Phosphene perception is due to the ultra-weak photon emission produced in various parts of the visual system: glutamate in the focus

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Abstract

Phosphenes are experienced sensations of light, when there is no light causing them. The physiological processes underlying this phenomenon are still not well understood yet. Previously we proposed a novel biopsychophysical approach concerning the cause of phosphenes based on the assumption that cellular endogenous ultra-weak photon emission is the biophysical cause leading to the sensation of phosphenes. Briefly summarized, the visual sensation of light (phosphenes) is likely to be due to the inherent perception of ultra-weak photon emission of cells in the visual system. If the intensity of spontaneous or induced photon emission of cells in the visual system exceeds a distinct threshold, it is hypothesized, that it can become a conscious light sensation. Discussing several new and previous experiments we point out that the ultra-weak photon emission theory of phosphenes should be really considered as a scientifically appropriate and provable mechanism to explain the physiological basis of phosphenes. In the present paper we also present our idea that some experiments may support that the cortical phosphene lights are due to the glutamate related excess ultra-weak photon emission in the occipital cortex.

Keywords: Phosphenes, ultra-weak photon emission, visual system, glutamate

Introduction

Phosphenes are perceived sensations of lights in the absence of any external light stimulation. They can be emerged as spots or bars as well as disordered structures of colorless or colored lights (Oster, 1970). Phosphenes can be produced by means of different stimuli (e.g., mechanic, magnetic or electric.) of cells of the visual systems (Lindenblatt and Silny, 2002; Merabet et al., 2003; Reznikov, 1981). The minimum magnetic or electric intensity required to induce a conscious experience of phosphene has been used as a measure of the excitability of the visual cortex (Boroojerdi ez al., 2000; Delbeke et al,. 2001) Phosphenes can be early symptom in a variety of retinal diseases or of the visual pathways, but healthy persons can observe them as well (Ashtari et al., 2014; Brigatti and Maguluri, 2005). The occurrence of phosphenes is also related to intoxications (drugs, alcohol, etc.) or psychologial conditions (Cervetto et al., 2007). Phosphenes are only perceived by blind people who have prior visual experience, suggesting that early visual experience is necessary to maintain any level of residual visual function (Merabet et al., 2003). The perceived phosphenes lie within the visual hemifield contra-lateral to the stimulated cortical hemisphere and reflects the retinotopic organization of the visual cortex.

During natural metabolic processes, ultra-weak photons are continuously emitted by all living cells without any excitation (Alvermann et al., 2015; Cohen and Popp, 1997; Kobayashi et al., 1999a, 1999b; Scott et al., 1991; Takeda et al., 1998; Tang and Dai, 2014a, 2014b; Kobayashi, 2014; Takeda et al., 2004; Murphy and Sies, 1990; Cifra and Pospíšil, 2014; Nerudová et al, 2015; Van Wijk et al., 2013; Van Wijk, 2014; Prasad and Pospíšil, 2015). This measured ultra-weak photon emission (UPE) is termed differently in the scientific literature but all these terms refer to the same phenomenon (e.g., “ultra-weak bioluminescence”, “low-intensity chemiluminescence”, “ultra-weak photons”, “biophotons”, “biophoton emission”, etc.). UPE from living cells can be detected non-invasively, in real time, and without physical contact. UPE can be caused by various biochemical reactions, predominantly through light-producing radical reactions of reactive oxygen species (ROS) and non-radical ROS leading to oxidation of biomolecules, self-recombination of organic radicals and excitation energy transfer to chromophores (Prasad & Pospíšil, 2015). Some examples include processes in the mitochondrial respiration chain, lipid peroxidation, peroxisomal reactions, oxidation of catecholamines, oxidation of tyrosine and tryptophan residues in proteins (Kruk et al., 1989; Nakano, 2005; Steele, 2003; Watts et al., 1995). The

wavelength spectrum of the emitted photons includes the infrared, visible and ultraviolet range (from approx. 200-800 nm).

We previously pointed out (Bókkon et al., 2010) that the term "ultraweak biophoton emission" can be misleading since it could be interpretated that photon emission in biological systems does not have any meaning for cellular processes but is rather a byproduct of cellular metabolism. It is very possible that externally measured UPE from diverse cells is originating mainly from naturally ocuring oxidation (mainly ROS-mediated reactions) processes in cellular membrane surface areas. According to Thar and Kühl (2004), the real photon intensity inside cells can be drastically higher than one would expect from the measurements on ultra-weak bioluminescence, which is usually measured some centimeters apart from the cells. It is a known fact that photons are strongly scattered and absorbed in cellular systems; there are estimations for a given measured intensity of the UPE that the corresponding intensity of biophotons within the organism or cell can even be two orders of magnitude higher than measured (Slawinski, 1988; Cliento, 1988). Recent experiments by Blake et al. (2011) support our notion that externally measured UPE from cells and neurons is principally produced from natural oxidation processes on the surfaces of cellular membranes and the real intensity of photon emssion can be fundamentally higher inside cells (e.g., neurons). Methods to measure the photon emission inside cellular environments and tissue have to be developed in the future. Until this issue is resolve and measurements of the "real" photon intensity were realized we assume that this intensity is higher than the measured UPE which we use to justify our assumption that UPE could elicit changes of electrical activity in the occipital cortex to create phosphenes.

During normal metabolism, neural cells also continuously generate UPE through ROS-mediated reactions (Imaizumi et al., 1984; Isojima et al., 1995; Kataoka et al., 2001). It was reported that this UPE is correlated with cerebral energy metabolism, cerebral blood flow, oxidative processes, and neuronal brain activity (measured using electroencephalography, EEG) in the rat's brain in vivo (Kobayashi et al., 1999b).This implies that there is neural activity-dependent UPE constantly happening in the brain (Isojima et al., 1995).

When the endogenously generated photons are absorbed by natural chromophores it could have effects on the electrophysiological activity of cells and neurons. Explicitly, photons from UPE can be absorbed by natural chromophores of cells (such as porphyrin and pyridinic rings, flavinic and lipid chromophores (Karu et al., 1999; Kato et al., 1981)) that produce

electronically excited states which may excite nearby molecules and trigger or regulate cellular signal processes.

The aim of this paper is to point out that there is increasing experimental and theoretical evidence that various phosphene perceptions are due to the UPE happening in the visual system that should be regarded as a scientifically suitable and demonstrable mechanism in the future. These evidences will be discussed in the next section. We also highlight the role of glutamate in the generation of UPE and thus the triggering of phosphenes.

Retinal phosphenes as a result of increased UPE due to ROS-mediated associated lipid peroxidation in photoreceptors

It is well known that diverse factors (e.g., mechanical effects on the visual system, magnetic or electrical stimulation of the visual system, stress, drugs, or high-energy ionizing radiation) can induce phosphenes. It was suggested by Bókkon (2008) that these factors can have a common feature, i.e., every one of them can generate an unregulated overproduction of free radicals and excited biomolecules in various parts of the visual system that changes the neural activity in the brain. This transient and non-specific overproduction of ROS can cause an excess of UPE in the visual system. If this excess UPE exceeds a distinct threshold it can appear as a sensation of light (phosphenes).

This new notion that retinal phosphenes are due to excess UPE can be supported by several experiments. Rod outer segments of photoreceptors contain a very high concentration of polyunsaturated fatty acids (Nielsen et al., 1986) that get easily oxidized. Catalá (2006) has proved that ROS induce lipid peroxidation in the photoreceptors which causes UPE visual optical range. We presented the first experimental *in vitro* evidence (Wang et al., 2011) about the existence of spontaneous and visible light induced UPE from freshly isolated rats' whole eye, lens, vitreous humor and retina. This finding also supports the hypothesis that phosphenes are the result of endogenous UPE.

Our prediction regarding one specific kind of phosphenes (i.e., retinal phosphenes during space travel (Fuglesang et al., 2006)) was supported by the experiments of Narici et al. (2009, 2012, 2013). Ionizing radiation (i.e., cosmic radiation) induced free radicals produce UPE by lipid peroxidation (Narici et al., 2009). The generated photons are then absorbed by the photoreceptors and initiated a photo-transduction cascade which produced the sensation of phosphenes, similar to that induced by external light during normal vision. Narici et al. (2012)

also reported that the peroxidation initiated lipid peroxidation of the photoreceptors produced an isomerization of the retinal (bleaching) of the rhodopsin, analogous to that induced by external photons during normal vision. Explicitly, lipid peroxidation of the photoreceptors, initiated by peroxidation, produced photons that generated anomalous visual effects such as those associated with retinal phosphenes.

In 2013 Narici et al. used irradiation of ^{12}C carbon ions that eliciting retinal rod outer segment rhodopsin of bovine eyes. Irradiation of ^{12}C carbon ions stimulated free radical production, propagation and recombination that produced photoluminescence. This effect could play a central role in the generation of phosphenes experienced by astronauts during space travel (Fuglesang et al., 2006).

Finally, since the cerebral cortex has a much higher threshold for detecting phosphenes induced by ionizing particles compared to the retina (Bókkon and Vimal, 2009) the major source of ionizing particle induced phosphenes appears in the retina.

Phosphene generation in the visual cortex by means of excess UPE produced from glutamate induced ROS

Glutamate is the principal excitatory neurotransmitter in the brain that can activate two types of glutamate receptors, i.e., ionotropic (iGluRs) and metabotropic glutamate receptors (mGluRs) (Nakanishi, 1992). Glutamate induces ROS formation in neurons (Alekseenko et al., 2012). ROS can be synthesized essentially by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and mitochondria. Explicitly, activation of metabotropic glutamate receptors (i.e., N-methyl-D-aspartate receptors, NMDARs) by glutamate triggers several signal processes such as calcium influx, activation of nitric oxide (NO) synthase and superoxide formation (Chetkovich et al., 1991; Lafon-Cazal et al., 1993). Following neuronal NMDAR activation, the increased NADPH oxidase activity can be the key source of superoxide ($O_2^{\cdot -}$) production (Bókkon and Antal, 2011; Brennan et al., 2009; Tsai et al., 2012). In addition, initial superoxide signals produced by the NADPH oxidase can stimulate secondary mitochondrial superoxide and various ROS productions. It could be also that proton channels play a role in UPE generation since the NADPH-$NADP^+$ balance (Blacker et al., 2014) has a key role in redox and ROS-mediated processes that are the bases for photon emission processes.

Kobayashi et al. (1999b) reported an increase in UPE induced by the addition of 10 mM glutamate. They found that UPE intensity correlated with EEG activity that was measured on the cortical surface, and this intensity was associated with the cerebral blood flow and hyperoxia.

Sun et al. (2001) demonstrated that photons associated with endogenous UPE can be conducted along neural fibers. Later, experiments by Tang and Dai (2014a, 2014b) provided evidence that the glutamate-induced UPE intensity reflects photon transmission along the axons and neural circuits. In detail, they revealed that the long-lasting application of high concentration of glutamate in mouse coronal and sagittal brain slices created a gradual and significant increase of UPE that achieved the maximal effect within 90 min. The glutamate induced photon emission could be significantly blocked by means of oxygen and glucose deprivation as well as with the application of a cytochrome c oxidase inhibitor (sodium azide). In addition, the initiation and maintenance of UPE triggered by glutamate could be blocked only partly by Tetrodotoxin (TTX, an action potential inhibitor), procaine (a local anesthetic drug), or the removal of intracellular and extracellular Ca^{2+}.

Terhune et al. (2015) studied the neurochemical basis of phosphene perception by measuring basal γ-Aminobutyric acid (GABA) and glutamate levels in the primary visual (V1) cortex by means of magnetic resonance spectroscopy (MRS). Phosphenes were produced by the application of transcranial magnetic stimulation (TMS) to the occipital cortex. They reported that the phosphene threshold correlated negatively with the concentrations of basal glutamate in V1.

The mentioned experiments in this section support that the conclusion that cortical phosphenes can be due to the glutamate related excess UPE in the occipital cortex.

Phosphenes due to excess UPE caused increased ROS production triggered by fever (high body temperature)

Neuronal membrane processes and synaptic responses are temperature-dependent (Mrozek et al., 2012). Neurotransmitter release, reuptake and diffusion change when the temperature is altered in the brain. Hyperthermia can produce a release of excitatory amino acids and free radicals, and perturb the blood-brain barrier. Studies have reported (Dietrich and_Bramlett, 2007) that mild hyperthermia (>37 °C) can cause excitotoxicity, free radical generation, inflammation, apoptosis, and other pathophysiological reactions. In addition, glutamate diffusion and toxicity rise with temperature. Glutamate, i.e., the principal excitatory

neurotransmitter in the central nervous system, is distributed widely throughout the neuroaxis. L-glutamate has a significant role in thermoregulation through N-methyl-D-aspartate (NMDA) ionotropic receptors (Paro et al., 2003; Yoshimatsu et al., 1993). There is a tight association between temperature and glutamate excitotoxicity (Campos et al., 2012).

ROS formation, lipid peroxidation, and UPE are also temperature-dependent processes (Alvarez and Storey, 1985; Kobayashi et al., 2014; Miura et al., 1998; Misík et al., 1994; Niggli, 2003; Player and Hultin, 1977). In addition, UPE, free radical production, and lipid peroxidation are Ca^{2+} *concentration* dependent mechanisms (Pandya et al., 2013; Tang and Dai, 2014b).

Phosphene-like phenomena are common side effect of fever (high temperature) (Cervetto et al., 2007). Considering the mentioned findings, it supports that fever induces an elevated glutamate production that activates NMDA receptors. Activated NMDA receptors induce increased NADPH oxidase acivity and secondary mitochondrial free radical production. This unregulated excess free radical production can generate excess UPE in the visual systems that finally create phosphene sensations in the subject having the elevated body temperature.

Electric pulses induced glutamate release, cortical phosphenes and UPE

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation procedure that can alter the cortical excitability. It uses a constant low intensity current delivered to the brain area of interest via electrodes on the scalp. tDCS is a promising treatment for cognitive enhancement, chronic pain as well as for neuropsychiatric and neurological diseases. Depending on the current flow, tDCS increases or decreases neuronal excitability. The anodal stimulation (positive stimulation, +) increases neuronal excitability in the stimulated region but cathodal (negative stimulation, -) decreases neuronal excitability (Medeiros et al., 2012). MRS studies revealed that the application of tDCS is associated with glutamatergic, GABAergic, serotonergic, dopaminergic, and cholinergic activity modulation, among other physiological effects.

Previous pharmacology studies suggested that anodal stimulation can be associated with changes in glutamatergic signaling (Liebetanz et al., 2002; Nitsche et al., 2003). Tamura et al. (1990) studied the release of amino acids from V1 during visual and electrical stimulation of the dorsal lateral geniculate nucleus (LGN) and of the optic tract in cats. They found

increased release of glutamate from the visual cortex following activation of afferent pathways. In You et al. (1998) experiments were reported showing that electrical stimulation of the prefrontal cortex increased glutamate release in the nucleus accumbens in rats.

It has been shown that electrical stimulation of primary V1 could produce phosphenes in monkeys and humans (Brindley and Lewin, 1968; Schmidt et al., 1996; Tehovnik and Slocum, 2007).

Long time ago, Artem'ev et al. (1967) reported the detecion of optical emission of frog nerves exited by electric pulses. Researchers found that the nerve excitation caused UPE in the visible region of the optical spectrum. When the nerve was killed, UPE stopped. The authors concluded that the UPE was apparently due to chemical reactions accompanying assistance in the work. In 1997 Zhang et al. measured UPE and light-induced photon emission from intact brains isolated from chick embryos using a single photon counting device. They revealed that the UPE intensity was higher from intact brain's than from the medium in which the brain was immerged.

Unfortunately, the study by Artem'ev et al. (1967) is the only one to date that studied the electrically induced UPE from nerve cells. In the future, studies have to be conducted regarding electrically (and spontaneous) induced photon generation of neuronal cells and tissues, as well as in vivo experiments have to be performed.

Glutamate triggered UPE and phosphenes

Regarding the mentioned experimental results, it can be concluded that phosphenes are due to the glutamate induced and redox related UPE in the visual cortex. Glutamate is the most prevalent neurotransmitter in the visual pathway. Bókkon (2008) proposed that retinal and cortical phosphenes may have similar mechanisms, namely, both are due to the natural redox related (free radical) excess UPE. Regarding retinal phosphenes, they essential originate from excess free radicals of lipid peroxidation in the photoreceptors that can generate an excess UPE in the visual range. In the case of cortical phosphenes, they may be originated from glutamate induced redox processes. For example, an electric (tDCS) current can induce a membrane depolarization (increased firing and excitability of the cortical neurons during anodal stimulation) that increases the glutamate release which activates the NMDA receptors. Activated NMDA receptors stimulate NADPH oxidase acivity and a secondarily an increased

mitochondrial ROS production. This unregulated temporary excess ROS production can generate additional UPE in the visual cortex that finally create the phosphene sensation in the subject (for a visualization see Figure 1). Of course, a large number of other signaling processes are also activated during a tDCS application (e.g., GABAergic, serotonergic, dopaminergic, and cholinergic activity modulation). Glutamate release is also associated with the creation of nitric oxide (NO) free radicals and with local increases in cerebral blood flow (Faraci and Brian, 1994). However, here we focused on the key role of glutamate.

– Please inserte Figure 1 here –

Transcranial magnetic stimulation (TMS) is a non-invasive technique that applies relatively strong electromagnetic pulses over the scalp of a subject to induce a random noise electrical current in specific regions in the brain. TMS can transiently disrupt and modulate neural activity in local brain areas. TMS inhibition possible reflects the activity of GABAergic interneurons, but facilitation depends on the activation of intracortical fibers by the subthreshold stimulus, inducing local release of glutamate (Oliveri and Caltagirone, 2006). The TMS-induced electric field could induce phosphenes in the striate cortex (V1) of the macaque (Tehovnik and Slocum, 2007) and selective stimulated V1 and V2 (Salminen-Vaparanta et al., 2014) that were able generating phosphene perception to a similar degree It seems that TMS induced phosphenes are due to the glutamate related UPE.

In addition, as mentioned, glutamate has a significant function in thermoregulation by means of the NMDA ionotropic receptors (Paro et al., 2003; Yoshimatsu et al., 1993) and there is a significant association between temperature and glutamate excitotoxicity (Campos et al., 2012). Thus, glutamate related phosphene induction through UPE may also be a possible mechanism relating fever (high body temperature) and phosphenes (Cervetto et al., 2007).

Summary, discussion, implicationa and outlook

There is important demand to better understand the physiological aspects of the phosphene phenomena. In prosthetic vision, a visual scene is composed of relatively large, isolated, spots of light so-called phosphenes. Artificial prosthetic vision is based on the notion that phosphenes patterns can be used to convey visual information to blind patients. During space

travel, the phosphene phenomenon is a significant problem that can perturb the astronauts' normal sleep. This is a particular problem in the long-term space travel. It is known that over 300 drugs can produce visual phosphene-like hallucinations (Fountain, 2002). Phosphenes can be an early symptom of various diseases, for examples diseases of the retina (Swerdloff et al., 1981; Brigatti and Maguluri, 2005).

Dotta et al. (2012) and Dotta and Persinger (2011) observed coupling with UPE in the brain during subjective visual imagery. They reported that the photon emissions were strongly correlated with EEG activity and the emergence of action potentials in axons. Phosphenes can also interfere and impair the detection of visual stimuli and imagery (Abrahamya et al., 2011; van de Ven and Sack, 2013).

As an additional aspect concerning the topic discussed in this poper we would like to mention briefly, without discussing it in detail, that it may be possible that our UPE-based explanation of phosphenes may also help to more understand some kind of the synesthesia phenomenon (Afra et al., 2009; Bolognini et al., 2013) since the visual cortex processes both visual and sound information via crossmodal mechanisms (Vetter et al., 2014).

Although the mentioned experiments by Tang and Dai (2014b) as well as Kobayashi et al. (1999) revealed that UPE increased under unphysiologically concentrations of glutamate (i.e., > 25 mM and 10 mM, respectively), such elevated concentrations of glutamate are still within the range of the glutamate concentration stored in the presynaptic vesicles (60–200 mM, Clements et al. 1992). It has been accepted that extracellular exposure to a high concentration of glutamate can be toxic to neurons ("glutamate neurotoxicity") (Lau and Tymianski, 2010). Nevertheless, there is also increasing evidence that glutamate neurotoxicity varies significantly under different experimental conditions. For example, Obrenovitch (1999) revealed that local, high extracellular concentrations of glutamate could be tolerated in the intact brain, but not when the energy supply is limited (i.e., stroke and anoxia). Obrenovitch et al. (2000) suggested that glutamate neurotoxicity is a multifactorial processes and glutamate neurotoxicity is not directly related to glutamatergic transmission but to inadequate energy supply (i.e., a mitochondrial dysfunction). It is also very possible that other neurotransmitters also correlate with UPE (and phosphene-experience), but in the present paper we focus on glutamate since it the relationship between glutamate, UPE and phosphenes is supported by the most empirical data currently available.

According to Tang and Dai (2014b),"the glutamate-induced biophotonic activities reflect biophotonic transmission along the axons and in neural circuits, which may be a new

mechanism for the processing of neural information". However, for the real interpretation of many visual related phenomena, future research should consider for the role of redox related UPE in neural information processes, since it makes possible to design better prosthetic devices, to reduce phosphenes that perturb normal astronauts' sleep during space travel, to use phosphenes as early markers for various visual related diseases (as we pointed out previously (Ashtari et al., 2014), to reduce drug induced side effects, among them.

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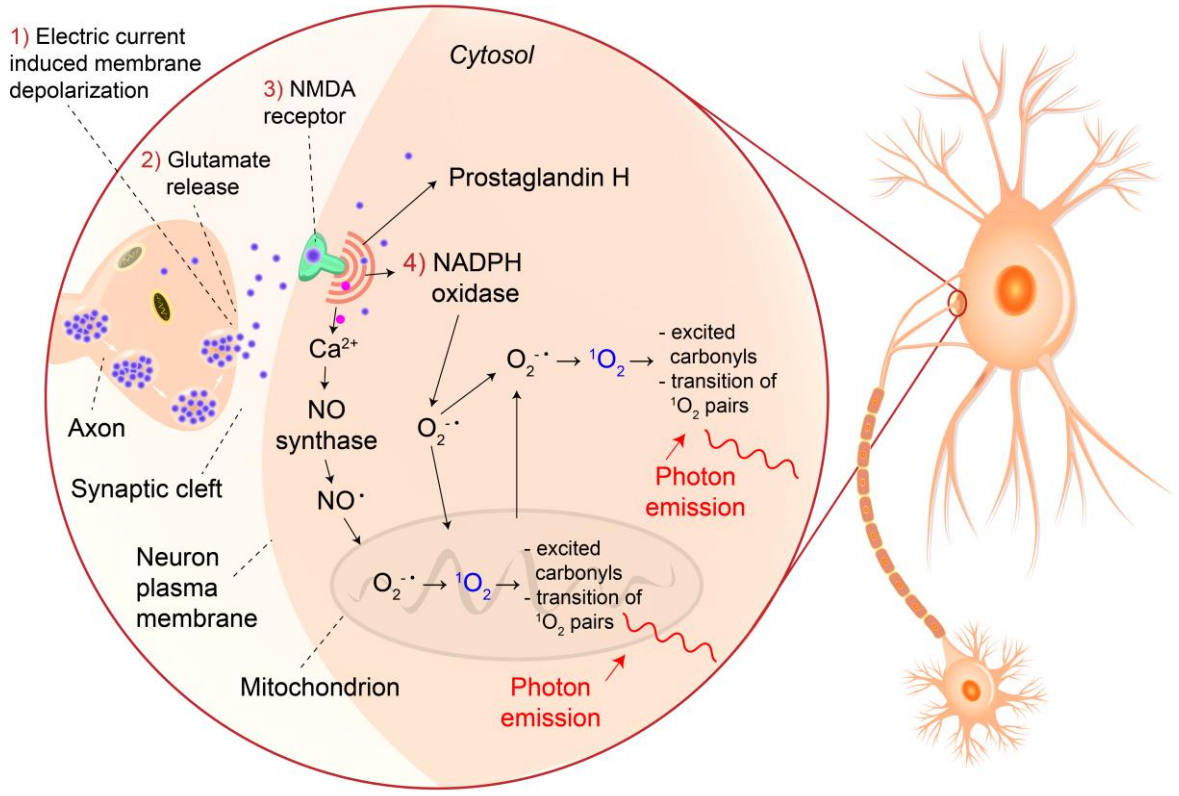

Figure 1. Visualization of the biochemical and biophysical processes and structures involved in the generation of phosphenes by endogenous UPE. First, an electric current induces membrane depolarization that increases the glutamate release which activates NMDA receptors. Activated NMDA receptors then stimulate NADPH oxidase acivity and secondarily mitochondrial ROS production. Next, unregulated temporary excess ROS production can

generate increased UPE in the neurons of the visual cortex that finally produce phosphene sensation in the subject. The reaction of singlet oxygen ($^1O_2$) with unsatturated fatty acids leads to the formation of excited carbonyls that cause UPE in the spectral range of approx. 420-540 nm (Boveris et al., 1980; Nakano and Sugioka; Nakano et al., 1976). Vibrational transitions of various $^1O_2$ pairs lead to UPE emission with spectral peaks around 470-480, 510-530, 560-580, 630-640 and 670 nm (Nakano et al., 1976). Another peak is at 703 nm (Khan and Kasha, 1970) and at approx. 1270 nm (Baker and Kanofsky, 1991).

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