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Short Communication

"Poppers Maculopathy" is an Electrochemical Overload

Fabrizio Magonio, MD*

Department of Ophthalmology, Igea Private Hospital, Via Marcona, 69 20129 Milano, Italy

*Author for correspondence: Email: fabrizio.magonio@alice.it

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Abstract

Poppers maculopaty is a rare retinal disease which is poorly understood. It is characterized by disruption of inner segment/outer segment junction of central cones and yellow foveal lesions causing photophobia, central scotoma and impaired visual acuity. "Poppers" is a slang term referring to recreational substances of abuse belonging to the alkyl nitrite family of compounds. Inhalation of the fumes from these volatile nitric oxide donors provides a brief sense of euphoria, sexual arousal and myorelaxation. High concentrations of nitric oxide are suspected to represent the underlying cause of retinal damage linked to poppers intake. Nitric oxide regulates photoreceptor metabolism in rods and cones primarily through activation of guanylate cyclase, a key enzyme of phototransduction. In this manuscript two famous physicists, Georg Simon Ohm (1789 – 1854) and James Prescott Joule (1818 – 1889), help me to explain the etiopathogenesis of poppers maculopathy.

Keywords: Poppers maculopathy, Phototransduction, Photoreceptor, Cone, Nitric oxide, Electrochemical overload, Joule effect

Poppers maculopathy is a rare retinal disease which is poorly understood. It is characterized by disruption of inner segment/outer segment junction of central cones and yellow foveal lesions causing photophobia, central scotoma and impaired visual acuity [1]. The prognosis of this disease is unclear given the paucity of cases in the literature: some patients demonstrated reconstitution of ellipsoid zone and resorption of hyperreflective intraretinal material upon follow-up. "Poppers" is a slang term referring to recreational substances of abuse belonging to the alkyl nitrite family of compounds. Inhalation of the fumes from these volatile nitric oxide (NO) donors provides a brief sense of euphoria, sexual arousal, myorelaxation, but also hypotension, syncope and flushing due to vasodilation. In the UK, 10% of the population had exposure to poppers, with higher levels of consumption in the "clubbing" collective and gay men. High concentrations of NO are suspected to represent the underlying cause of retinal damage linked to poppers intake [2]. One hypothesis suggests that alkyl nitrates are directly toxic to photoreceptors [1,3]. Some authors have proposed that alkyl nitrates make photoreceptors more susceptible to photopic damage [4]. Still others have speculated that poppers may disrupt blood flow to the photoreceptors via vasodilation [5,6]. Fluorescein angiography (FA) of eyes with poppers maculopathy typically shows either mild hyperfluorescence at the fovea or normal findings. FA and indocyanine green angiography (IGA) do not demonstrate any abnormal vascular changes. While FA and IGA are limited to two-dimensional analysis and do not allow for selective analysis of choriocapillaris, optical coherence tomography angiography (OCTA) allows for three-dimensional analysis of flow signal of the paravascular arcade. Poppers maculopathy patients do not show vascular anomalies in qualitative and quantitative analysis in OCTA [5,6]. The structure of a photoreceptor consists of an outer segment (shorter in cone than in rod) which is the light sensitive portion of the cell and contains the visual pigment molecules, a costricted segment called "the cilium" which resembles the structure of other cilia in that it contains a number of paired microtubules and an inner segment which contains the nucleus and cytoplasmic organelles. Phototransduction is the process by which light energy is transformed into electrical signals. It begins in the outer segment of photoreceptor where electrotonic potentials that oscillate between -40 mV (at darkness) and -70 mV (at light) are generated and transmitted to the inner segment. Light activates the enzyme 6-phosphodiesterase (6-PDE) which hydrolyses guanosine-monophosphate-cyclic (cGMP) and closes Na channels inducing hyperpolarization, reduction of Ca input and glutamate (GLU) release into extracellular space. On the contrary, 6-PDE is inactive at darkness, guanylate cyclase (GC) synthesizes cGMP,

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numerous Na channels open, depolarization onsets, intracellular Ca increases and much GLU is released. Then, photoreceptors do not generate action potentials but transmit light signals as electrotonic hyperpolarizing pulses rather than depolarizing ones. Furthermore, cones unlike rods are less sensitive to light but have a rapid electrical response and do not saturate. Phototransduction creates an electrical circuit which allows free electrons to continuously move through the photoreceptor which represents the conductor: this flow is called *electrical current* or *intensity* (I). The force motivating electrons to flow in a circuit is called *voltage* (V). Voltage is a specific measure of potential energy which is always relative between two points (-40mV and -70 mV in photoreceptor). Free electrons tend to move through conductor with some degree of friction or opposition to motion. This opposition to motion is called *resistance* (R). These three factors are regulated by Ohm's first law: I=V/R [7]. Instead, Ohm's second law [7] states that "R" is directly proportional to the length of the conductor (L) and inversely proportional to the area of its section (A): $R=\rho \cdot L/A$; "ρ" represents the constant of resistivity, which is the specific electrical resistance of each material and is influenced by temperature [$\rho=\rho_0$ (1+ αT), α= thermal coefficient]. In fact, increase in temperature causes a greater difficulty in the movement of electrons due to collisions with the atoms of the conductor. In addition, the movement of electrical current along a conductor requires energy which, encountering a resistance, produces heat (Joule effect) [8].

NO regulates photoreceptor metabolism in rods and cones primarily through activation of GC, a key enzyme of phototransduction. It is known that the volatile nitrites undergo rapid systemic clearance [9]. After inhalation, volatile alkyl nitrites release NO which can quickly spread through cell membranes and reach the retina through the eyeballs or tear pathways. NO exercises its activity as a second messenger activating GC and increasing the levels of cGMP. In a state of excess light exposure and extreme hyperpolarization, high concentration of cGMP in the outer segment of photoreceptor induces a rapid increase in voltage and electrical current (Ohm's first law) generating an electrochemical overload: the photoreceptor will be depolarized at light! Photoreceptor is a particular conductor because its section is not constant but is drastically reduced at the level of the cilium. The outer segment of a cone is shorter than a rod's one and at first it will oppose less resistance to high current flow ($R=\rho \cdot L/A$). Therefore, according to Ohm's second law, the greater flow of electrical current moving through the outer segment will find higher resistance to cross the smaller section of the cilium which will burn behaving like a fuse and blocking electrotonic transmission to the inner segment. The disruption of foveal inner segment/outer segment junction on SD-OCT is a characteristic feature [3] (Figure 1).

Furthermore, continuous high levels of intracellular cGMP, Ca and GLU might cause excitotoxicity, oxidative stress and apoptosis [10]. Finally, the author suspect that an analogous mechanism, characterized by small electrochemical interferences repeated for a long time, may contribute to onset of age-related macular degeneration. Voltage and electrical current will increase especially in the foveal cones. In fact, the probability of this electrochemical overload occurring will be greater at the posterior pole, due to the higher temperature, miosis, accommodation of the lens and morphology of the macula which promote hyperpolarization of cones, the photoreceptors most exposed to light (Figure 1).

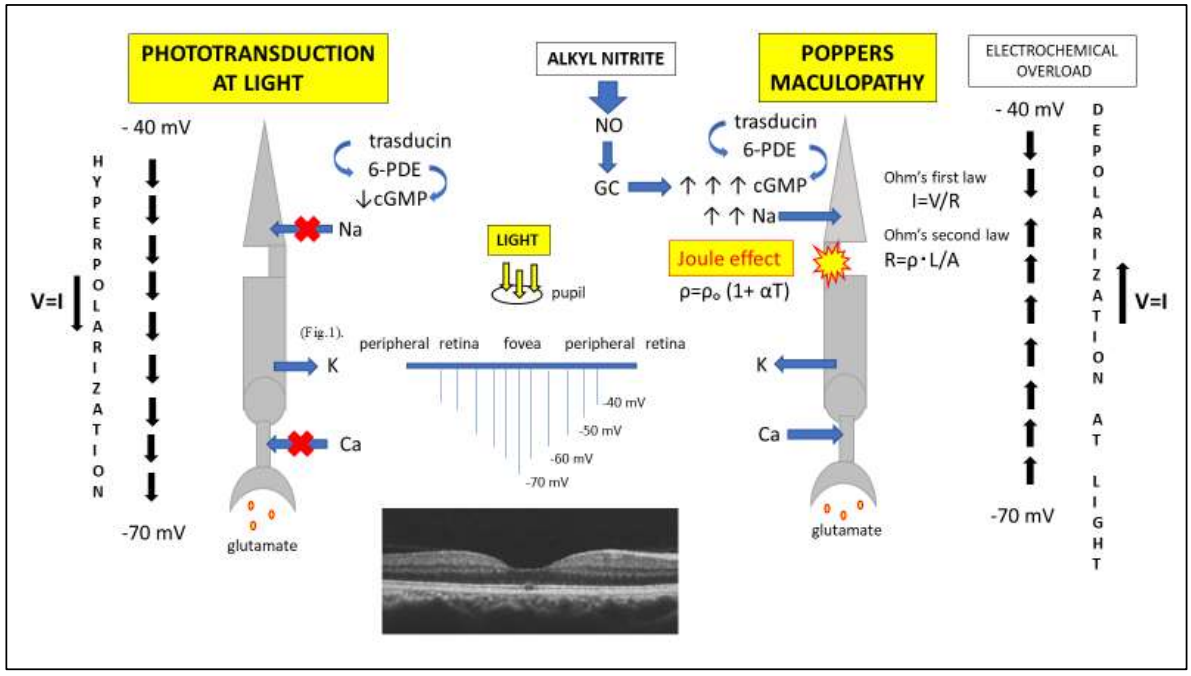

Figure 1: Poppers Maculopathy: at light, NO actives GC which synthesizes cGMP in outer segment of the foveal cone inducing a rapid increase in voltage and intensity (electrochemical overload). High electrical current flow finding higher resistance crossing the smaller section of the cilium burns it (Joule effect).

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