\alpha_{i3}$, and $G\alpha_o$
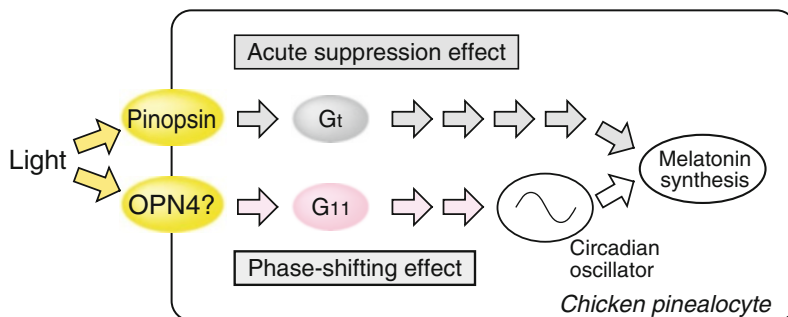
Fig. 13.2 Light signaling pathways in chicken pineal photoreceptor cells

(Okano et al. 1997; Matsushita et al. 2000; Kasahara et al. 2000). The rod-type transducin, G_{t1}, is activated by chicken pinopsin in a light-dependent manner in in vitro reconstitution assays as well as in the pineal homogenate (Max et al. 1998; Nakamura et al. 1999; Kasahara et al. 2000) and is colocalized with pinopsin in the "rudimentary" outer segment of pinealocytes (Matsushita et al. 2000; Kasahara et al. 2000). Taken together, the pinopsin-transducin (G_t) pathway is likely to be involved in the pineal phototransduction cascade and to account for the acute suppression effect of light in the melatonin production of the pinealocytes (Fig. 13.2).

The PTX-sensitive acute effect of light might be mediated by another photopigment, OPN5 (OPN5m), which has been recently reported to be present in chicken pineal glands (Yamashita et al. 2010). OPN5 is an ultraviolet light (UV)-sensitive photopigment and can activate G_i-type G protein in a UV-dependent manner (Yamashita et al. 2010; Kojima et al. 2011). $G_{i/o}$-type G proteins, being susceptible to PTX, are expressed in the pineal gland (Okano et al. 1997), although a direct effect of ultraviolet light on melatonin production in the chicken pineal gland has not been reported.

As just described, the circadian rhythm of melatonin production in the chicken pinealocytes is phase shifted by light in a PTX-"insensitive" manner (Zatz and Mullen 1988). Several classes of heterotrimeric G proteins, such as $G_{q/11}$ and G_s, are insensitive to PTX treatment as they lack the (PTX-catalyzed) ADP-ribosylated amino acid in the C-terminal region. Among these members, the α-subunit of G_{11} ($G\alpha_{11}$) is expressed in the chicken pineal gland (Matsushita et al. 2000; Kasahara et al. 2002). In a gain-of-function experiment using cultured chicken pinealocytes, selective activation of G_{11} caused phase shift of the circadian rhythm of melatonin production in a manner very similar to a light-triggered phase shift (Kasahara et al. 2002). G_{11} is thus likely to mediate the circadian phase-shifting effect in chicken pinealocytes (Fig. 13.2). Now an important question is the identities of photopigments triggering this pathway. There has been no report on activation of $G_{q/11}$-type G protein mediated by pinopsin, red cone opsin, or Opn5, although chicken rhodopsin can interact with $G\alpha_{11}$ in a light-dependent manner (Kasahara et al. 2002). It should be noted that vitamin A depletion in the culture medium only

reduces the acute melatonin supression but does not affect the circadian phase shift (Zatz 1994). Therefore, the two phototransduction pathways (Fig. 13.2) causing acute melatonin supression and the circadian phase shift in the chicken pineolocytes are likely to couple with different photopigments from each other. A potential candidate for the phase-shifting photopigment is OPN4, or melanopsin (Bailey and Cassone 2005; Chaurasia et al. 2005; Holthues et al. 2005; Bellingham et al. 2006; Torii et al. 2007), which is closely related in sequence to invertebrate G_q-coupled rhodopsins (Fig. 13.1). Invertebrate rhodopsins as well as the cepholochordate melanopsin homologue have been shown to activate G_q-type G protein in a light-dependent manner (Koyanagi et al. 2005; Terakita et al. 2008). The photoproduct (active state) of OPN4 is stable in the dark, and it is photo-convertible to the original state without further supply of its chromophore 11-*cis*-retinal. Such a bistable nature of OPN4 is consistent with the fact that the circadian phase-shifting pathway does not require a vitamin A supply in the pineal cell culture (Zatz 1994). The chicken pineal gland expresses two kinds of melanopsin genes, OPN4-1 (OPN4x) and OPN4-2 (OPN4m) (Bailey and Cassone 2005; Chaurasia et al. 2005; Holthues et al. 2005; Bellingham et al. 2006; Torii et al. 2007). The OPN4-1 and OPN4-2 genes encode blue-sensitive photopigments with absorption maxima at 476 and 484 nm, respectively (Torii et al. 2007). It is not known whether any of these OPN4 proteins contributes to the phase shift in the chicken pineal gland.

13.2.2 Teleost Pineal Organ

In contrast to pinopsin expression in the pineal gland of birds (Okano et al. 1994; Max et al. 1995; Kawamura et al. 1999) and reptiles (Kawamura and Yokoyama 1997; Taniguchi et al. 2001), the pineal organ of teleosts does not express pinopsin but it has, instead, a novel rhodopsin-like molecule, exo-rhodopsin (named after extraocular rhodopsin). The exo-rhodopsin was first identified in the zebrafish pineal gland (Mano et al. 1999), and later in the pineal gland of salmon (Philp et al. 2000a) and other teleosts. In zebrafish, exo-rhodopsin is specifically expressed in the pineal gland (but not in the retina), whereas rhodopsin is specifically present in the retinal rod photoreceptor cells but not in the pineal gland (Mano et al. 1999). Such mutually exclusive expression patterns between exo-rhodopsin (pineal gland) and rhodopsin (retina) were also reported in salmon (Philp et al. 2000a). A detailed mutational analysis of the zebrafish *exo-rhodopsin* promoter led to identification of a 12-bp *cis*-acting element, PIPE (p̲ineal expression-p̲romoting e̲lement), that is required for pineal specific gene expression (Asaoka et al. 2002).

Molecular phylogenetic analyses clearly indicate that the *exo-rhodopsin* gene emerged from the *rhodopsin* gene by gene duplication in the ray-finned fish lineage (Mano et al. 1999; Bellingham et al. 2003; Rennison et al. 2012). Interestingly, the teleost *exo-rhodopsin* genes retain the exon-intron structure that is conserved among the tetrapod *rhodopsin* genes, whereas the teleost *rhodopsin* genes are intronless.
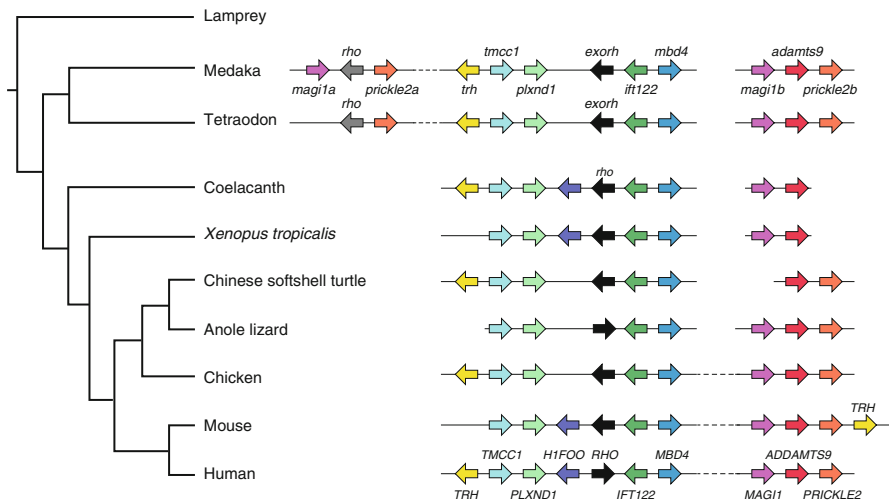
Fig. 13.3 Genome synteny of chromosomal regions containing vertebrate *rhodopsin/exo-rhodopsin* genes. In the genomes of teleosts (medaka and tetraodon), the *exo-rhodopsin* gene (*exorh*) is located between *plxnd1* and *ift122* loci. The *plxnd1-exorh-ift122* arrangement shows a synteny to the chromosomal region containing the *rhodopsin* gene in the coelacanth and tetrapods including humans (*PLXND1-H1FOO-RHO-IFT122*). Note that the teleost *rhodopsin* gene locus (*rho*) is located adjacent to *prickle2a* and *magi1a* loci, which appear to have emerged by a whole-genome duplication event in the teleost lineage. (From Taylor et al. 2003)

These observations suggest that a retroposition occurred in the teleost "*rhodopsin*" gene lineage just after the *exo-rhodopsin* gene had arisen (Bellingham et al. 2003). In this sense, *exo-rhodopsin* may be the true orthologue of tetrapod *rhodopsin* (Bellingham et al. 2003), and this idea is supported by a synteny analysis of *rhodopsin/exo-rhodopsin* genes (Fig. 13.3).

The zebrafish pineal gland also expresses the red cone opsin gene in a smaller subset of the cells (Robinson et al. 1995; Mano et al. 1999), whereas most of the zebrafish pineal photoreceptor cells express exo-rhodopsin (Mano et al. 1999). As are most of the vertebrate rhodopsins, exo-rhodopsin is a green-sensitive photoreceptive molecule having its absorption maximum at 498 nm (Tarttelin et al. 2011). The zebrafish red cone opsin, LWS1 or LWS2, has its absorption maximum at 558 nm (LWS1) or 548 nm (LWS2) (Chinen et al. 2003). Consistently, light-induced suppression of melatonin release measured in cultured zebrafish pineal glands has a spectral sensitivity peaking at ~500 nm with a shoulder at ~570 nm, suggesting that multiple photopigments including exo-rhodopsin and red cone opsin are involved in this response (Ziv et al. 2007). On the other hand, the pineal gland of rainbow trout showed an action spectrum of melatonin suppression, peaking at ~500 nm without any obvious shoulder in the longer-wavelength region (Max and Menaker 1992), and it also showed maximal sensitivity between 500 and 530 nm in electrophysiological recordings of photoresponses of projection neurons and photoreceptor cells (Dodt 1963; Meissl and Ekstrom 1988). The difference in

spectral sensitivity at a longer-wavelength region between zebrafish and trout pineal glands may reflect species variation in the composition of photoreceptive molecules whose identities have not yet been reported in the trout pineal gland. As an example of species variation, VA-opsin gene expression was detected in the 'salmon' pineal gland (Philp et al. 2000b) but not in the 'zebrafish' pineal gland (Kojima et al. 2000; Ziv et al. 2007).

With light illumination, exo-rhodopsin, similar to rhodopsin, is converted into its active state, meta II, which was shown to activate G-protein transducin in vitro (Tarttelin et al. 2011). As in the chicken pineal photoreceptor cells, transducin is likely to mediate the light-induced melatonin suppression in the pineal gland of teleosts, where immunoreactivity to the α-subunit of transducin was detected (van Veen et al. 1986). The meta II state of exo-rhodopsin has a lifetime more than tenfold shorter than that of meta II of rhodopsin (Tarttelin et al. 2011), which is a characteristic rather similar to cone opsins (Shichida and Imai 1998). This molecular behavior of exo-rhodopsin was in contrast to the prediction, because exo-rhodopsin is more similar to rhodopsin than to cone opsins in its primary structure (Mano et al. 1999), including the determinant amino acid residues for meta II lifetime of rhodopsin, Glu122, and Ile189 (Imai et al. 1997; Kuwayama et al. 2002). The structural basis for the shorter meta II lifetime for exo-rhodopsin appears quite different from the cone opsins but remains unsolved (Tarttelin et al. 2011).

13.2.3 Lamprey Pineal Complex

The lamprey has a pineal complex consisting of the pineal body in the dorsal part and parapineal body in the ventral part. The pineal body is located just under the pineal window, which is a less-pigmented part of the skull. The ventral portion of the pineal body shows immunoreactivities to rhodopsin antibody (Tamotsu et al. 1990) and rhodopsin mRNA expression (Koyanagi et al. 2004). Expression of the rhodopsin gene is consistent with the fact that the ventral pineal body has achromatic (luminosity-type) interneurons, which are maximally sensitive to green light (Morita and Dodt 1973; Uchida and Morita 1994). These observations suggest potential signal inputs from the rhodopsin-expressing photoreceptor cells to the luminosity-type interneurons. On the other hand, the dorsal and peripheral portion of the lamprey pineal body expresses a UV-sensitive opsin, parapinopsin (Koyanagi et al. 2004), which was originally identified in the catfish parapineal organ (Blackshaw and Snyder 1997). The lamprey parapinosin shows a bistable nature such that it is converted with UV light illumination to a thermally stable, green-sensitive photoproduct, which can be converted with green light illumination again to the original, UV-sensitive state (Koyanagi et al. 2004). The existence of the UV-sensitive pigment is consistent with the fact that the lamprey pineal body

contains "chromatic"-type interneurons, whose activity is inhibited maximally by 380-nm UV light but enhanced by 540-nm green light (Morita and Dodt 1973; Uchida and Morita 1994). The inhibitory action of the UV light on the chromatic-type interneurons is likely to be mediated by the parapinopsin-expressing cells, whereas the excitatory action of green light is unlikely to originate from rhodopsin-expressing cells in the ventral pineal body but could be mediated by unidentified photopigments, which must be present in the dorsal and peripheral portion of the lamprey pineal gland.

The parapineal body of the lamprey, as does the pineal body, has rhodopsin expression in the ventral part and parapinopsin expression in the dorsal part (Kawano-Yamashita et al. 2007; Koyanagi et al. 2004). In addition to rhodopsin and parapinopsin, red cone opsin immunoreactivities are observed in the pineal and parapineal bodies of lamprey (Tamotsu et al. 1994; Koyanagi et al. 2004). Some of the red cone opsin-immunoreactive signals were observed in the serotonin-containing pineal neurons (Tamotsu et al. 1994).

13.2.4   Reptile Parietal Organ

The parietal eye in reptiles is an extracranial photoreceptive organ that is considered to be a parapineal organ homologue (Ekstrom and Meissl 2003). Similar to vertebrate lateral eyes, the parietal eye has a retina-like layered structure, which consists of two cellular layers: the inner layer has photoreceptor cells and the outer has ganglion cells. In contrast to lateral eyes, the parietal eye has no interneurons, but the ganglion cells exhibit antagonistic chromatic responses (Dodt and Scherer 1968; Miller and Wolbarsht 1962): Green light induces an excitatory response in the parietal ganglion cells, whereas blue light causes an inhibitory response. The spectral sensitivities of these responses peak at ~520 nm (excitatory) and at ~450 nm (inhibitory) in the European lizard *Lacerta sicula campestris* (Dodt and Scherer 1968). The antagonistic chromatic response was found to originate from the individual photoreceptor cells in the parietal eyes of the desert night lizard *Xantusia vigilis* and the side-blotched lizard *Uta stansburiana* (Solessio and Engbretson 1993). In the parietal photoreceptor cells, green light depolarizes the membrane potential by increasing Na^+ conductance, and blue light on the background green illumination hyperpolarizes it by decreasing Na^+ conductance (Solessio and Engbretson 1993). It was proposed that the antagonistic nature of these photo-responses may provide lizards with a mechanism for enhanced detection of dawn and dusk (Solessio and Engbretson 1993).

The green light-induced depolarization in the parietal eye photoreceptor cells arises from openings of the cGMP-gated (CNG) cation channels located in their outer segments, and they are similar in properties to those found in retinal rod photoreceptor cells (Finn et al. 1997). The CNG channel openings in the parietal

Fig. 13.4 Antagonistic
phototransduction pathway
in the parietal eye
photoreceptor cells
of side-blotched lizards.
CNG channel, cGMP-gated
cation channel
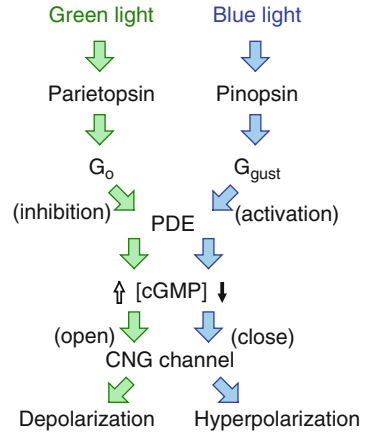
eye photoreceptor cells result from a rise in intracellular cGMP caused by a
decrease in activity of phosphodiesterase (PDE), which hydrolyzes cGMP, rather
than an increase in activity of guanylyl cyclase synthesizing cGMP (Xiong
et al. 1998). It is proposed that PDE activity is regulated by a G protein (putatively
termed G_1, active in the dark) and is antagonistically inhibited by another G protein
(G_2) activated by light (Xiong et al. 1998). It remains unknown whether the G_1 is
constitutively active or is activated by an upstream signal in the dark.

Consistent with the presence of two antagonistic light signaling pathways
(Fig. 13.4), the parietal eye photoreceptor cells of side-blotched lizards were
found to have blue- and green-sensitive photoreceptive molecules (opsins) in the
same cells (Su et al. 2006): The blue one was pinopsin, originally found in
the chicken pineal gland (Okano et al. 1994), and the green one was named
parietopsin, having an absorption maximum at 522 nm with 11-*cis*-retinal bound.
Interestingly, the parietal eye photoreceptor cells have two kinds of G-protein
α-subunits, $G\alpha_{gust}$ and $G\alpha_o$, but do not have transducin-α (Su et al. 2006). Electro-
physiological and pharmacological examination suggested that the $G\alpha_o$ inhibits the
PDE to generate the depolarizing response to green light, probably via activation by
parietopsin (Su et al. 2006) (Fig. 13.4). On the other hand, the structural similarity
of pinopsin to rod/cone opsins together with the close similarity among $G\alpha_{gust}$ and
$G\alpha_{t1/2}$ (transducin-α) suggested the hypothesis that the blue-light induced hyper-
polarization in parietal eye photoreceptor cells could be mediated by a pinopsin-
$G\alpha_{gust}$ pathway via PDE activation (Su et al. 2006) (Fig. 13.4). It should be noted
that the parietal eye photoreceptor cells in another lizard, the green iguana (*Iguana
iguana*), contain a combination of parietopsin and UV-sensitive opsin,
parapinopsin, instead of pinopsin (Wada et al. 2012), indicating species variation
in the opsin repertoire of the parietal eye photoreceptor cells among reptiles.

13.3   Light-Dependent Synthesis of 7α-Hydroxypregnenolone in Chicken Pineal Gland

The chicken pineal gland has been recently found to actively produce a neurosteroid hormone, 7α-hydroxypregnenolone (Hatori et al. 2011). This finding came from our pineal transcriptome analysis that aimed at understanding molecular mechanisms underlying light-dependent regulation of the circadian clock. The pineal transcripts prepared from dark-reared chicks or those exposed to light at various times of the day were subjected to a differential microarray analysis to search for the genes important for the light-dependent phase shift of the clock. This global transcriptome analysis revealed light-induced transcriptional activation of a set of genes involved in cholesterol biosynthesis (Hatori et al. 2011) along with upregulation of a transcript for *E4bp4*, a clock transcription factor gene that is known to repress *Per2* gene expression and hence associated with the phase delay of the chick pineal clock (Doi et al. 2001; Doi et al. 2004) (Fig. 13.5). The light induction of these genes turned out to be regulated by light activation of the transcription factor, sterol regulatory element-binding protein SREBP (Hatori et al. 2011) (Fig. 13.5). From these observations, a possibility emerged that pineal cholesterol biosynthesis is activated by light. In fact, we found that the chick pineal gland produces and secretes 7α-hydroxypregnenolone (Fig. 13.5) in organ culture in a light-stimulated manner (Hatori et al. 2011). It should be noted that the light stimulation of 7α-hydroxypregnenolone production occurs only at a specific time of the day: that is, this steroid production was not activated by light at late night nor during daytime but by light given at early night (Hatori et al. 2011), which is the time when the circadian clock is phase delayed by light exposure (Okano and Fukada 2003). Interestingly, locomotor activities of dark-reared chicks are stimulated far more strikingly by light exposure at early night when compared to light/dark ratios at late night and in daytime (Hatori et al. 2011) (Fig. 13.5). It is well
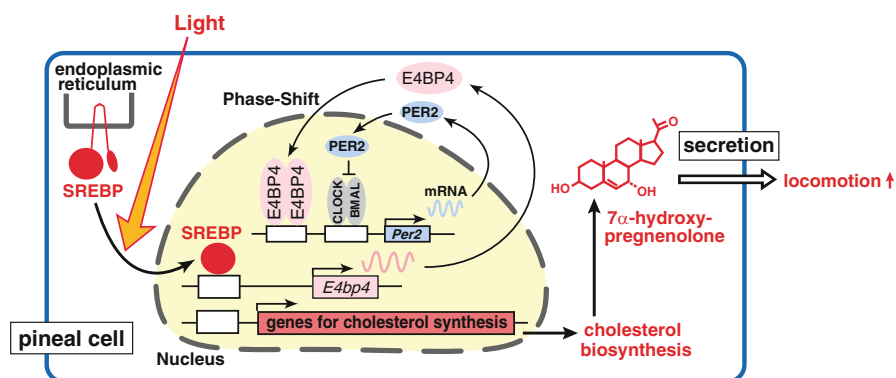

Fig. 13.5 Light-stimulated production of pineal cholesterol biosynthetic genes is associated with light-stimulated production of 7α-hydroxypregnenolone. (Modified from Hatori et al. 2011)

established that the canonical pineal hormone melatonin regulates sleep rhythms (Arendt and Skene 2005). The pineal gland appears to participate in the regulation of the sleep–wake state, not only by circadian production of melatonin in the dark but also by synthesis and secretion of 7α-hydroxypregnenolone in the light.

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