NEUROSCIENCE

REVIEW

I. Fasciani et al. / Neuroscience 432 (2020) 216–228

A New Threat to Dopamine Neurons: The Downside of Artificial Light

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Abstract—Growing awareness of adverse impacts of artificial light on human health has led to recognize light pollution as a significant global environmental issue. Despite, a large number of studies in rodent and monkey models of Parkinson's disease have reported that near infrared light has neuroprotective effects on dopaminergic neurons, recent findings have shown that prolonged exposure of rodents and birds to fluorescent artificial light results in an increase of neuromelanin granules in *substantia nigra* and loss of dopaminergic neurons. The observed detrimental effect seems to be dependent on a direct effect of light on the *substantia nigra* rather than a secondary effect of the alterations of circadian rhythms. Moreover, inferences from animal models to human studies have shown a positive correlation between the prevalence of Parkinson's disease and light pollution. The present article discusses experimental evidence supporting a potentially deleterious impact of light on dopaminergic neurons and highlights the mechanisms whereby light might damage neuronal tissue. Moreover, it analyses epidemiological evidence that suggests light pollution to be an environmental risk factor for Parkinson's disease.

Key words: Parkinson's disease, dopamine neurons, melatonin, artificial light, opsins, photoactivation.

THE INCREASE OF ARTIFICIAL LIGHT OVER THE YEARS AND ITS IMPACT ON HUMAN HEALTH

Light pollution is an excessive and inappropriate introduction of artificial light by humans, directly or indirectly, into the outdoor and indoor environments. Since 1970s, night-time satellite images of Earth have provided a striking illustration of the extent of artificial light. Meanwhile, growing awareness of adverse impacts of artificial light at night on scientific astronomy, human health, ecological processes and aesthetic enjoyment of the night sky has led to recognition of light pollution as a significant global environmental issue (Bennie et al., 2014). In a recent review, it has been calculated that if the trend of artificial lighting continues to grow with the actual speed, it will be doubled well before 2050 (Kyba et al., 2017). While the association between artificial light and sleep disorders is quite intuitive, the connection between artificial light and other human diseases is less obvious. Nevertheless, in recent years evidence suggests that light pollution could be a risk factor for several diseases including cancer, brain, cardiovascular and metabolic disorders (Lambert et al., 2015; Zubidat and Haim, 2017).

SOURCES AND PROPERTIES OF NATURAL AND ARTIFICIAL LIGHT THAT AFFECT THE BRAIN

Visible light, or simply light, is a radiation within a narrow segment of the electromagnetic spectrum ranging between 380 and 780 nm (Contin et al., 2016), although primate retina can only perceive wavelengths between 400 and 700 nm of the electromagnetic spectrum. Incandescent lighting is the oldest electrical lighting technique. However, because of its low efficiency and high operating cost, it has been progressively replaced by fluorescent lighting and Light Emitting Diodes (LEDs) that are more efficient light sources with lower operating costs, higher illumination efficiency and longer lasting.

These three types of artificial light sources produce different light spectra (Fig. 1). While incandescent and LED illuminations have continuous light spectra with all

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Abbreviations: LEDs, Light Emitting Diodes; SCN, suprachiasmatic nucleus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

https://doi.org/10.1016/j.neuroscience.2020.02.047
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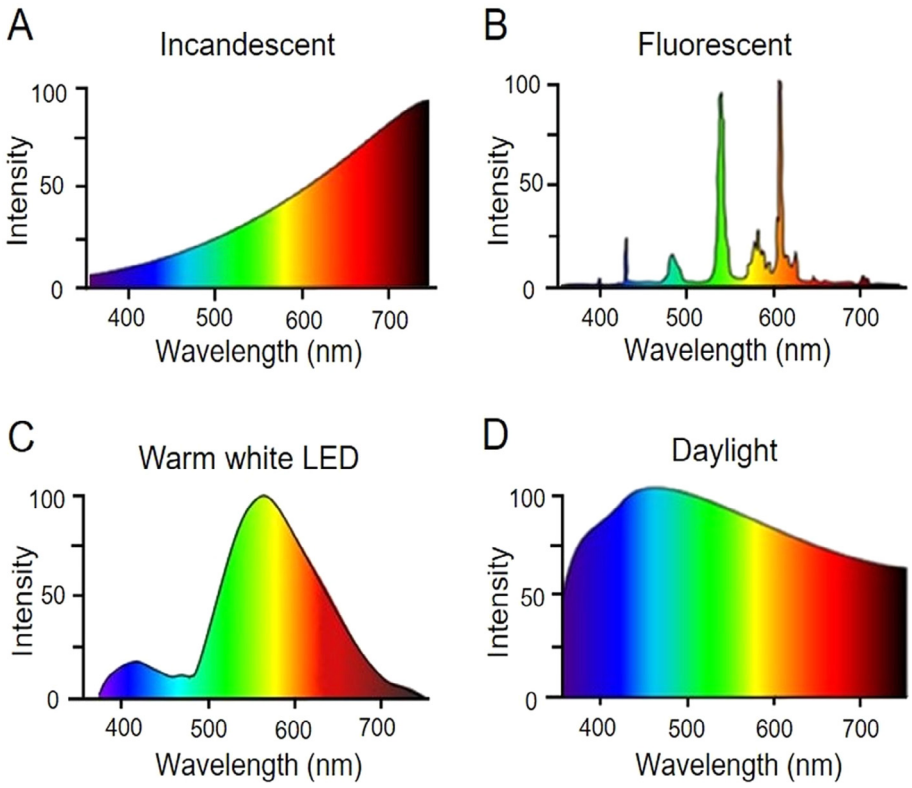

Fig. 1. Spectral characteristics of **(A)** incandescent light, **(B)** fluorescent light, **(C)** LED warm light and **(D)** sun light.

visible colors present, the spectrum of fluorescent light is produced by a blend of phosphors whose wavelength peaks in the range of primary colors, such as red, green and blue, generating the white light. Furthermore, fluorescent lamps flicker at 100 or 120 Hz depending on the frequency of the power supply (50 or 60 Hz), and this flickering has been associated to health problems for individuals with light sensitivity (Sandström et al., 1997; Inger et al., 2014). In comparison, sunlight has a continuous spectrum with no bright lines or peaks at specific wavelengths and extends from the ultraviolet to the near and far infrared region (Fig. 1D).

Biological tissues through retinal and non-retinal photoreceptor molecules, known as opsins, can detect light. Retinal photoreceptors are deputed to vision and are found in the eyes, while non-retinal photoreceptors are present in a variety of vertebrates, normally in the diencephalons, where they usually respond to seasonal variation of light. For example, opsin 5 in the paraventricular organ of quail appears to be a deep brain photoreceptive molecule that regulates seasonal reproduction (Nakane et al., 2010). Apart from the brain, opsins have also been found in other organs like for example the lung (Barreto Ortiz et al., 2017) but their role is currently unknown.

In addition to opsin photoreceptors, other endogenous and exogenous photosensitive compounds can mediate non-visual responses to light. Ultraviolet (UV) light is essential for vitamin D synthesis and reduced levels of this vitamin, for example by inadequate sun exposure, can lead to osteomalacia or rickets when it occurs in children (de Borst et al., 2011). Although the energy for photoactivation decreases at longer wavelengths (Ala-Laurila et al., 2004), photoactivation can also occur in the visible range spectrum; for example, both UV and visible light activate porphyrins (Giovannetti, 2012). Furthermore, Shell et al. (2014) were able to induce the scission of the weak Cobalt-Carbon bond of Vitamin B_{12} using wavelengths at up to 800 nm. Since longer wavelengths penetrate deeper in biological tissues (see below), the occurrence of photoactivation at these wavelengths indicates how profoundly visible light could affect biological processes.

INFLUENCE OF LIGHT ON THE BRAIN: CIRCADIAN ENTRAINMENT VIA THE SUPRACHIASMATIC NUCLEUS (SCN) AND DIRECT PHOTOCHEMICAL DAMAGE

Light can affect biological organism in two ways: a) by altering the circadian rhythm or b) by photothermal, photomechanical and photochemical mechanisms. Introduction of artificial light at night or shifting away from the naturally occurring solar light cycle in favor of artificial and sometimes irregular light schedules produces alteration of circadian rhythms and is associated with increased risk for cancer (Stevens, 2009), sleep disturbances (Kohyama, 2009), mood and metabolic disorders (Driesen et al., 2010; Fonken et al., 2013). The pathological consequences of the alteration of circadian rhythms seem to be correlated with the desynchronization of clock gene expression in the hypothalamus and in peripheral tissues that are entrained by the endocrine system or the central nervous system (Guo et al., 2005; Fonken et al., 2014).

While photothermal and photomechanical mechanisms can be reconducted exclusively to incandescent and laser light, photochemical damage can be produced also by fluorescent and LED light (Contin et al., 2016). Photochemistry has a huge importance in nature as it is the basis of photosynthesis, vision, and the formation of vitamin D, and it can be driven by UV, visible and infrared light (Glusac, 2016) (Fig. 2). Photochemical reactions access high energy intermediates that cannot be generated in temperature-driven reactions, in this way they overcome large activation barriers in a short period of time

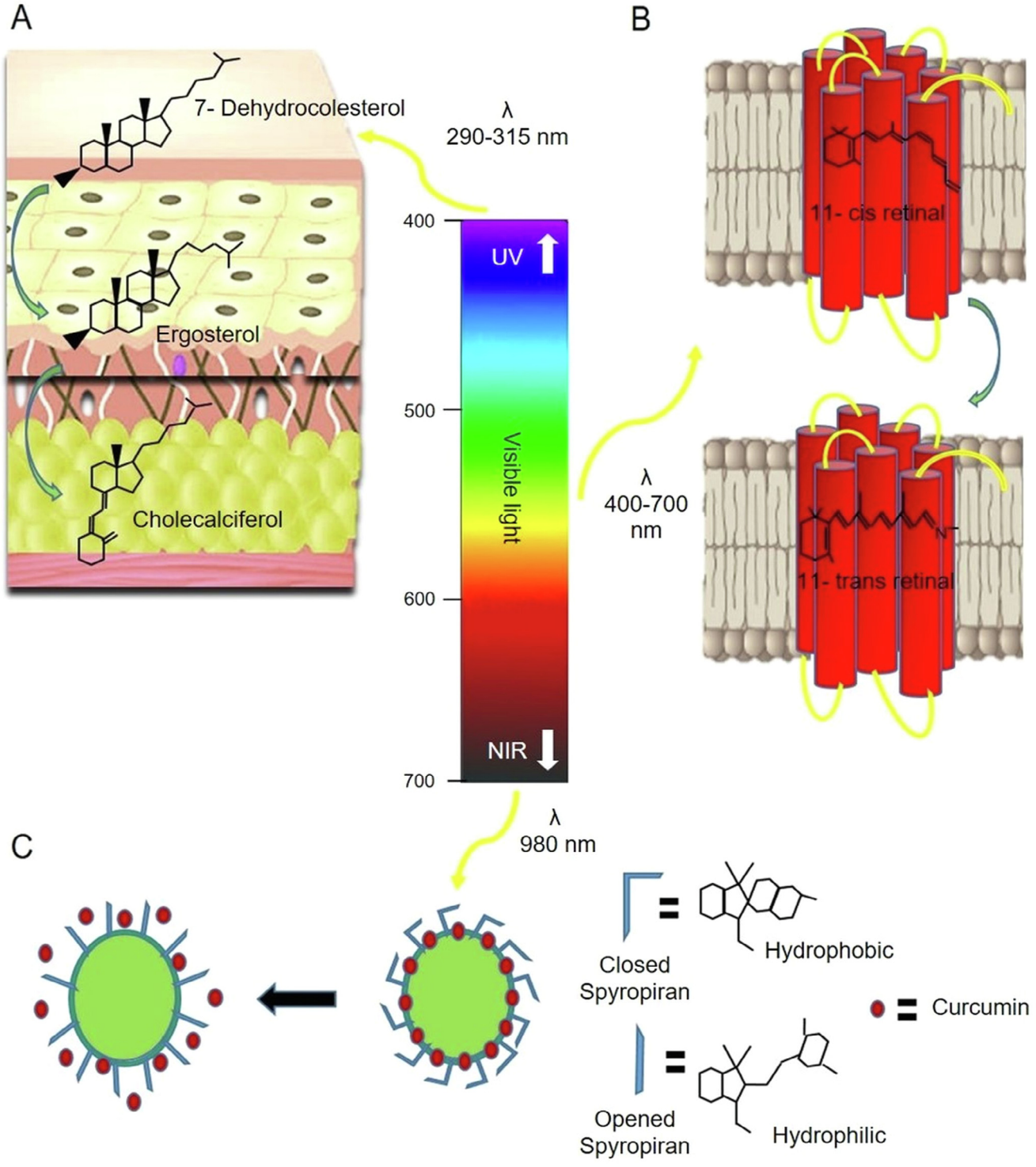

Fig. 2. Photochemical modification of biological molecules by light. Differently from temperature-driven reactions, photochemical reactions access high energy intermediates that overcome large activation barriers, allowing reactions that otherwise would have been impossible or extremely long by thermal processes to occur in a short period of time. Photoactivation can be induced by UV light, as illustrated by the transformation of 7-dehydrocholesterol in Vitamin D **(A)**, and visible light, as illustrated by the transformation of 11-cis retinal in all-trans retinal in the opsin receptor **(B)**. Likewise, the low energy near infrared light (NIR) can induce photoactivation, and it has been explored recently as an uncaging instrument in small molecule drug delivery. As illustrated in **(C)**, NIR light can transform spiropyran from a hydrophobic to a hydrophilic molecule that leads to the uncaging and release of drugs encapsulated inside a supramolecular structure (Alabugin, 2018).

allowing reactions that otherwise would have been impossible or extremely long by thermal processes. In these reactions, light provides the excitation to elevate the molecule to a higher energy state, and, in general, excited species are prone to participate in electron transfer redox reaction.

Interestingly, strong evidences have recently suggested that artificial light can damage the retina by a photochemical mechanism. In fact, it seems that excessive artificial illumination can cause retinal degeneration by inducing massive activation of retinal chromophores, which in turn might lead to the production of free radicals able to oxidize lipids, proteins, and DNA, thus producing intracellular oxidative stress (Contin et al., 2016). Notably, in order to cause damage by direct photosensitization, light must reach the target tissue. While light can easily reach the retina by passing through the transparent tissues composing the eye, it is less intuitive how it can reach deep brain structures and cause photosensitization.

ROUTES OF LIGHT INTO CEREBRAL MATTER AND PENETRATION OF *SUBSTANTIA NIGRA*

Penetration depth of light in biological tissues depends both on its wavelength and on the composition of the irradiated tissue. The lower absorbance, and consequently, the best transmission of light in tissues, occurs in the red and near infrared range between 600 and 1300 nm, which is the region of the light spectrum known as "the diagnostic and therapeutic window" (Taroni et al., 2003). UV light is highly photosensitizing, as it carries strong activation energy, but it is poorly penetrating, and thus, it affects only the skin. On the contrary, longer wavelength light has proportionally less energy but penetrates more deeply in the tissues.

Van Brunt et al. (1964) provided the first evidence that light can penetrate deeply into the brain of a variety of mammals, crossing the scalp and the skull and reaching the temporal lobe and the hypothalamus. Furthermore, in 1977 Jobsis showed that light photons can travel a 13.3 cm path from side-to-side of the human head. In 10 seconds, he was able to register, from one side of the head, a higher than background (darkness) photon count emitted from a light source positioned at the contralateral side of the head. Finally, in a recent article, Wang and Li (2018) by comparing the fluence distribution, penetration depth and the intensity of light-tissue-interaction of four candidate wavelengths (660, 810, 980 and 1064 nm) within the brain, found that the 660 nm light was the best, retaining a fluence rate of 10^{-5} W/cm^2 at 6 cm depth after crossing the scalp and the skull. It is worth to note that 660 nm is within the range of visible light. These observations suggest that tiny amount of light can reach deep brain structures proportionally to the time of exposure, the brightness of the light source, the wavelength used, and the composition of the crossed tissues. At shorter wavelengths, hemoglobin and melanin play the major role in absorbing light in tissues, while at longer wavelengths light is heavily absorbed by water.

Preliminary data from our group showed that fluorescent light with wavelength above 600 nm can cross the scalp and the skull of rats and mice, and reach the *substantia nigra* (Romeo et al., 2013, 2014, 2017). These results do not exclude that shorter wavelengths can reach the *substantia nigra* inasmuch as the amount of light at shorter wavelengths could be under the detection limit of the spectroradiometer used to detect light. By covering different parts of the animal's head with aluminum foil, it was shown that the shorter path that light should take to reach the *substantia nigra* is through the eyes or the sinus cavities, as supported by the ~50% reduction of the light signal when eyes were covered (Romeo et al., 2014, 2017). Retrospectively, this is not surprising if we consider that eyeballs in rodents occupy a large portion of the forehead and their tissues (*cornea*, *aqueous humor*, *lens* and *vitreous humor*) are transparent to light while *sinus cavities* are mostly empty. Furthermore, difference in the intensity of light penetration was observed between black and white mice, with light reaching the *substantia nigra* twice as much in white than black mice (Romeo et al., 2017).

Neuroradiological and magnetic resonance imaging indicated that also in the human brain the shortest path that light should take to reach the *substantia nigra* would be through the eyes or the *sinus cavities* (Romeo et al., 2014) (Fig. 3). Light reaching the retina has already travelled part of its path inside the head with a minimal reduction of its intensity as eye tissues are mostly transparent. Then, through the retro-orbital tissue, light could reach the large superior orbital fissure and enter the internal cavity of the skull reaching the mesencephalon. The *superior orbital fissure* is an area of the orbit lacking bone. A preliminary study was conducted to measure the distance that light should travel to reach the *substantia nigra* through this path in human, and it was calculated that, ~8 cm stands, on average, between external light and dopamine neurons in the *substantia nigra*. Within this path, ~5.6 cm is occupied by transparent fluids (eye vitreous and aqueous humor, and cerebrospinal liquid) and only ~2.4 cm by biological tissue (Romeo et al., 2014). A statistical evaluation showed a gender differences in the anatomy of this light path, with males having a superior orbital fissure much larger than females (La Marra et al., 2016). This anatomical difference could allow a much greater amount of light to reach the *substantia nigra* in males compared to females.

ARTIFICIAL LIGHT AND ITS DETRIMENTAL EFFECT ON DOPAMINE NEURONS IN RODENTS AND BIRDS

In order to test whether light has a detrimental effect on dopamine neurons in *substantia nigra*, Romeo et al. (2013, 2017) exposed rats and mice to a fluorescent lamp positioned 30 cm above the cage and kept on 24 h a day. In both, rats and mice, three months of continuous light exposure resulted in about 30% reduction of tyrosine hydroxylase positive neurons in *substantia nigra* and a parallel decrease in dopamine and its metabolites in the *striatum*. We excluded that this alteration was the consequence of the interruption of the circadian rhythms by using blind rats in which a similar reduction of tyrosine hydroxylase positive neurons was observed (Romeo et al., 2013). This conclusion was also supported by data generated in mice. One of the most sensitive markers of the alteration of the circadian rhythms is the level of corticosterone. Remarkably, the only difference between mice

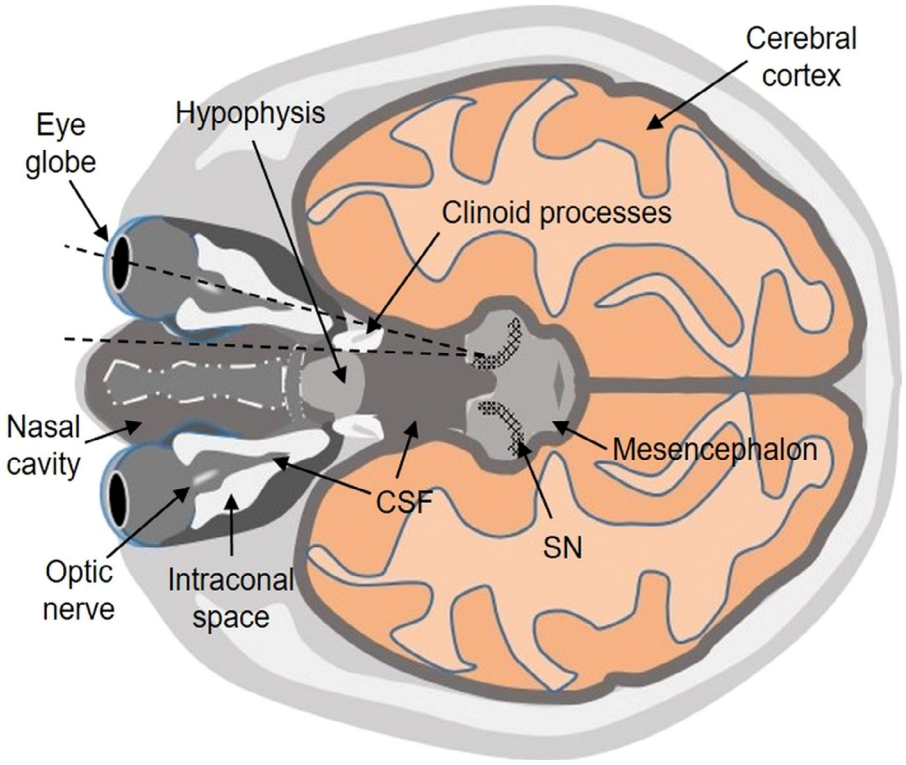

Fig. 3. Schematic representation of an axial Magnetic Resonance Image scan of the human head. This image shows that the cerebrospinal fluid (CSF) occupies most of the space interposed between the superior orbital fissure and the mesencephalon, furthermore, CSF is present around the optical nerve in the intraconal space. The superior orbital fissure is a small hole which connects the orbit to the middle cranial fossa. The dashed black lines indicate the shortest paths light should take to avoid most of the brain tissue and the bone and reach the *substantia nigra* (SN) in the *mesencephalon*. Light crossing the eye globe has already travelled part of its path inside the head with a minimal reduction of its intensity as eye tissues are mostly transparent. Then, through the retro-orbital tissue, light could reach the large superior orbital fissure, enter the middle cranial fossa that is occupied by CSF and reach the mesencephalon. In alternative, light could access the middle cranial fossa through the nasal cavity that is mostly empty.

under continuous fluorescent light treatment and mice under a normal 12 h light/12 h dark cycle, was the sharp increase in urine corticosterone level during the first 24 h of treatment that returned to normal levels after 48 h and throughout the rest of the examination period (Romeo et al., 2017), suggesting that this stimulated increase undergoes rapid habituation. These data point to a direct effect of light on dopaminergic neurons rather than an indirect influence of the alteration of the circadian rhythms. Though, we cannot exclude that this detrimental effect could derive by the indirect activation of dopamine neurons through the specific anatomical pathway linking the retina to the *substantia nigra*. This pathway has been described by Comoli et al. (2003) and run from the retina to the superior colliculus that send direct projection to the substantia nigra. Dommet et al. (2005) have shown that through this pathway, light flashes delivered to the retina, can increase the phasic release of dopamine. Therefore, it cannot be excluded that in condition of excessive light stimulation this pathway could convey dead input to the *substantia nigra.*

Another interesting observation was the appearance of melanized neurons in the *substantia nigra* of rats under continuous fluorescent light. Neuromelanin is normally absent in dopamine neurons of young rats but it appears in very old (23 months) rats, as detected by electron microscopy (DeMattei et al., 1986). Since neuromelanin derives from the oxidation of dopamine and DOPA into dopaquinone and semiquinone in presence of iron (Zecca et al., 2001), it is likely that the formation of neuromelanin in *substantia nigra* follows the direct oxidation of dopamine by light. It is interesting to note that dopamine in complex with Fe^{3+} shows two bands of absorbance, with maxima at 437 and 740 nm (Barreto et al., 2009). Using the iron chelator deferoxamine in order to inhibit neuromelanin synthesis, Zecca and co-workers (2001) have shown that iron is involved in neuromelanin synthesis. As a matter of fact, iron is abundant in areas rich in dopaminergic neurons, namely the *globus pallidus*, *putamen*, and *substantia nigra* (Sian-Hülsmann et al., 2011). The spectrum of the fluorescent lamp we used to irradiate rats and mice shows peaks in the same range of the absorbance of dopamine in complex with Fe^{3+} (Barreto et al., 2009).

If light causes neuromelanin formation, it is likely that diurnal animals living in open fields, e.g., savannas and deserts, should have a more pigmented *substantia nigra* than nocturnal animals. Re-examining the pivotal work published in 1961 by David Marsden, entitled ‘‘Pigmentation in the nucleus *substantiae nigrae* of mammals’’, where the pigmentation of the *substantia nigra* of 49 species of animal including man were examined, we classified these species on the basis of their exposure to sunlight (see Table 1 in Romeo et al., 2013) and found that there was a good correlation between light exposure and nigral pigmentation, with pigmented animals being significantly more exposed to light than non-pigmented ones.

In order to magnify the detrimental effect of light in *substantia nigra*, we exposed a group of mice to fluorescent light for 6 months, to see if the percentage of neurons undergoing degeneration could increase due to the longer period of exposure. Contrary to expectations, only a modest increase in dopamine neuron degeneration was observed in the *substantia nigra* of these animals (40% reduction of tyrosine hydroxylase positive neurons respect to 30% in mice exposed for 3 months), although the pattern of dopamine content and its metabolites changed completely, with the content of dopamine and HVA

normalized while DOPAC increased over the control levels (Romeo et al., 2017). These results suggest that when dopamine neurons are reduced below a critical threshold, the remaining neurons may compensate for the loss by establishing new synapses and synthesyzing a larger amount of dopamine, which in turn results in an increased metabolism. Such effect has been demonstrated by Stanic et al. (2003), who clearly showed that after 16 weeks of a 6-hydroxydopamine-induced partial lesion of dopamine neurons, axons in the *pars compacta* of the rat *substantia nigra* establish new synapses and reinnervate the dorsal striatum, restoring normal dopamine content and increasing DOPAC levels.

A set of experiments was done to test the ability of light to cause neurodegeneration also in albino C57Bl/6J/Tyr^{-} mice, a white mice mutant for the tyrosinase enzyme gene that does not synthesize melanin, causing a higher amount of light to penetrate the skull and scalp and reach the *substantia nigra*. Despite this difference, albino mice exposed to fluorescent light for three months showed a loss of dopamine neurons in *substantia nigra* equivalent to that occurring in black mice, indicating that the greater amount of light reaching the *substantia nigra* in white mice did not cause more damage (Romeo et al., 2017). The most parsimonious hypothesis explaining this result is that compensatory mechanisms would prevent further damage when a threshold loss of dopamine neurons is reached. Whether tyrosinase is expressed in *substantia nigra* and whether it is involved in the neuromelanin-biosynthetic pathway is controversial (Tief et al., 1998; Tribl et al., 2007). Nevertheless, the presence of tyrosinase activity in the *substantia nigra* was reported by Greggio et al. (2005), who demonstrated the incorporation of [^{14}C]-tyrosine into melanin in dopaminergic neurons. The lack of this alternative route of dopamine metabolism in *substantia nigra* could explain why in albino mice lacking the tyrosinase enzyme and exposed to light damage, the dopamine content was not altered in contrast to its metabolites, DOPAC and HVA, that decreased. The lack of this alternative route of dopamine metabolism could compensate the decrease induced by the reduction in dopamine neurons. This concept is reinforced by the fact that in albino mice the basal level of DOPAC was almost double than in black mice, suggesting that in the absence of tyrosinase the metabolism of dopamine to DOPAC is increased.

Supporting the detrimental effect of light on dopamine neurons, Taufique and Kumar (2016) showed a significant reduction in the number, density and area occupied by tyrosine hydroxylase-immunoreactive neurons in the ventral tegmental area and in the *substantia nigra* of Indian crows exposed to constant fluorescent light for two weeks. Such a short time to induce damage could be explained by the smaller volume of the crow head that would allow a greater amount of light to reach deep brain structure.

In contrast with the detrimental effects of light documented above, many experimental data demonstrate that near infrared light plays a protective role against dopamine neurons degeneration induced by neurotoxins like 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Johnstone et al., 2014; Moro et al., 2013; Oueslati et al., 2015; Peoples et al., 2012; Purushothuman et al., 2013; Reinhart et al., 2015; 2016a,b; Shaw et al., 2010). Near infrared light ranges from about 700 to 2500 nm of the light spectrum, and the spectrum of the fluorescent light includes a small peak at 710 nm. Endorsing the lack of toxicity of light at this wavelength, mice exposed to a 710 nm LED light for 3 months did not show any alteration in the number of dopamine neurons in *substantia nigra* nor in the levels of dopamine or its metabolites (Romeo et al., 2017). These data underpin the concept that only specific components of the fluorescent light spectrum can damage dopamine neurons.

EFFECT OF LIGHT ON THE FIRING ACTIVITY OF DOPAMINE NEURONS IN *SUBSTANTIA NIGRA*

Even though the 710 nm LED light did not have detrimental effect on dopamine neurons in *substantia nigra*, primary cultures of mouse mesencephalic neurons exposed for 20 minutes to this wavelength responded with an increase in dopamine release (Romeo et al., 2017). A major issue arising from this observation concerns the possibility that the 710 nm LED light could induce electrophysiological changes in the activity of dopaminergic neurons *in vivo*. This was investigated by local opto-stimulation of dopamine neurons in the *pars compacta* of the *substantia nigra* in anesthetized rats. By a micro-optical fiber stereotaxically implanted in the *substantia nigra pars compacta*, a 710 nm LED light was delivered, and the firing rate of dopamine neurons was registered. Surprisingly, light stimulation induced a four-fold increase of spontaneous firing rate of dopamine neurons, from ~2.2 impulse/s to ~8.8 impulse/s and a shifting of the firing from a slight irregular pattern to a burst pattern. When stimulation ceased, firing did not significantly decrease maintaining significantly higher values compared to the pre-stimulus period. This effect seems to be specific for dopamine neurons inasmuch as neurons in the *ventrobasal thalamic nuclei* did not change their discharging pattern upon light stimulation (Romeo et al., 2017).

Importantly, while several works have demonstrated that neurons transfected with the light-gated ion channel rhodopsin can be specifically activated by light (Stauffer et al., 2016), Romeo et al. (2017) recorded activation in native dopamine neurons after light illumination has never been detected. The mechanism whereby light directly influences neuronal firing is puzzling and undoubtedly requires further studies to clarify how it works. It is possible to exclude the role of heat on the tissues nearby the optical fiber in triggering the observed changes, since the calculated temperature increase would have been less than 0.1 °C per hour, besides, the activity of the *ventrobasal thalamic nuclei* would have otherwise been affected and it was not. Furthermore, it can be excluded that changes in the *substantia nigra* neuronal activity were driven by the stimulation of retinal photoreceptors, since light was delivered directly in the *substantia nigra* through

a micro optical fiber. A hypothesis that could explain these results entails the role of opsin receptors in mediating the effect of light on dopaminergic neurons firing rate. Recent studies have provided evidence that opsin receptors have a wider diffusion in the brain than previously thought and are not strictly confined to brain areas primarily concerned with vision and light-induced circadian rhythms (Nissilä et al., 2012). For example, OPN3 has been reported to be abundant in the interneurons and striosomes of the monkey striatum (El Massri et al., 2018). A similar localization of OPN3 has been observed in the human *substantia nigra* (White et al., 2008). Given that, it is possible that the starting stimulus that leads to the increase in the firing activity of dopaminergic neurons is probably through the activation of opsin receptors, afterward, the release of dopamine, probably by dendrites (Ludwig et al., 2016), may account for the sustained electrical activity that continued after the light stimulus is turned off (Fig. 4). This interpretation would fit with the result in mesencephalic cell lines which respond to the 710 nm LED light exposure with an increase in dopamine release.

It is worth noting that *in vivo* electrical stimulation that changes the activity of dopamine neurons from a regular or slight irregular pattern to a burst-rich pattern is accompanied by an increase in dopamine release (Gonon et al., 1988). Since dopamine is released by nigrostriatal neurons also at dendritic level (Cheramy et al., 1981), an increased intranigral release of dopamine would affect a large population of neurons, exerting excitatory effects as reported in the literature (Berretta et al., 2010). Furthermore, changes in the dendritic release of dopamine are generally of long duration (Ludwig et al., 2016) and could well explain the persistence of the firing rate change observed by Romeo et al. (2017) when light was turned off. Further support to a possible involvement of dopamine in the sustained effects of light arises from recent optogenetic studies in which brief pulses of light delivered to genetically-modified dopamine ventral tegmental area neurons expressing channelrhodopsin-2 (ChR2), have been reported to induce a phasic release of dopamine in the ventral striatum (Adamantidis et al., 2011; Stauffer et al., 2016). Other than stopping neurodegeneration in Parkinson's disease as suggested by the preclinical studies reported above (Johnstone et al., 2016), the stimulating effect of 710 nm LED light on dopaminergic neurons suggests that, near infrared light could potentially have a direct beneficial effect on the motor performance of patients by promoting dopamine release.

POTENTIAL INDIRECT TOXICITY OF LIGHT ON DOPAMINE NEURONS: BLUNTING THE CIRCADIAN RHYTHMS OF MELATONIN SECRETION

Light has a fundamental role in synchronizing circadian rhythms and melatonin, a neurohormone secreted by the pineal gland, coordinates this effect by binding to MT_1 and MT_2 receptors located in the SCN, the master circadian pacemaker. Melatonin is secreted rhythmically with decreased synthesis during the light period of the day (Arendt, 1998), from this follows that an excessive exposure to light can diminish the total amount of melatonin secreted during the day.

A growing number of evidences indicates a beneficial effect of melatonin on the dopamine system: melatonin can reduce the amphetamine-induced dopaminergic fiber degeneration in the *striatum*, *nucleus accumbens* and prefrontal cortex (Kaewsuk et al., 2012) as well as α-synuclein overexpression after amphetamine treatment in postnatal rats (Sae et al. 2012). Expression of both MT_1 and MT_2 melatonin receptors has been observed in mouse, rat and human *striatum*; furthermore, neuroanatomical mapping of rat *substantia nigra* revealed a high level of the MT_1 receptor in the *pars compacta* and the MT_2 receptor in the *pars reticulata* of the *substantia nigra* (Ng et al., 2017). Moreover, a direct interaction between melatonin MT_1 and MT_2 receptors and dopamine transporter (DAT) has recently been demonstrated, in which MT_1 and MT_2 regulate dopamine transporter cell-surface availability, limiting dopamine reuptake (Benleulmi-Chaachoua et al., 2018).

In addition to its actions on MT_1 and MT_2 receptors, melatonin regulates cytokine production in immunocompetent cells thus contributing to reduce chronic and acute inflammation (Esposito and Cuzzocrea, 2010) and has a direct free radical scavenger and an indirect antioxidant effects (Luo et al., 2018). According to these anti-inflammatory and antioxidant effects, melatonin plays a neuroprotective role in neurodegenerative diseases, and its reduction could increase the sensitivity of tissues to damage. For instance, retinal photoreceptors, as well as pineal cells, do contain the metabolic compounds necessary for the synthesis of melatonin and its antioxidant action against light-induced oxidative stress and retina degeneration has been reported (Longoni et al. in 1997; Marchiafava and Longoni, 1999). These authors observed that the protective action of endogenous melatonin in rod outer segment, which are characterized by high energy demand to sustain phototransduction, is abolished in rod photoreceptors isolated from inner segment as melatonin diffuses to the outer segment to reach, by night, peak levels needed to scavenge the light-induced peroxyl radicals.

Melatonin has been also shown to attenuated MPTP-induced loss of nigral dopaminergic neurons in mice *substantia nigra* (Naskar et al., 2015). In the MPTP model of Parkinson's disease mitochondrial respiration impairment and neuroinflammation concur to promote neurodegeneration; melatonin possesses the double characteristic to recover mitochondrial bioenergetics and block neuroinflammation (López et al., 2017). These results support the concept that reduction in melatonin secretion by excessive light exposure could have a negative impact not only on sleep but also on dopamine neurons survival in Parkinson's disease. Along with these findings, Videnovic et al. (2014) and Breen et al. (2014) reported a significant reduction in the amplitude of melatonin secretion in Parkinson's disease patients, supporting the involvement of melatonin in the sleep disorders commonly reported in these

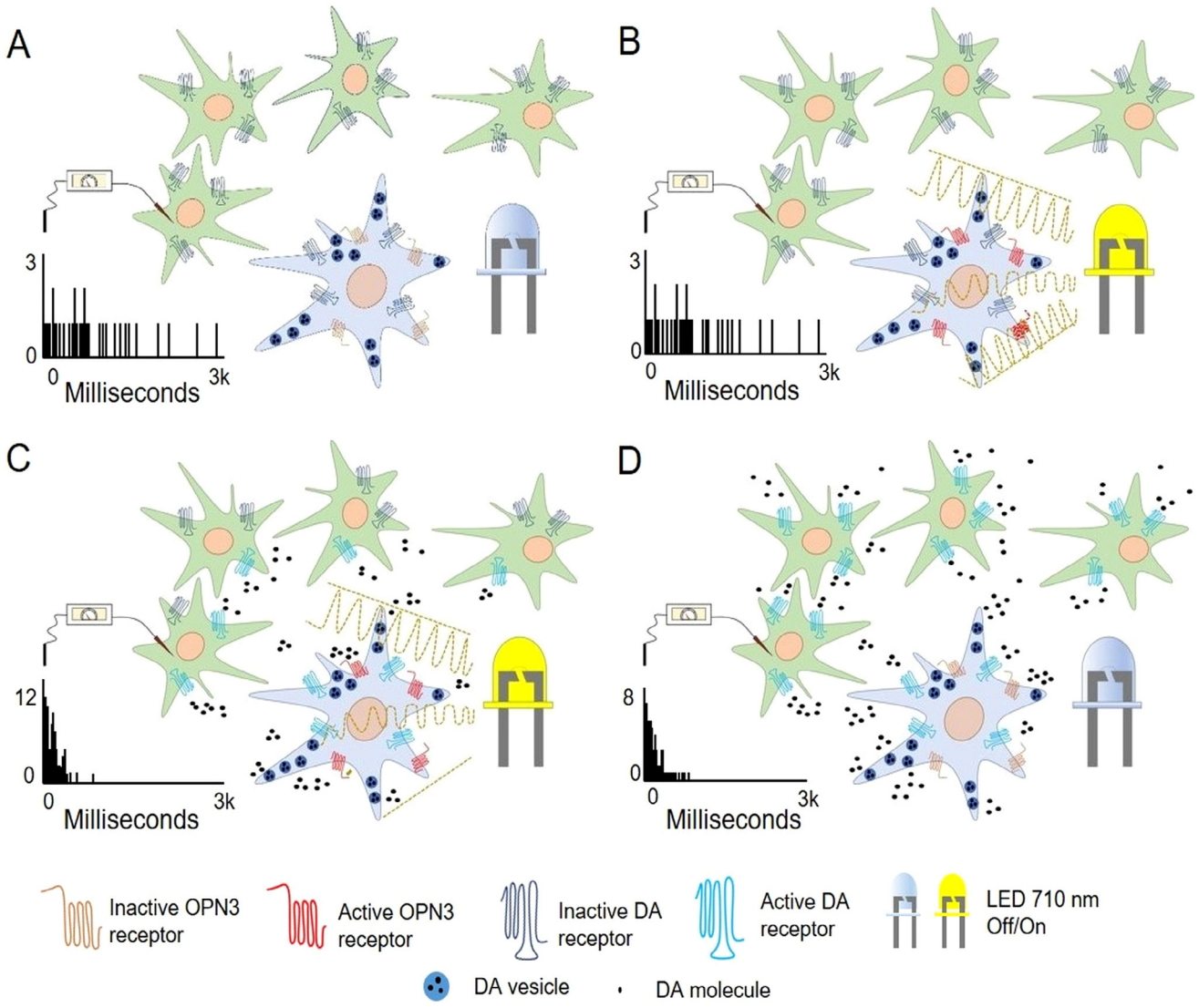

Fig. 4. Hypothetical mechanism of the firing rate change of dopamine neurons in substantia nigra after 710 nm LED light illumination. Spontaneously active dopamine neurons typically fire in a slow (3–8 Hz) irregular pattern **(A)**. 710 nm LED light illumination changes this firing pattern probably by activating the OPN3 receptors expressed on the plasma membrane of these neurons **(B)**. After light switch-on, OPN3 receptors stimulates the dendritic release of dopamine (Ludwig et al., 2016), that in turn activates dopamine auto and etero-receptors changing the firing pattern of dopamine neurons from the slight irregular pattern to the burst pattern **(C)**. This effect persists after light switch-off suggesting a slow clearance of dopamine from the tissue **(D)**, that is consistent with a volumetric release of dopamine by dendride (Ludwig et al., 2016).

patients (Barone et al., 2009) and in the progression of the neurodegeneration.

POTENTIAL DIRECT TOXICITY OF LIGHT ON DOPAMINE NEURONS: NEUROMELANIN FORMATION, MITOCHONDRIAL DAMAGE AND DOPAMINE OXIDATION

An alternative mechanism through which light may induce toxicity could be by the direct photosensitization of biological molecules in the target tissue. As mentioned above, the only clear evidence of a direct damaging effect of artificial light on biological tissues has been reported for the retina (Contin et al., 2016 and reference therein). Two types of damages induced by light on the retina are recognized: a) a damage produced by low irradiance levels of white light, mediated by the activation of rhodopsin in photoreceptor cells, and b) a damage produced by exposure to high irradiance with an action spectrum peaking at short wavelength of white light, that injuries the retinal pigment epithelium and some photoreceptor cells (Contin et al., 2016; Grimm et al., 2001; Organisciak et al., 1989). The second effect is due to the formation of free radicals by light exciting photosensitive molecules (Contin et al., 2016). Gorgels and van Norren (1995) reported two types of damage depending on the wavelength used. Morphologic changes in retinas exposed to threshold doses of wavelengths from 320 to 440 nm were similar and consisted in pyknosis of photoreceptors. Retinas exposed to threshold doses of 470–550 nm had different morphologic appearances. In fact, retinal pigment epithelial cells were swollen, and their melanin had lost the characteristic apical distribution. Some pyknosis was found in photoreceptors.

Interestingly, mitochondria respiratory chain enzymes like cytochrome and flavin oxidases are source of free radicals that are produced by exposure to 400–760 nm light (Eichler et al., 2005; Osborne et al., 2008).

As a matter of fact, a great number of evidences suggests that mitochondrial dysfunction plays a critical role in the pathogenesis of Parkinson's disease (Winklhofer and Haass, 2010). The most compelling evidence that mitochondria play a pivotal role in the pathogenesis of this disease is the discovery that MPTP, a neurotoxin responsible for parkinsonism in young drug addicts (Langston et al., 1983), blocks the mitochondrial electron chain (Bové and Perier, 2012). MPTP crosses the blood brain barrier due to its lipophilicity and is oxidized to a pyridinium ion (MPP^+) by monoamine oxidase B. MPP^+ enters into dopaminergic neurons via the dopamine transporter and blocks the complex I (NADH ubiquinone oxidoreductase) enzyme in mitochondria (Markey et al., 1984; Javitch et al., 1985; Fornai et al., 1997; Winklhofer and Haass, 2010). Because of this block, ATP production decreases while generation of reactive oxygen and nitrogen species increases (Winklhofer and Haass, 2010; Osborne et al., 2016). Corroborating MPTP data, complex I activities are significantly reduced in patients with Parkinson's disease (Schapira et al., 1989). Considering that light can affect mitochondrial flavin and cytochrome oxidases causing an increase in reactive oxygen species, the most parsimonious hypothesis is that mitochondria could be the possible target for light to induce neurodegeneration in *substantia nigra* of rodents and birds.

As shown by Berman and Hastings (1999), exposure of mitochondria to dopamine quinone, generated by the addition of dopamine together with the enzyme tyrosinase, resulted in a large increase in the resting rate of mitochondrial respiration. Furthermore, they observed that exposure to dopamine quinone induced mitochondrial swelling. They attributed these effects to the oxidation of the sulfhydryl group of the mitochondrial permeability transition pore, a calcium-dependent pore that renders the inner mitochondrial membrane permeable to solutes. Changes in the permeability of this pore has been associated with osmotic swelling of mitochondria, loss of oxidative phosphorylation and finally to cell death (Rottenberg and Hoek, 2017). In this scenario, light irradiation could achieve tissue selectivity by inducing the formation of dopamine quinone (Sánchez-Rivera et al., 2003) that in turn could open the inner mitochondrial membrane permeable pore and promote mitochondrial dysfunction and cell death as illustrated in Fig. 5.

LIGHT EXPOSURE IN RELATION TO THE INCIDENCE OF PARKINSON'S DISEASE

Parkinson's disease is one of the most common neurodegenerative diseases with late-life onset. The disease occurs when 60–80% of the dopaminergic neurons in *substantia nigra* are damaged and the dopamine produced is not enough for a correct motor control. Several environmental factors have been identified in the last few years and they either confer increased risk or are inversely correlated with the appearance of Parkinson's disease. For example, the exposure to certain types of pesticides has been associated with an increased risk of developing Parkinson's disease, while instead, cigarette smoking, consuming tea and/or coffee have been inversely correlated with the Parkinson's disease appearance (Delamarre and Meissner, 2017).

While light has never been considered as a risk factor for Parkinson's disease, some studies deserve consideration. A geographical relationship between latitude and proportional mortality ratios for Parkinson's disease by state of birth in the U.S.A. was originally found by Kurtzke and Goldberg (1988) and Lux and Kurtzke (1987) with a north-to-south gradient. However, such a north-to-south gradient was not observed in the studies of Lilienfeld et al. (1990) and Betemps and Buncher (1993). The latter studies found a geographical relationship between longitude and proportional mortality ratios for Parkinson's disease by state of birth in the U.S.A. with an east-to-west gradient. These differences could reflect changes in lifestyle of the population as the studies of Lilienfeld et al. (1990) and Betemps and Buncher (1993) consider geographic distribution of Parkinson's disease death rates in the same regions two decades later. The geographical variation of Parkinson's disease could be correlated to vitamin D insufficiency in patients who are not sufficiently exposed to sunlight (Evatt et al., 2008). As a matter of fact, a nationwide French study including 69,010 subjects confirmed that deficiency in vitamin D, which is strictly correlated to sunlight exposure, is associated with Parkinson's disease (Kravietz et al., 2017).

On the other hand, considering artificial light, in a correlation analysis that accounted for population density, the age- and race adjusted Parkinson's disease prevalence significantly correlated with average satellite-observed sky light pollution (Romeo et al., 2013). This correlation can be appreciated by comparing the prevalence of Parkinson's disease in U.S.A., as illustrated by Willis et al. (2010), with a graded color map of light pollution (see: https://www.lightpollutionmap.info). A notable exception to this correspondence is the south/west coast of California, where there is a high level of light pollution but a low prevalence of Parkinson's disease. This comparison does not give any information on whether there is any causal link between Parkinson's disease and light pollution. For instance, there are many reasons why this parallelism could exist. Among them, the fact that higher urbanized areas are at a higher risk of industrial pollutants. Release of manganese and copper during the manufacture of some industries, have been associated with a higher risk of Parkinson's disease in U.S.A. (Willis et al., 2010). Furthermore, car emission is greater in high traffic urbanized areas, and two recent studies have linked this type of pollution with an increased risk of Parkinson's disease (Lee et al., 2016; Ritz et al., 2016).

Despite these confounding factors, the correspondence between light pollution and Parkinson's disease requires careful consideration, as indirect evidence points to this relationship. An increased risk of

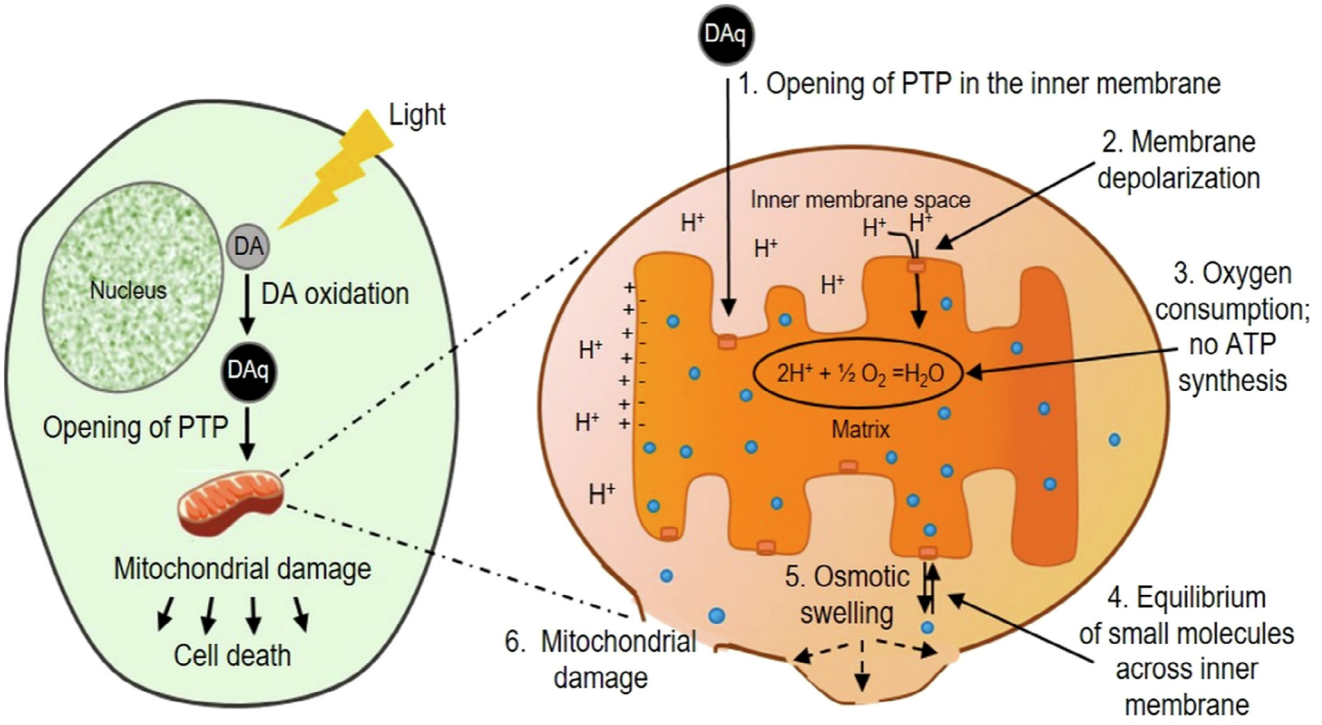

Fig. 5. Hypothetical mechanism of damage to dopaminergic neuron by light. As shown by Berman and Hastings (1999), dopamine quinone, by oxidizing sulfhydryl group, could open the inner mitochondrial membrane permeable pore (PTP). Solutes will equilibrate across the inner mitochondrial membrane through the open pore, increasing the osmotic pressure of the inter membrane space, that in turn will cause swelling of the mitochondria and finally cell death (Rottenberg and Hoek, 2017). Light could enter in this mechanism by inducing the formation of dopamine quinone and by this way damaging selectively the dopamine neurons.

Parkinson's disease has been observed in teaching and health care workers (Firestone et al., 2010; Park et al., 2005; Tsui et al., 1999) and generally in subjects with higher education (Frigerio et al., 2005). Conversely, subjects with occupations presumed to involve significant levels of physical activity have a decreased risk of Parkinson's disease (Frigerio et al., 2005). These observations may reflect ascertainment bias, resulting from better access to care or, in alternative, they might be correlated with the fact that subjects with higher education, including teachers and health care workers, generally spend more time in front of artificial light sources, such as computers. As a matter of fact, computer programmers tend to be diagnosed with Parkinson's disease at a younger age compared to other patients (Goldman et al., 2005). At this stage, any assumption based on the correspondence between light pollution and Parkinson's disease is highly speculative and the causal relation between these two phenomena is still to be demonstrated by appropriate epidemiological studies. Nevertheless, data on the detrimental effect of light on human wellbeing and age-related disorders are accumulating and deserve further evaluation (Hatori et al., 2017).

In the last twenty years, the increasing energy efficiency and the lower operating cost of modern lighting technology has dramatically increased the amount of artificial light to which we are exposed every day. While, by no doubt, artificial light has contributed to the human progress, mounting evidence demonstrates that the excessive and inappropriate introduction of artificial light, directly or indirectly, into the outdoor and indoor environments, has a harming effect on the natural word and on the human health (Aisling, 2018). In this review we highlighted the potential deleterious effect of light exposure on dopaminergic neurons and we discussed the potential mechanisms how light could damage these neurons. As consensus exists that genetic and environmental factors concur to the pathogenesis of Parkinson's disease, the fact that excessive light exposure could be an adjunctive environmental risk factor for this disease should not be neglected and would require the scrutiny of rigorous epidemiological studies.

On the other hand, we underpinned the fact that 710 nm light can directly influence the electrophysiological activity of native dopamine neurons in *substantia nigra* and can induce dopamine release in dopaminergic mesencephalic cell cultures. These effects could be regarded as positive rather than negative and could explain why in a primate trial, monkey treated with MPTP and near infrared light developed fewer clinical and behavioral impairments than those treated with MPTP alone (Darlot et al., 2016). To conclude, the comprehension of the intimate mechanism how light exerts beneficial and detrimental effects on dopaminergic neurons, and the definition of the exact wavelength range responsible for these effects, will be critical for a more rational use of artificial light in the future.

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(Received 18 October 2019, Accepted 27 February 2020)
(Available online 4 March 2020)