

Let There Be Light: Brain's Photosensitivity Beyond the Visual System and its Relevance to Photic Stimulation for Mood and Sleep Disorders

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Light therapy, also known as phototherapy, has been studied for treating depressive episodes of major depressive disorder and bipolar disorders especially when associated with seasonal patterns in the form of "winter depression" [1-3]. In addition, light therapy can be very effective in circadian rhythm sleep disorders to retard or advance the sleep cycle depending on the time of photic stimulation. But can the human brain be also sensitive to light beyond the visual system?

According to emerging research, the answer is yes. Not only is light therapy (with certain intensity and wave length) perceived by the retinal rod and cone opsins (OPN4) and transferred to action potentials to stimulate different areas of the occipital cortex, but also cumulative evidence now indicates that the brain can perceive light beyond the visual system.

Studies have identified photosensitive proteins named opsins. Opsins are divided into visual and non-visual opsin. The visual opsins are divided into rhodopsin and cone opsins. Cone opsins are subdivided into four subtypes that represent their absorption wavelength: long-wavelength opsins (or red), short-wavelength opsins (or UV/violet and blue), and middle-wavelength opsins (or green) [4,5]. Non-visual opsins are melanopsin, peropsin, RGR, neuropsin, and encephalopsin. Opsins consist of G-protein-coupled receptors [6] and have a seven-transmembrane structure that mostly functions as light sensors [5,7]. In both the visual and non-visual systems, most opsins function as pigments, which activate G proteins in a light-dependent fashion [6]. Encephalopsin (OPN3) is one of the most studied extra-retinal opsins and a light-sensitive photoreceptor protein [8,9] Encephalopsin is predominant in the preoptic area and paraventricular nucleus of the hypothalamus.

Photic stimulation of encephalopsin (and other non-visual opsins) outside the visual system has been shown in early studies to be beneficial in winter depression [10]. Thus, the ear canal can do more than hearing. In fact, light headphones for treating seasonal affective disorder have been tested in an initial small study. The study showed beneficial effects of transcranial brain-targeted bright light treatment via ear canals even when used for few minutes [10]. Although this data needs replication in a larger randomized controlled study, these light headphones or the transcranial brain-targeted bright light device is currently sold for public use. These photo signals are transformed by photosensitive receptors to neural action potentials in certain areas of the brain. Initial investigations show involvement of brain areas responsible for production and storage of neurotransmitters/neurohormones that play important roles in mood and sleep, including serotonin, dopamine, and melatonin [8]. Non-ocular photic stimulation of the human brain via ear canal has been shown to alter brain activity and resting-state BOLD fMRI and increase functional connectivity of the lateral visual network [11].

Interestingly, although the non-canonical opsins may have great applications in brain diseases, they also may offer promise in other areas of medicine. For instance, opsins have been identified beyond the brain and may have other benefits. For instance, early evidence suggests that opsins may have a potential role in treatment of liver cancer [12].

OPN3 levels may help apoptosis of cancer cells and in improving sensitivity to chemotherapy in hepatocellular carcinoma. Interestingly, melatonin (one of the neurohormones that is affected by diurnal light variation) also shares the same origin to pineal opsins [9] and may also have beneficial effects in programmed cell death (apoptosis) of cancer cells [13].

There are still many unanswered questions regarding functions of non-visual opsins as encephalopsin. Encephalopsin has been suggested to play a role in melatonin production from the pineal body and circadian rhythm regulation [14]. Efforts to further understand these functions include recent studies using genetic experiments with knockout and/or transgenic animals [15]. Mutant mice lacking visual opsins, and thus photoreception, shed light on the function of melanopsin in the circadian clock [16]. Another approach for investigating function of opsins is functional replacement of one opsin with another and observing the phenotypic change [17]. Understanding function can also inform therapeutic approaches. As opsins' structure has been well described with high resolution (as other G-protein-coupled receptors), they thus offer a great target for drug discovery.

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