PERSPECTIVE

Remote photobiomodulation: an emerging strategy for neuroprotection

Photobiomodulation (PBM) - the irradiation of cells or tissues with low-intensity red to near-infrared light - is emerging as an effective means of enhancing cell and tissue resilience and repair. As reviewed elsewhere (Gordon et al., 2019), the intracellular effects of PBM appear to be primarily mediated by cytochrome C oxidase, a key enzyme in the mitochondrial respiratory chain and a primary photoacceptor of red to near-infrared light. Absorption of light by cytochrome C oxidase alters its redox state, resulting in increased ATP production, the liberation of nitric oxide and a transient burst in reactive oxygen species. This, in turn, triggers a cascade of secondary downstream effects that collectively enhance cell and tissue resilience, including the reactive oxygen species-mediated activation of key transcription factors and consequent effects on the expression of genes involved in cell proliferation and migration and in the production of cytokines and growth factors. In the context of neurodegenerative diseases, the disease-modifying or "neuroprotective" effects of PBM have been demonstrated in animal models of retinal degeneration, stroke, traumatic brain injury, Alzheimer's disease, frontotemporal dementia and Parkinson's disease (PD) (Johnstone et al., 2016; Gordon et al., 2019).

While the majority of pre-clinical work in animal models has understandably focused on transcranial PBM, where light is targeted at the head to directly irradiate vulnerable brain regions, it is questionable whether this approach will be effective in human patients. Measurements using human post-mortem samples have determined that penetration of red to near-infrared light across the human scalp and skull ranges from ~1–3%, with less than 0.03% of the emitted light energy penetrating 12 mm of brain tissue (Hart and Fitzgerald, 2016). Thus, for neurodegenerative diseases such as PD, in which degeneration is primarily localised to regions deep within the brain (*i.e.*, nigrostriatal pathway), it appears unlikely that transcranial PBM will provide neuroprotection as a result of therapeutic doses of light directly reaching vulnerable cells.

In recognition of these limitations, researchers have been working to uncover alternative treatment modalities. For example, the team of Alim-Louis Benabid in Grenoble has developed an implantable light-emitting device that has been trialled in mouse, rat and monkey models of PD, by embedding the light-emitting device in close promixity to the midbrain. In these models, "intracranial" PBM protected against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine-induced dopaminergic cell loss and mitigated functional deficits, as reviewed elsewhere (Gordon et al., 2019). Additionally, VieLight, Inc. has developed a device to enable the intranasal delivery of light. A recent pilot study of five patients with mild to moderate cognitive impairment treated with a combination of transcranial and intranasal PBM reported a significant improvement in measures of cognitive function by the end of the 12-week treatment period, and a decline in cognitive performance following the cessation of treatment (Saltmarche et al., 2017).

Interestingly, there is growing evidence that the beneficial effects of PBM are not confined to the tissue that is irradiated. Instead, PBM appears capable of having indirect effects on a range of organs, including the brain (Johnstone et al., 2016). The landmark work of Rochkind et al. (1989) laid the foundation for this line of research, by demonstrating in rat models of wound, burn injury and sciatic nerve injury that unilateral PBM treatment has bilateral effects on tissue healing. A number of studies, particularly in the context of wound healing, have since followed that collectively demonstrate the beneficial indirect effects of PBM on tissue protection and repair, as reviewed elsewhere (Gordon et al., 2019). In analogy with the well-established phenomenon of remote ischemic conditioning, we use the term "remote PBM" to refer to the irradiation of one tissue or organ in order to induce protection of distant, non-irradiated tissues or organs, such as the brain (Kim et al., 2017).

Johnstone et al. (2014) reported the discovery of neuroprotection by remote PBM. Using an MPTP mouse model of PD, they showed that irradiating the dorsum of mice with 670 nm light, while shielding the head with aluminium foil, mitigated loss of functional dopaminergic cells in the substantia nigra pars compacta. This finding was confirmed in a subsequent study using a different strain of mouse (Kim et al., 2018). Importantly, both of these studies used a 'per-conditioning' treatment regimen, where PBM was administered concurrently with MPTP insult, raising questions around whether the observed beneficial effect might simply result from remote PBM interfering with the pharmacokinetics of MPTP.

A recent study by Ganeshan et al. (2019) has addressed this limitation by delivering remote PBM as a pre-conditioning intervention. Again using an MPTP mouse model of PD, the authors treated the dorsum of mice with 670 nm PBM for 2, 5 or 10 days, and delayed the injection of MPTP until 24 hours after the cessation of treatment. Using the number of functional dopaminergic neurons in the substantia nigra pars compacta and the number of hyperactive cells in the caudate-putamen complex as primary outcome measures, this study revealed that daily pre-conditioning with remote PBM for 10 days provided significant neuroprotection against MPTP insult (Ganeshan et al., 2019).

While these studies and others provide strong evidence for the indirect effects of PBM, little is known about the mechanisms that underlie this systemic signalling phenomenon. In seeking to address this gap in knowledge, the study by Ganeshan et al. (2019) also surveyed the transcriptomic response of the brain to 10 days of remote PBM treatment.

More than 500 genes showed altered brain expression as a result of remote PBM pre-conditioning; a number of these clustered into molecular pathways that could provide clues to the mechanisms of action. One prime example was enrichment of pathways related to stem cell signalling, which other investigators have proposed as a mechanism underlying the systemic effects of remote PBM. For example, using a rat model of myocardial infarction, Tuby et al. (2011) provided the initial evidence that PBM targeted at the bone marrow can stimulate the proliferation and mobilisation of bone marrow-derived c-kit$^+$ cells, which appear to be recruited specifically to sites of damage, where they are associated with mitigation of said damage. Although it remains to be determined whether bone marrow-derived stem cells are involved in remote PBM-induced neuroprotection, cell populations such as mesenchymal stem cells, which reside in the bone marrow and other tissues, are strong candidates. As reviewed elsewhere (Johnstone et al., 2016; Gordon et al., 2019), a small proportion of mesenchymal stem cells can cross the blood-brain barrier, home specifically to areas of tissue damage and release a range of trophic factors that enhance cell protection and repair. The recent transcriptomic findings of Ganeshan et al. (2019) provide support for the hypothesis that remote PBM triggers signaling systems within the brain that recruit stem cells, strengthening the rationale for more focused future studies to directly investigate whether remote PBM stimulates the mobilisation of stem

cells in the periphery and their recruitment to injured regions of the brain.

The transcriptomic analysis also revealed enrichment of molecular pathways relevant to the brain vasculature, suggesting that remote PBM may be involved in modulating the integrity of the blood-brain barrier (BBB) (Ganeshan et al., 2019). While the effects of PBM on the BBB have not been widely studied, there is evidence that PBM improves vascular health in another central nervous system structure: the retina. For example, in rat models of oxygen-induced retinopathy, Natoli et al. (2013) found that PBM reduced neovascularisation, vaso-obliteration and abnormal peripheral branching patterns of retinal vessels, while Cheng et al. (2018) found that PBM mitigated leakage and degeneration of retinal vessels in a mouse model of diabetic retinopathy. Given that BBB dysfunction is an increasingly-recognised feature of various neurodegenerative diseases, one of the mechanisms by which PBM (whether transcranial or remote) might induce neuroprotection is through effects on the BBB. Further studies are required to confirm whether this is indeed the case, and to identify the system(s) that transduce this signal from the periphery to the brain.

In summary, evidence continues to mount in favour of the phenomenon of remote PBM - that irradiating a peripheral tissue with light can have indirect, possibly body-wide beneficial effects. This treatment modality is likely to have particular importance in addressing conditions of the brain, given the difficulties in delivering therapeutic doses of PBM transcranially due to the limited penetration of light across the human scalp, skull and superficial brain tissue. Many unanswered questions remain for this emerging field of research. Is remote PBM effective when delivered as a post-conditioning intervention (*i.e.*, after damage has occurred)? Can indirect effects of PBM be elicited in humans? If so, is there an optimal target tissue/organ in the periphery for inducing neuroprotection? Does PBM dose need to be tailored to an individual based on their body composition? And, importantly, what are the systemic mechanisms that mediate the indirect effects of PBM, and how do these act on the brain to induce neuroprotection? The recent study by Ganeshan and colleagues provides some clues to this last question, opening the way for more focused investigations to assess these possibilities directly.

The idea that something as simple as light can produce such wide-ranging beneficial effects on organismal physiology initially seemed far-fetched, yet the increasing number of rigorous scientific reports that support this idea suggests that it is time to move beyond our scepticism and start exploring in earnest how this biological phenomenon might be harnessed to improve human health, and what new knowledge it provides about our integrative physiology. Substantial knowledge gains have been made since the discovery of remote PBM-induced neuroprotection 5 years ago; we now eagerly await the advances that will be made over the next 5 years.

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