Photobiomodulation and the brain – has the light dawned?

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Evidence is mounting that photobiomodulation therapy (shining near-infrared light) can benefit a wide range of brain disorders. The photons can penetrate into the brain where they stimulate production of energy in brain cells, and trigger numerous signaling pathways. Acute ischaemic stroke was the first indication that progressed to human clinical trials. Acute and chronic stages of traumatic brain injury were then investigated. Currently, psychiatric disorders such as depression, and neurodegenerative diseases such as Alzheimer's and Parkinson's are under investigation. Although showing great promise, more trials are clearly needed before the therapy will be accepted.

Photobiomodulation therapy

Photobiomodulation therapy (PBMT) is defined as the use of low (non-thermal) levels of visible or near-infrared (NIR) light to stimulate or inhibit biological cells and tissues via a photochemical mechanism (without the addition of an external photosensitizer). PBMT was discovered almost 50 years ago (1967) by Endre Mester in Hungary. He was trying to cure a tumour implanted in a rat using a beam produced by the newly discovered ruby laser. As it happens, the power of the laser beam was much lower than he expected and he was unsuccessful in curing the tumour. However, he was surprised to observe in treated animals that the incisions made to implant the tumour healed faster than the controls, and the shaved hair also grew back faster. Mester called this phenomenon 'laser biostimulation' and it later became known as 'low-level laser therapy', or LLLT [1].

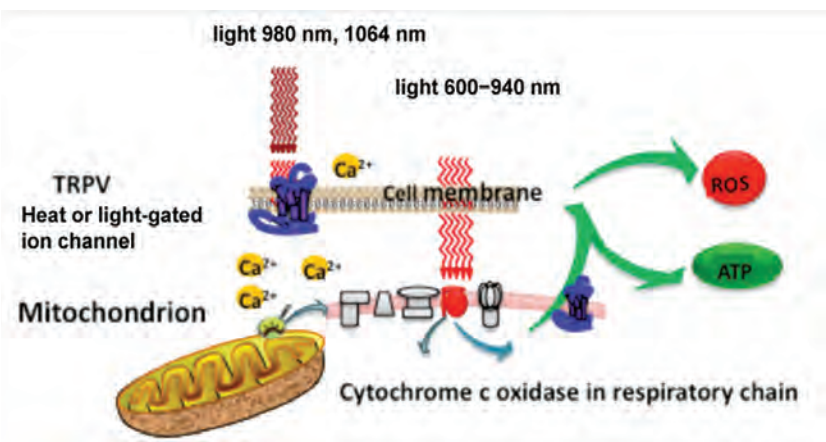

Figure 1. Mechanism of absorption of light by chromophores in cells. ATP = adenosine triphosphate; ROS = reactive oxygen species; TRPV = transient receptor potential vanilloid

The mechanism of action of PBMT has been under intense investigation ever since it was discovered, but in recent years there has been some consensus among experts on this thorny topic[2]. The principal chromophore (light-absorbing molecule) has been identified as cytochrome c oxidase (CCO), which is unit IV of the mitochondrial respiratory chain and responsible for reducing oxygen to water with the simultaneous production of protons that are used to drive the synthesis of adenosine triphosphate (ATP), i.e. the cellular energy source. The fact that CCO absorbs light in the red region of the visible spectrum (600–690 nm) and in the NIR (760–940 nm), which are the most clinically effective wavelengths, bolsters this hypothesis. One of the most general observations made in PBMT is an increase in ATP in cells and tissues. Recently, it has become likely that there is a second chromophore that absorbs longer wavelengths (980 nm and 1064 nm), and this has been tentatively identified as water (possibly in the form of nanostructured water which is a thin layer that forms on biological membranes). This may be particularly important in activating transient receptor potential (TRP) ion channels. The mechanism of PBM absorption by chromophores is shown in Figure 1.

A single brief exposure of animals or humans to light during PBMT can have surprisingly long-lasting effects (days or weeks). It has been shown that signalling pathways are triggered within the cells, transcription factors are activated and gene expression patterns are altered. Exposure to PBMT results in key physiological changes – increased anti-inflammatory cytokine levels, decreased pro-inflammatory cytokine levels, upregulation of anti-oxidants and survival factors, increased cell proliferation and reduced levels of apoptosis. At the tissue level, blood flow is increased, lymphatic drainage is also increased leading to reduced oedema (fluid build-up), healing is improved as shown by improved angiogenesis, cell migration and collagen synthesis (Figure 2). One recent and exciting development has been the observation that stem cells respond very well to PBMT. It has even been possible to shine light on the leg bones of mice to activate stem cells in the bone marrow that can then migrate throughout the body via the bloodstream and can repair defects in the heart, kidney or brain [3].

There have been a wide variety of clinical applications of PBMT that have been tested to date, including wound healing indications for non-healing leg ulcers, diabetic foot ulcers and pressure sores, and reducing the pain and inflammation of the musculoskeletal system, in such disorders as tendinopathies, osteoarthritis, sprains, neck pain, carpal tunnel syndrome and tennis elbow. Many applications of PBMT have been in the field of dentistry, such as post-extraction pain, orthodontics, periodontitis, oral mucositis and temporomandibular joint disorder. Some purely aesthetic applications include the reduction of facial wrinkles, hair regrowth to treat baldness and fat layer reduction. A graphical illustration of the diverse medical applications of PBMT is shown in Figure 3.

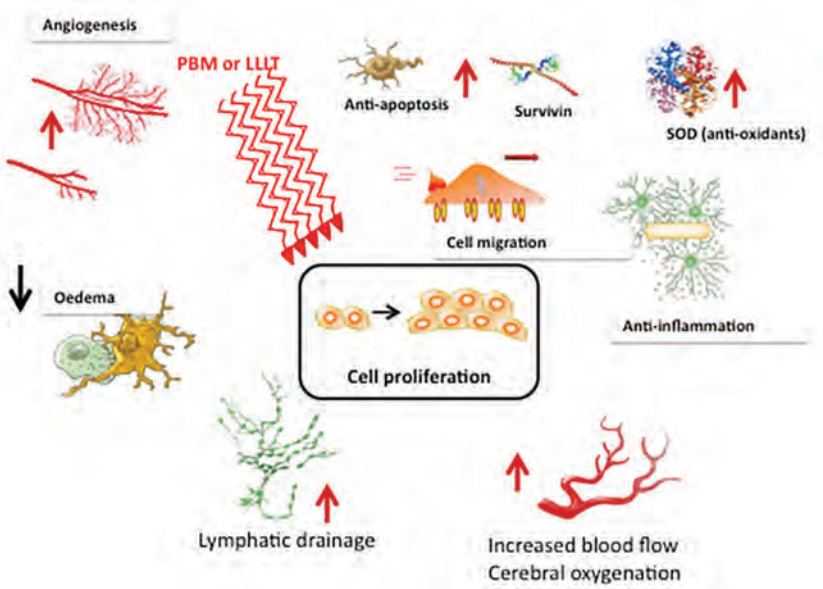

Figure 2. Cellular and tissue mechanisms of PBM. SOD = superoxide dismutase.

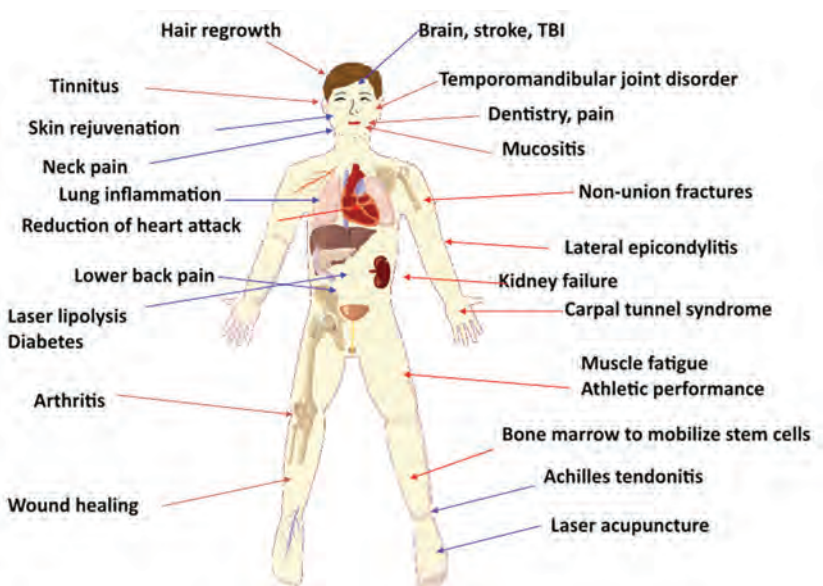

Figure 3. Diversity of medical applications of PBMT. TBI = traumatic brain injury.

Lighting the brain

Workers in tissue optics have estimated that between 2–5% of light incident on the head, depending on the wavelength and exact location on the skull, penetrates to the surface of the brain[4]. However, there is some evidence that there may also be a systemic effect of PBMT mediated via the bloodstream, and that the bone marrow in the skull may also be stimulated. While much of the work until now has used lasers, the recent advent of NIR light emitting diode (LED) arrays with reasonable power outputs has provided a cost-effective and safer alternative.

Focus on stroke

Uri Oron in Israel and the Photothera company in the US were the first to test PBMT for brain disorders in an animal model of acute ischaemic stroke[5]. Rats had a filament introduced into the middle cerebral artery to create a permanent blockage, and were treated with a single exposure to an 808 nm laser spot on the shaved head 24 hours post-stroke. Improvements were seen in neurological function that lasted for 4 weeks. They went on to show that motor functioning and clinical behaviour ratings were improved in a rabbit small clot embolic stroke model that had been irradiated 6–24 hours post-stroke. These promising results led to three human clinical trials NEST-1, NEST-2 and NEST-3. Although the first two trials showed positive results, the last trial (planned for 1000 patients) was

prematurely halted for futility at an intermediate stage. Many reasons have been put forward to explain this failure, including an insufficient dose of light, the fact that only a single application was given, and the possibility that the areas of the head that were illuminated were sub-optimal [6].

Treating traumatic brain injury

Oron was again the first to test PBMT in an animal model of traumatic brain injury (TBI). In a mouse model of closed head injury, he showed that a single application of an 808 nm laser to the head within 6 hours of a TBI, produced long-lasting improvements in neurological function[7]. The Hamblin laboratory in the US[8] went on to show, in a mouse model of closed head injury, that 660 nm and 810 nm lasers (but not 730 nm or 980 nm), delivered 4 hours post-TBI, produced significant improvements in neurological function. The same group went on to show in mice with TBI that exposure to an 810 nm laser increased neuroprogenitor cells and brain-derived neurotrophic factor (BDNF) in the dentate gyrus (part of the hippocampus) and in the subventricular zone at 7 days post-TBI. Interestingly, there was upregulation of synapsin-1 (a marker of formation of newly formed synapses) in the cortex at 28 days post-TBI. This process of synaptogenesis or neuroplasticity describes how the undamaged part of the brain can remodel itself to take over the functions of the damaged parts. Taken together, these observations show that PBMT can help the brain to repair itself after suffering damage. Other workers have also shown that PBMT can reduce activated microglia in mouse brains after TBI, showing that neuroinflammation can also be reduced. Increased neuroinflammation, reduced neurogenesis, lowered BDNF and impaired synaptogenesis are characteristic observations in a wide variety of brain disorders, including psychiatric disorders and neurodegenerative diseases.

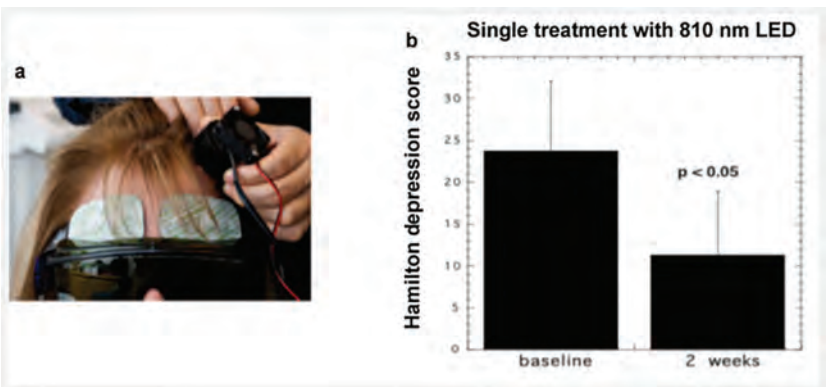

Figure 4. Transcranial PBMT for major depression. **(a)** Application of NIR LED to the forehead **(b)** Improvement in Hamilton depression score after 2 weeks.

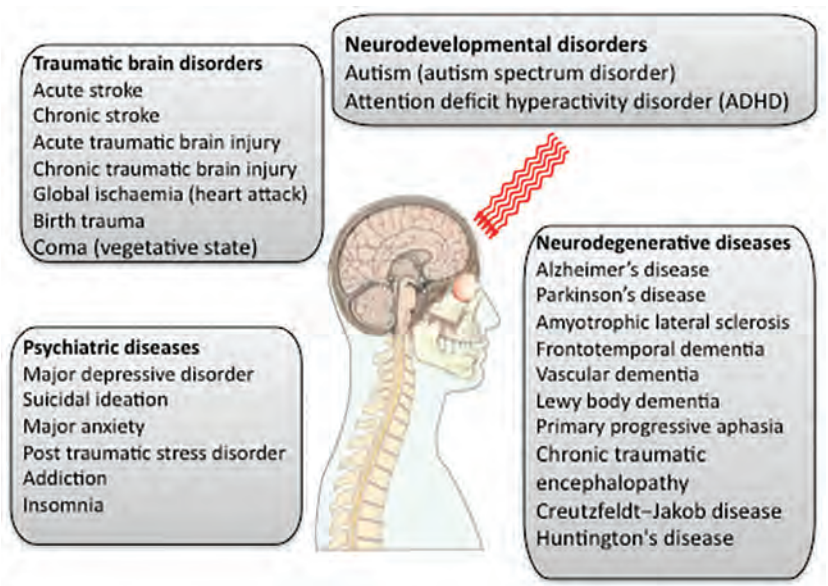

Figure 5. Diversity of brain conditions and diseases that may be amenable to treatment with PBMT

Initial clinical studies of PBM for chronic TBI in humans have been carried out by Margaret Naeser and co-workers[9]. They showed that after receiving a total of 18 LED (red and NIR) treatments, subjects saw improvements in executive functioning and verbal memory, as noted by improved scores on the Stroop test and California Verbal Learning Test. Patients with chronic TBI have abnormalities in the default mode network, the central executive network and the salience network areas of the brain (see glossary). Typically, they have impaired ability to deactivate the default mode network, meaning that rapid switching between networks cannot occur, hindering overall cognitive performance. The Naeser lab has carried out pilot research demonstrating that functional magnetic resonance imaging scans of the brains of patients with chronic aphasia, both before and after a series of 18 LED treatments, indicated increased connectivity between neural nodes in all three networks affected by TBI. In a further series of patients with chronic TBI, they found that eight out of 11 subjects had marked improvement in cognitive function.

PBMT for depression and anxiety

Animal experiments have shown that mice and rats subjected to PBMT demonstrate improvement in behavioural tests designed to measure depression and anxiety (for instance forced swim test and tail suspension test). Schiffer et al. conducted a pilot clinical study in 10 patients with major depression and anxiety,

in which they received a single 810 nm LED treatment to the forehead at two locations for 4 minutes each 10 (Figure 4). It was found that, after two weeks, the mean Hamilton Depression Rating Scale (HDRS) had decreased by about 10 points (23.9 to 13.2) although by the four-week mark symptoms had begun to reappear. Cassano and colleagues studied the effects of multiple PBMT treatments (810 nm laser) administered over three weeks. At completion of the study, two out of four patients had achieved remission, and the mean HDRS score had decreased from the baseline of 19.8 to 13.0.

PBMT for Parkinson's disease

John Mitrofanis and co-workers in Australia have studied PBMT for Parkinson's disease in animal models[11]. They found that dopaminergic cells in the substantia nigra pars compacta (SNc) were protected from toxicity caused by MPTP (a drug used to induce Parkinson's symptoms). They went on to test a surgically implanted intracranial fibre designed to deliver either 670 nm LED (low power) or 670 nm laser (high power) into the lateral ventricle of the brain in MPTP-treated mice. Both low-power LED and high-power laser were effective in preserving SNc cells, but the laser was considered to be unsuitable for long-term use (6 days) due to excessive heat production. These authors also reported a protective effect of light exposure when the head was shielded in this mouse model. Recently, this group has tested their implanted fibre approach in a model of Parkinson's disease in adult Macaque monkeys treated with MPTP. Clinical evaluation of Parkinson's symptoms (posture, general activity, slowness of movement and facial expression) in the monkeys were improved at low doses of light compared with high doses.

PBMT for Alzheimer's disease

De Taboada and colleagues tested the effects of PBM in a transgenic mouse model of Alzheimer's disease (amyloid-β protein precursor, AβPP)[12]. Beginning at three months of age, PBMT was administered three times a week. Aβ plaque numbers were decreased and amyloid levels within the brain were reduced. Importantly, PBMT also mitigated the behavioural effects seen with advanced amyloid deposition and reduced the expression of inflammatory markers in the AβPP transgenic mice. Other workers have seen similar results in different mouse models of Alzheimer's. A few small trials have already been conducted of PBMT for Alzheimer's in humans and the results seem promising.

PBMT for enhanced cognitive performance

While many studies have noted the positive effects of PBM on cognition and memory, very few have studied it for the sole purpose of improving the cognitive functioning of healthy subjects. A double-blind, placebo-controlled study conducted by Barrett and Gonzalez-Lima, tested the effect of PBM on the memory and attention of a class of 40 undergraduate students[13]. Subjects received treatment with 1064 nm light at two different sites on the right frontal pole of the cerebral cortex. After two weeks, it was found that subjects who received real treatment saw noticeable cognitive improvements (faster reaction times and better performance on a memory test).

What does the future look like?

The wide variety of brain conditions and diseases that may be amenable to treatment using PBMT are illustrated in Figure 5. There are at present no pharmaceutical drugs to treat brain damage caused by either stroke or TBI. Moreover, despite huge amounts of funding and research in both academic labs and industry, progress in discovering drugs to halt the progression of both Alzheimer's and Parkinson's disease has been frustratingly slow. Perhaps it is time to undertake serious well-designed clinical trials of transcranial PBMT for these indications, considering its established safety record and notable lack of adverse effects, not forgetting its relatively cost-effective nature. Although psychiatric drugs, such as anti-depressants and anxiolytics (anti-anxiety), are well-established and rank among some of the world's biggest selling pharmaceuticals, their rate of effectiveness is considered to be disappointing, and they can have high rates of distressing side-effects. Now that cost-effective and safe LED arrays in the NIR spectrum are becoming available, home-based treatments for these chronic diseases have become entirely feasible. ■

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Glossary	
Amyloid-β protein precursor	Leads to plaque formation in the brain of Alzheimer's patients
Adenosine triphosphate	The chief energy source for all cells and tissues
Aphasia	Problems understanding and forming words due to malfunction in specific brain regions
Brain-derived neurotrophic factor	The most important single factor for optimal brain function and repair
Cytochrome c oxidase	An enzyme inside mitochondria responsible for metabolizing glucose and oxygen to form ATP
Central executive network	An area in the brain responsible for decision-making
Default mode network	An area in the brain active during day-dreaming
Hamilton Depression Rating Scale	A questionnaire measuring symptoms of depression
Neurothera effectiveness and safety trial	A series of three clinical trials designed to test whether photobiomodulation therapy using an near-infrared laser was effective in acute stroke
Salience network	An area in the brain responsible for discriminating between sensory inputs
Substantia nigra pars compacta	An area of the brain that produces the neurotransmitter dopamine, and is damaged in Parkinson's disease
Transient receptor potential	A family of ion channels activated by diverse stimuli including heat and light

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