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Abstract: In 1963, it was suggested [Sperry, R.W. (1963). Chemoaffinity in the orderly growth of nerve fiber patterns and connections. Proc. Natl. Acad. Sci. USA *50*, 703–710.] that molecular cues can direct the development of orderly connections between the eye and the brain (the "chemoaffinity hypothesis"). In the same year, the amazing degree of functional accuracy of the visual pathway in the absence of any external light/photon perception prior to birth [Wiesel, T.N and Hubel, D.H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. J. Neurophysiol. *26*, 1003–1017.] was discovered. These recognitions revealed that the wiring of the visual system relies on innate cues. However, how the eye-specific retinogeniculate pathway can be developed before birth without any visual experience is still an unresolved issue. In the present paper, we suggest that Müller cells (functioning as optical fibers), Müller cell cone (i.e. the inner half of the foveola that is created of an inverted cone-shaped zone of Müller cells), discrete retinal noise of rods, and intrinsically photosensitive retinal ganglion cells might have key functions by means of retinal spontaneous ultraweak photon emission in the development of eye-specific retinogeniculate pathways prior to birth.

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Introduction

The retina is an extension of the brain, structured embryonically from neural tissue. Sperry (1963), as well as Wiesel and Hubel (1963), revealed that the wiring of the visual system relies on innate cues. The development and appearance of retinogeniculate pathways take place prior to birth in the absence of external light/photon perception. It has been suggested that the prenatal development of retinogeniculate pathways involves activity-dependent mechanisms driven by spontaneous retinal waves (Feller, 2009; Gjorgjieva and Eglen, 2011), which is, however, controversially debated (Chalupa, 2007, 2009). The exact role of retinal waves and the question if these may perform an instructive or a permissive role in the construction of eye-specific projections in the retinogeniculate pathways are not clear yet. To resolve this issue, we recently suggested (Bókkon and Vimal, 2013) a possible mechanism involving the continuous production of spontaneous ultraweak photon emission (UPE) caused by natural retinal lipid peroxidation that might have an instructive role in early development of the retinogeniculate pathways as well as the initial appearance of the topographic organizations of the primary visual cortex (V1) before birth. Here, we expand our idea and point out that Müller cells (functioning as optical fibers as shown by Franze et al., 2007), Müller cell cones (i.e. the inner half of the foveola that is created of an inverted cone-shaped zone of Müller cells; Gass, 1999), discrete retinal noise by rods (Firsov et al., 2002), as well as intrinsically photosensitive retinal ganglion cells (ipRGCs) (Pickard and Sollars, 2012) might have key functions based on the occurrence of retinal UPE (Wang et al., 2011) in the development of eye-specific retinogeniculate pathways prior to birth.

Müller cells

There are two types of macroglial cells in the vertebrate retina: Müller cells and astrocytes. Müller cells are the most common type of glial cells having a particular radial form that spans the entire thickness of the retina (Kumar et al., 2013). Müller cells are rather regularly distributed within the retina (Dreher et al., 1998). These cells are responsible for the homeostatic and metabolic support of retinal neurons. Müller cells perform several functions that are essential to the health of the retinal neurons. These functions include, for example, retinal glucose metabolism; neurotransmitter recycling/mediation; maintenance of the blood-retinal barrier; maintenance of survival of photoreceptors and neurons; performance of neuronal degeneration processes; mediation of transcellular ion, water, and bicarbonate transports; mediation of the extracellular space fluid; and being a source of stem cells (Bringmann et al., 2009; Reichenbach and Bringmann, 2013). Müller cells interact with all neurons in the retinal tissue and directly take part in the regulation of synaptic activity in the inner retina (de Melo Reis et al., 2008a). Trophic factors of Müller cells can regulate numerous functions of neuronal processes such as synaptogenesis, neuroprotection, and photoreceptor survival as well as neuron-glia interactions in the retina (de Melo Reis et al., 2008b; Ruzafa and Vecino, 2015).

Müller cells, *N*-methyl-D-aspartate receptors, and glutamate

Glutamate (glutamic acid) is the most prevalent excitatory neurotransmitter in the mammalian brain as well as in the retina (Récasens et al., 2007). There are two major classes of glutamate receptors (GluRs, G-protein-coupled receptors): metabotropic GluRrs and ionotropic GluRs (Willard and Koochekpour, 2013). When the presynaptic terminal releases glutamate, it binds to the postsynaptic glutamate receptors that produce the influx of Na^+ and Ca^{2+}, which create membrane depolarization. The *N*-methyl-D-aspartate receptor (NMDAR) is a subtype of ionotropic glutamate receptors that has important functions in the experience-dependent plasticity of the developing visual system.

In the developing retina, the neurotransmitter glutamate is expressed early. This implies that it has important functions in the emergence of specific retinal circuits (Chang et al., 2010). In addition, in the developing rat retina, the NMDARs can play essential roles in mediating neural plasticity. Within the retina, the synaptic complexes are surrounded by Müller cell sheets, and Müller cells are surrounded by glutamatergic and GABAergic synapses (Boulland et al., 2002). It is well known that communication between neurons is mediated by neurotransmitters; however, there is increasing evidence that neurotransmitters also affect glia cells. Puro et al. (1996) studied the effects of the glutamate agonist NMDA on Müller cells, which revealed that monoclonal antibodies, specific for the NMDAR1 subunit, were expressed by human Müller cells.

In darkness, the outer part of the retina continuously releases glutamate from photoreceptors, and this release can be regulated by light (Dowling and Ripps, 1972; Murakami et al., 1972; Rauen and Wiessner, 2000). Chang et al. (2010) reported that the expression of NR1 and NR2A/B receptor subunits of NMDAR was independent of visual experience and that light deprivation did not influenced the functional NMDARs in the developing retina of the rabbit.

Müller cell cone

The *macula lutea* is a yellowish central portion of the retina about 5.5 mm in diameter. The *fovea centralis* (or fovea) is the center of the macula, which is approximately 1.5 mm in diameter. In this area of the retina, there are only cone photoreceptors and no rods present. The foveola is about 0.35 mm in diameter and is placed in the center of the fovea with only cone cells.

It is a misconception that the foveola is completely composed of retinal cone cells (Gass, 1999). In 1969, Yamada investigated the fovea centralis by light and electron microscopy in the eye of a 45-year-old woman. Yamada pointed out that the inner half of the foveola consists of an inverted cone-shaped zone of Müller cells (also called Müller cell cones). The Müller cells' cytoplasm was found to have low density within the cone, but in contrast, it had a greater density elsewhere in the retina where the Müller cells were closely intertwined with the receptor neurites. The Müller cells' cytoplasm, composing the outer portion of the Müller cell cone, was optically empty. The internal limiting membrane lining the inner surface of the Müller cell cone was 10–20 nm thick and the peripheral foveal area was 1.5 μm. The Müller cell cone was free of neurites except near its apex, where the long outer cone fibers extended from the outer limiting membrane anteriorly and outwardly in a radiating fashion through the Müller cell cytoplasm into the surrounding cone nuclei. Later, Hogan et al. (1971) confirmed Yamada's findings.

Müller cells as optical fibers

To date, it is still a unresolved question why the retina is inverted in vertebrates. External photons have to go through numerous inner retinal tissue layers before reaching the photoreceptors. At first sight, this inverted structure should produce blurry vision since the external light/photons must propagate through all the reflecting and scattering cell layers before triggering the photoreceptors. Recently, however, new experiments revealed that Müller cells function as optical fibers that can guide photons through the inner retinal tissue (Franze et al., 2007; Agte et al., 2011; Reichenbach et al., 2014). Every Müller cell is coupled to one cone photoreceptor cell in mammalians (Reichenbach and Robinson, 1995). During photopic vision, the parallel arrayed Müller cells could preserve the initial image resolution by means of guiding external photons directly to their particular cone photoreceptor cell. The low photon scattering of Müller cells (increasing the signal-to-noise ratio, minimizing light reflection) is probably due to their special structure with abundant long thin filaments that are oriented along the Müller cell axis (Franze et al., 2007; Labin and Ribak, 2010). Labin et al. (2014) recently reported in *Nature Communications* that '…Müller cells are wavelength-dependent wave-guides, concentrating the green-red part of the visible spectrum onto cones and allowing the blue-purple part to leak onto nearby rods.' They suggested that '…photon propagation by Müller cells through the retina can be considered as an integral part of the first step in the visual process, increasing photon absorption by cones while minimally affecting rod-mediated vision.'

Xanthophyll is concentrated within Müller cell cones

Gass (1999) raised the notion that xanthophyll is concentrated within the Müller cell cone. The yellow color of the human macula lutea is due to the carotenoid lutein and zeaxanthin. The xanthophyll lutein and zeaxanthin have the highest density in the macula, and these pigments protect the eye from ionizing blue and ultraviolet photons (Schalch et al., 2007). The retinal xanthophyll is mostly concentrated within the inner part of the foveola and perifoveolar region, which are the fiber layers (i.e. receptor axon layer and inner plexiform layer) (Snodderly et al., 1984; Whitehead et al., 2006). In the foveolar part, there is only a minimal nerve fiber layer, which makes it likely that most of the xanthophylls is within the Müller cells. Xanthophylls may modulate light energy and perhaps serve as a photochemical quenching agent, which is overproduced during photopic vision (i.e. during high-photon-intensity exposition). It was suggested that the xanthophylls can reduce longitudinal chromatic aberration and improve acuity (Howarth and Bradley, 1986; Wooten and Hammond, 2002). Thus, during vision, xanthophylls within the Müller cells (i.e. optical fibers) may have an essential role in the modulation of light energy and/or wavelengths. Namely, xanthophylls do not simply protect the eye from ionizing blue and ultraviolet photons by absorption, but they also have a functional role in photon signaling processes while Müller cells function as optical fibers. This conclusion can be related to the experiments of Labin et al. (2014), which gave the following insight: 'Müller cells are wavelength-dependent wave-guides, concentrating the green-red part of the visible spectrum onto cones and allowing the blue-purple part to leak onto nearby rods.'

Spontaneous UPE in neurons and the retina

UPE (also referred to as ultraweak (bio)chemiluminescence, spontaneous ultraweak visible electromagnetic radiation, biophotons, etc.) is continuously generated by all living cells in general and in neurons in particular without any external excitation (Tilbury and Cluickenden, 1988; Devaraj et al., 1991; Scott et al., 1991; Cohen and Popp, 1997; Takeda et al., 1998; Chang, 2008; Rahnama et al., 2011; Kobayashi et al., 2014; Alvermann et al., 2015). UPE originates primarily from natural radical (redox) reactions and the deactivation of excited molecules (Imaizumi et al., 1984; Nakano, 2005; Kamal and Komatsu, 2015). Neurons produce UPE through radical reactions during normal metabolism (Artem'ev et al., 1967; Isojima et al., 1995; Zhang et al., 1997; Kataoka et al., 2001; Kobayashi et al., 1999a; Tang and Dai, 2014a; Salari et al., 2015).

The intensity of UPE has been correlated with cerebral energy metabolism, cerebral blood flow, oxidative reactions, and electroencephalogram (EEG) activity in the rat brain *in vivo* (Kobayashi et al., 1999b), which implies that there is neural activity-dependent UPE emission in the brain. In addition, the addition of 10 mM glutamate could induce increased UPE from brain slices. UPE intensity changes are correlated with the local tissue hemodynamic (i.e. blood flow) and oxygenation status (Scholkmann et al., 2013).

UPE can be generated by neuronal membrane depolarization by means of a high concentration of K^+ and attenuated by tetrodotoxin or elimination of extracellular Ca^{2+}, as demonstrated in rat cerebellar granule neurons in the visible range (Kataoka et al., 2001). This indicates that the UPE is dependent on neuronal activity and on

cellular metabolism. Additionally, UPE can be inhibited by 2,4-dinitrophenylhydrazine, indicating that UPE could be originated from oxidized molecules.

Recently, we presented the first experimental *in vitro* proof about the existence of spontaneous and visible light-induced UPE from freshly isolated rats' whole eye, lens, vitreous humor, and retina (Wang et al., 2011). Sun et al. (2010) revealed that ultraweak photons can be conducted along neural fibers. Tang and Dai (2014b) reported that glutamate-induced UPE intensity reflects UPE transmission along the axons and in neural circuits. They found that the long-lasting application of a high concentration of glutamate created a gradual and significant increase in UPE that peaked after 90 min in mouse coronal and sagittal brain slices.

Catalá (2006) revealed that radicals from lipid peroxidation of the photoreceptors can produce UPE in the visual spectrum. Narici et al. (2012) also reported that lipid peroxidation of the photoreceptors can create UPE. It is very likely that the so-created photons can be absorbed by the photoreceptors that initiate a photo-transduction cascade.

It should be considered that the real UPE intensity within cells can be fundamentally higher than one would expect from measurements of UPE, which are generally done macroscopically several centimeters apart from the tissue or cell cultures (Bókkon et al., 2010). Especially the cell/tissue interface causes a strong reflection so that a large fraction of UPE is back-reflected to the origin and is not measured. Thus, we conclude that a significant fraction of the naturally occurring UPE cannot be measured or quantified because it is absorbed and scattered during the transmission from origin to the measurement device. Light originating from biological tissue is attenuated according to the wavelength-dependent attenuation coefficient of the tissue (μ_{eff}), given as $\mu_{eff}=[(3\mu_a(\mu_a+\mu_s'))]^{0.5}$, with the absorption coefficient (μ_a) and the reduced scattering coefficient (μ_s') defined as $\mu_s'=\mu_s(1\text{-}g)$ with the scattering coefficient (μ_s) and the anisotropy factor (g). For biological tissue, μ_a and μ_s' generally vary in the optical range $\mu_a=0.03\text{–}1.6$ cm^{-1} and $\mu_s'=1.2\text{–}40$ cm^{-1}, and the anisotropy factor is in the range of 0.7–0.9 (Sandel and Zhu, 2011). Each absorbing and scattering structure within the tissue (e.g. chromophores) has specific optical properties so that the final transmitted light is attenuated by the sum of all attenuations by all these diverse structures. The damping of the light intensity follows an exponential function modeled by the modified Beer-Lambert law (Scholkmann et al., 2014). In addition, Blake et al. (2011) demonstrated that UPE steaming from cells and neurons are produced mainly from natural oxidation processes on the surfaces of cellular membranes.

It might be that biophotonic (i.e. based on UPE) and bioelectronic (i.e. spike-related neural electrical signals) activities are associated processes within the nervous system, and their synergistic action may play significant roles in neural signal processing mechanisms.

Hypothesis: formation of eye-specific retinogeniculate projections before birth by the help of UPE

Müller cells, UPE, and retinogeniculate pathways prior to birth

If we consider the facts mentioned in the previous sections, it might be implied that continuously generated UPE within the retinal system (Wang et al., 2011) may have a functional role in early development of the retinogeniculate pathways and in the initial appearance of the topographic organizations of the lateral geniculate nucleus (LGN) and the primary visual cortex (V1) before birth. Retinal UPE can continuously guarantee intrinsic cues through phototransduction cascades to the LGN and V1 regions that 'interpret' these retinal UPEs as if they originated in the external visual world. This hypothesis can meet Chalupa's (2009) proposal that instructive cues for the development of eye-specific retinogeniculate pathways are combined with retinal waves. Thus, UPE may guarantee specific instructive cues.

More explicitly, it is possible that Müller cells have essential roles in the development of the eye-specific retinogeniculate pathways. Spontaneously emitted ultraweak photons originating from Müller cells (since all living cells emit UPE; Wang et al., 2011) can also achieve specific cues and activity on cone photoreceptors because every Müller cell is coupled to one cone photoreceptor cell in mammalians.

The communication between neurons is mediated by neurotransmitters, but neurotransmitters also affect glia cells (bi-directional communication). It seems that Müller cells can express NMDARs (Puro et al., 1996). The glutamate-induced UPE intensity reflects UPE transmission along the axons and in neural circuits (Tang and Dai, 2014a,b). The intensity of UPE correlates with cerebral energy metabolism, cerebral blood flow, and oxidative reactions, and glutamate could induce increased UPE activity (Isojima et al., 1995; Kobayashi et al., 1999a,b). Müller cell sheets and Müller cells are surrounded by glutamatergic synapses (Boulland et al., 2002). On the basis of these facts, we conclude that the bi-directional communication between retinal neurons and Müller cells

by glutamate may also produce bi-directional glutamate-induced UPE optical communication that may guarantee specific instructive cues for the development of eye-specific retinogeniculate pathways.

Müller cell cone, UPE, and retinogeniculate pathways prior to birth

UPE may also have a functional role in the development of cortico retinogeniculate topographic maps via Müller cell cones. In this case, endogenous UPE produced inside Müller cells is conducted and absorbed by natural photosensitive chromophores within Müller cells. These absorbed ultraweak photons then could produce excited biomolecules, and a resonance energy transfer to nearby biomolecules could take place. Next, these processes could induce conformation changes and trigger complex signal processes steps within and between (e.g. glutamate releasing) retinal cells.

Discrete dark noise of rods, UPE, and retinogeniculate pathways prior to birth

Spontaneous rhodopsin activation produces discrete noise events that are indistinguishable from single-photon responses. Recently, we proposed that the discrete dark noise of rods can be due to the naturally occurring spontaneous UPE in the retina (Bókkon and Vimal, 2009). Namely, under physiological conditions, lipid oxidation is a naturally occurring process in cells and also in retinal membranes. Since natural lipid oxidation is an essential source of UPE and since photoreceptors have the highest oxygen demand and polyunsaturated fatty acid (PUFA) concentration (Nielsen et al., 1986; Youdim et al., 2000; Yu and Cringle, 2001), there can be a continuously occurring UPE taking place without external photonic stimulation in the retina. During photopic or scotopic vision, retinal UPE is negligible, but in dark-adapted retinal cells, this UPE is not negligible. Rods can absorb the released ultraweak photons, which originated from the lipid peroxidation of PUFAs of adjacent rods (Bókkon and Vimal, 2009). It is also possible that a given rod generated UPE, which changes its direction, and a little later, it might absorb its own UPE.

However, the naturally occurring lipid peroxidation takes place not only during scotopic vision and photopic vision but also during the development of retinogeniculate pathways. It was revealed that there are gap-junction and gap-junction-independent rod signal pathways from rod photoreceptors to ganglion cells in mammalian retina (DeVries and Baylor, 1995; Brown et al., 2011). UPE from rods may also have roles when it might absorb its own ultraweak photons via ganglion cells during the development of retinogeniculate pathways before birth. Thus, it is probable that discrete noise events of rods, produced by UPE, are in direct connection with the development of retinogeniculate pathways prior to birth.

ipRGCs, UPE, and retinogeniculate pathways prior to birth

Rod and cone photoreceptors transform light/photon signals into electrical signals and convey this information for both image- and non-image-forming visual functions by means of RGCs. Among their several structural and functional differences from the classical rod and cone photoreceptors, ganglion cells send direct axonal projections to the brain. In the mammalian retina, about 0.2–4% of RGCs express melanopsin photopigments that are directly photoreceptive, termed ipRGCs. ipRGCs have numerous functions, including photoentrainment of the biological clock, pupillary light reflex/constriction, light-induced suppression of pineal melatonin secretion, sleep regulation, and some aspects of vision (Ecker et al., 2010; Zhao et al., 2014). The most part of ipRGCs produces extrinsic and synaptically driven photoresponses as well as intrinsic light responses (Wong et al., 2007). ipRGC cells can project to the superior colliculus that has a precise retinotopic map. The superior colliculus area of the brain can detect novel objects in the visual scene, suggesting that ipRGCs may contribute to visual function as signals giving information about form and motion. ipRGCs also contribute to the modulation of retinal waves by intraretinal signals via gap junctions and glutamate receptors. RGCs project ions to the brain, one reflecting the eye of origin and the other, retinotopic location. Recent experiments by Xu et al. (2015) suggest the instructive role for spontaneous retinal activity in both eye-specific segregation and retinotopic refinement.

Since all living cells as well as neurons continuously emit UPE without any external excitation; since we experimentally proved (Wang et al., 2011) the existence of UPE from a freshly isolated rats' whole eye, lens, vitreous humor, and retina; and since the glutamate-induced UPE intensity reflects UPE transmission along the axons and in neural circuits (Tang and Dai, 2014a,b), we hypothesize that UPE is also produced within ipRGCs. UPE, produced inside ipRGCs, can be absorbed by natural photopigments of ipRGCs that can trigger and modulate retinal waves or

send signals to the retinotopic superior colliculus (Chan et al., 2011) (among others structures) prior to birth.

Summary

- Before birth, UPE is produced by Müller cells, which may create specific cues and activity by glutamate-induced ultraweak photons on cone photoreceptors (because every Müller cell is coupled to one cone photoreceptor cell). UPE generated by Müller cells can be absorbed by cone photoreceptors and can be converted into retinal electrical signals. These UPE-induced retinotopic electrical signals may be then conveyed to the LGN and to V1, where spike-related electrical signals are induced along classical axonal-dendritic pathways that may guarantee specific instructive cues for the development of eye-specific retinogeniculate pathways.
- The Müller cell cone area may also guarantee specific instructive cues for the development of retinogeniculate pathways, but in this case, ultraweak photons inside Müller cells are conducted and absorbed by natural photosensitive chromophores (xanthophylls may have some functions in these processes), which may induce electric signal processes within and between retinal cells offering instructive signals that are than conveyed to LGN and to V1 for the development of eye-specific retinogeniculate pathways prior to birth.
- UPE from rods may also have functional roles when rods might absorb their own ultraweak photons and with this send signals via ganglion cells in the development of retinogeniculate pathways before birth.
- UPE created within ipRGCs may be also absorbed by photopigments of ipRGCs that can elicit and modulate retinal waves or send signals to the retinotopic superior colliculus prior to birth.

It is well known that there are about 6 million cone cells and about 120 million rod cells in the human retina. What is not known is the real UPE intensity within the retina. Thus, in the present stage, we cannot support our hypothesis by calculations or quantitave modeling. However, experimental findings support our notion that UPE also can induce retinotopic electrical signals conveyed to the LGN and to V1 and initial appearance of the topographic organizations of the primary visual cortex before birth. Namely, rod cells in the eye can perceive and transform a single photon into a neural signal (Field et al., 2005) and cone cells require the coincident absorption of only four to seven photons to generate a detectable signal (Schnapf

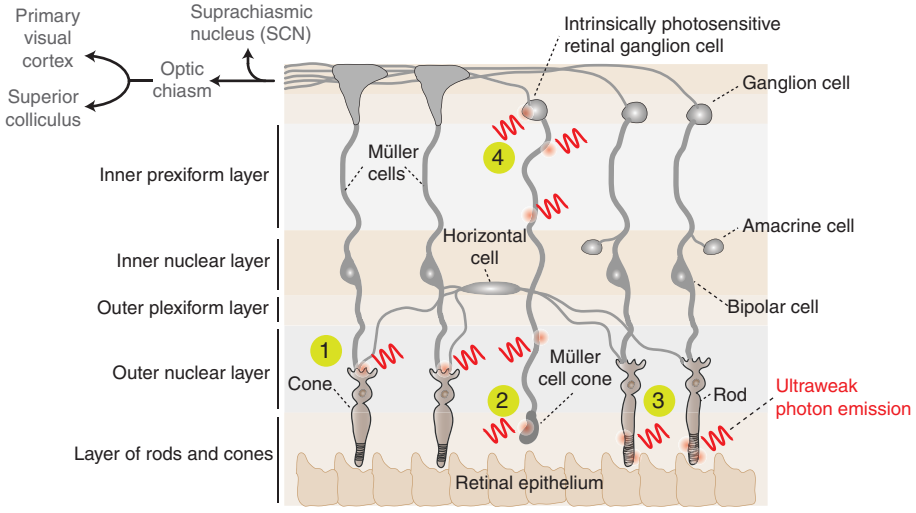

Figure 1: Visualization of the retinal ultraweak photon emissions as biophysical molecular cues in the development of retinogeniculate pathways prior to birth.
1: Before birth, UPE produced by Müller cells may create specific cues and activity by glutamate-induced UPE on cone photoreceptors. 2: Müller cell cone areas may also guarantee specific instructive cues for the development of retinogeniculate pathways, but in this case, ultraweak photons inside Müller cells are conducted and absorbed by natural photosensitive chromophores that can induce electric signal processes within and between retinal cells. 3: UPE from rods may also have functional roles when rods might absorb their own ultraweak photons and send signals via ganglion cells in the development of retinogeniculate pathways before birth. 4: UPE created within ipRGCs can be absorbed by photopigments of ipRGCs that can elicit and modulate retinal waves or send signals to the retinotopic superior colliculus prior to birth.

et al., 1990; Miller and Korenbrot, 1993; Donner et al., 1998). The fact is that rods and cones can detect extremely weak optical signals.

We are of the opinion that the bioelectric and, possibly, biophotonic processes taking place in the retinal system form a complex system of regulation and information exchange, whereas the functional and complex roles of retinal ultraweak photons might act as biophysical molecular cues (Figure 1) in the development of retinogeniculate pathways.

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