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PERSPECTIVE

Why and how does light therapy offer neuroprotection in Parkinson's disease?

Red and infrared light (λ = 600–1,070 nm) therapy, known also as photobiomodulation, has been reported to offer neuroprotection and to improve locomotor behaviour in animal models of Parkinson's disease, from rodents to non-human primates (Rojas and Gonzalez-Lima, 2011; Hamblin, 2016; Johnstone et al., 2016). The neuroprotective aspect of this therapy is particularly relevant; the saving of neurons that would normally die as a result of the parkinsonian degeneration, is without doubt, the "holy-grail" for this, and indeed all other neurodegenerative disorders. The stage is set for translation of light therapy to human patients and there is much hope for beneficial outcome. In this perspective article, I would like to consider two major issues of light therapy that relate to its neuroprotective function, issues that have intrigued many scientific colleagues, together with the wider community.

The first issue is "why"? Why, in the first place, would neurons - other than the opsin-containing neurons of the retina involved in either vision or circadian rhythms - have a rather ubiquitous response to light? Why would photons stimulate chemical changes within neurons, why would they have the means to convert light energy to metabolic energy with a subsequent influence on intrinsic neuronal function and survival (Rojas and Gonzalez-Lima, 2011)? This issue is particularly puzzling when considering those central neurons located deep within the mammalian brain, those encased by skin, muscle, bone and meningeal coverings, those that are not normally exposed directly to light.

An answer may lie in the evolutionary process that the response of neurons to light is an "hang-over" from primal invertebrate cells, cells that were once exposed directly to light. These invertebrate cells may have used the rich and abundant light energy available from the sun to drive intrinsic cellular mechanisms, in much the same way as plants cells use this energy for photosynthesis (Tafur and Mills, 2008). The invertebrate light-responsive mechanisms could have driven normal cell function, together with providing protective "safeguard" measures against pathology or distress. The central neurons of vertebrates, even those evolved to the deepest and darkest corners of the very large primate brain, appear to have kept these light-responsive mechanisms in place. The light therapy used experimentally in animal models of Parkinson's and other diseases (Rojas and Gonzalez-Lima, 2011; Hamblin, 2016; Johnstone et al., 2016), seems to provide sufficient light energy to trigger these primal intrinsic mechanisms within the deep lying central neurons.

In practical terms, evolution thence appears to have rather conveniently presented us with a means by which we can experimentally (and hopefully clinically too) help central neurons to survive pathology and distress (see below). Notwithstanding, this practicality or convenience for our purposes, there could be a little more to the story. In a fascinating twist, although the central neurons of vertebrates have lost their direct light exposure, evolution may have devised a means by which external light energy can still be used to protect them when distressed. Recent studies have reported that light applied to peripheral body structures (*e.g.*, dorsum of body, legs) helps protect - presumably by recruiting a "middle-man" such as the immune and/or stem cell system - distressed central neurons located in the brain (Johnstone et al., 2016). This indirect stimulation of distressed central neurons - although not quite as effective as the direct one - could form part of an evolutionary compensation for their loss of direct light exposure. Taking it a step further, the light-activated immune and/or stem cells from the periphery may well trigger the same intrinsic safeguard mechanisms in distressed central neurons as those triggered by direct light application. These particular mechanisms will be discussed in detail below.

It should be noted that the ubiquitous light-responsive mechanism apparent in many, if not all, central neurons is distinct from the one operating within the smaller number of opsin-containing neurons, not only within the retina for vision and circadian rhythms, but also within select groups of neurons within the brain itself (encephalopsin, OPN3). The precise function of these brain opsin-containing neurons is not known, but they - like some of their counterparts in the retina - have been suggested to have a role in circadian rhythms (Blackshaw and Snyder, 1999).

The second major issue is "how"? How does light therapy offer neuroprotection, what does it do to make neurons better placed to survive a parkinsonian injury? As touched on above, light may activate intrinsic safeguard mechanisms that the neurons have in place, a left-over from the evolutionary process. When exploring the details of these mechanisms, two general effects of light therapy have been described, the so-called primary and secondary effects (Rojas and Gonzalez-Lima, 2011; Khan and Arany, 2015; Hamblin, 2016).

The primary effects involve light being absorbed by a chromophore, lying within a photoreceptor molecule. A main and well-recognized photoacceptor in mammals is cytochrome c oxidase, lying on the membranes of the mitochondria, the engine room of neurons (Eells et al., 2004; Karu, 2010; Rojas and Gonzalez-Lima, 2011; Khan and Arany, 2015; Hamblin, 2016). This then leads to an increase in both electron transfer in the respiratory chain and in the mitochondrial membrane potential, leading to a surge of adenosine triphosphate energy production. Nitric oxide is released also that, among other things, triggers the vasodilation of nearby blood vessels, increasing blood (and lymphatic) flow. These primary effects are thought to be short-term, principally in operation when the light is directly on the cells (Rojas and Gonzalez-Lima, 2011; Khan and Arany, 2015; Hamblin, 2016). Although cytochrome c oxidase is the best known photoacceptor, absorbing many wavelengths across the near infrared range (600–700 nm and 760–940 nm), it is not the only one. Recently, it has been reported that at a higher wave-length (*i.e.*, 980 nm), temperature/light-gated calcium ion channels on cell mem-

branes are stimulated. By contrast, cytochrome c oxidase is not stimulated at this shorter wavelength, but at the longer one (*e.g.*, 810 nm; Hamblin, 2016). There may well be many other photoacceptors within cells, each of which activate different intrinsic mechanisms.

The secondary effects of light therapy follow on from the primary ones. Following stimulation of cytochrome c oxidase, there is a brief burst of reactive oxygen species, molecules that have important roles in the activation of transcription factors in the nucleus. This then leads to an up-regulation of various stimulatory and protective genes involved in many beneficial outcomes, including neurogenesis, synaptogenesis and a release of growth factors (*e.g.*, brain derived growth factor). These secondary effects are thought to be of more long-term benefit and to operate after the light exposure has finished. They may well reflect the findings that even after brief light exposure, beneficial effects are evident for days, weeks or even months thereafter (Rojas and Gonzalez-Lima, 2011; Hamblin, 2016).

In short, light stimulates intrinsic mechanisms to boost energy production within the neuron, to increase local blood flow and to activate the expression of genes involved in neuronal survival (Eells et al., 2004; Karu, 2010; Rojas and Gonzalez-Lima, 2011; Hamblin, 2016; Johnstone et al., 2016). These all contribute to a "healthier" neuron, in a better position to defend and to repair itself from distress. Indeed, it has been suggested that light will aide distressed neurons in any way possible to ensure their survival (Hamblin, 2016). For instance, neurons suffering oxidative stress show an increase in reactive oxygen species from dysfunctional mitochondria; in these cases, light exposure decreases the toxic levels of reactive oxygen species, restoring the balance. In addition, when neurons suffer excitotoxicity and an increase in intracellular calcium, light exposure stimulates a reduction in intracellular calcium, again aiming to restore the balance.

This feature of light therapy - that it stimulates a bespoke intrinsic mechanism that gives the neuron the best chance of survival (Hamblin, 2016) - is exemplified further by findings indicating that patterns of neuronal survival are similar whether the light is applied either at the same time or well after the injury (Johnstone et al., 2016). That light not only helps to defend and protect healthy neurons against degeneration, but also to repair and rescue distressed neurons after injury. The repair and rescue of distressed neurons are particularly relevant to the clinical reality of Parkinson's disease, where patients first suffer degeneration and then receive therapeutic intervention. Given the particular functional or "health" state of the neuron, whether it requires protection or rescue, light may, for example, prompt an activation of a certain set of genes to ensure its survival (see above).

In conclusion, although we may never be sure of "why" it works, why light has such an ubiquitous impact on central neurons that normally live and work in the total darkness of the brain - although as scientists we like to ponder - clearer inroads can be made into the "how" it works. It is the more feasible of the two issues raised in this article and, at present, we certainly do have the methods to make the inroads. In particular, the identity of other photoacceptor molecules and different genes, whether stimulatory, protective or for rescue and repair, stimulated with a range of different wavelengths, remains to be discovered. As it stands, light therapy in the experimental setting has been shown to both protect and rescue neurons from degeneration after parkinsonian injury, something that current therapies in patients do not do; that in itself, should be an incentive for trial in the clinical setting.

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