# Photobiomodulation for Alzheimer's Disease: Has the Light Dawned?

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## Abstract

Next to cancer, Alzheimer's disease (AD) and dementia is probably the most worrying health problem facing the Western world today. A large number of clinical trials have failed to show any benefit of the tested drugs in stabilizing or reversing the steady decline in cognitive function that is suffered by dementia patients. Although the pathological features of AD consisting of beta-amyloid plaques and tau tangles are well established, considerable debate exists concerning the genetic or lifestyle factors that predispose individuals to developing dementia. Photobiomodulation (PBM) describes the therapeutic use of red or near-infrared light to stimulate healing, relieve pain and inflammation, and prevent tissue from dying. In recent years PBM has been applied for a diverse range of brain disorders, frequently applied in a non-invasive manner by shining light on the head (transcranial PBM). The present review discusses the mechanisms of action of tPBM in the brain, and summarizes studies that have used tPBM to treat animal models of AD. The results of a limited number of clinical trials that have used tPBM to treat patients with AD and dementia are discussed.

**Keywords:** photobiomodulation, Alzheimer's disease, dementia, mechanisms of action, animal models, clinical trials
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## 1. Introduction

### 1.1. Introduction to Photobiomodulation

Photobiomodulation (PBM) describes the therapeutic use of red or near-infrared light to stimulate healing, relieve pain and inflammation, and prevent tissue from dying. PBM used to be called "low-level laser (or light) therapy" (LLLT) but the name was changed to reflect the fact that the term "low" was undefined, lasers were not absolutely required, and inhibition of some processes was beneficial [1,2]. Photobiomodulation therapy (PBMT) describes the use of PBM as a treatment for various diseases or disorders. PBM was discovered over 50 years ago by Endre Mester in Hungary working with hair regrowth and wound healing in mice [3]. Since then, PBM has gradually become more accepted by the medical profession, physical therapists, and the general public. This increase in acceptance is partly due to the increased availability of light-emitting diodes (LEDs) with wavelengths in the red and NIR regions and substantial levels of power density (up to 100 mW/cm$^2$ over fairly large areas). Most available evidence suggests that

LEDs perform equally well compared to lasers of similar wavelengths and power density [4]. However, LEDs have the advantages of more safety, lower cost, and better suitability for home use.

## 1.2. Mechanisms of PBM

It is the first law of photobiology that a photon must be absorbed by a specific molecular chromophore in order to have any biological effect. The chromophores that have been postulated to be useful in PBM, absorb at different wavelength regions of the electromagnetic spectrum (blue, green, red, NIR), and are shown in Figure 1 and discussed below.

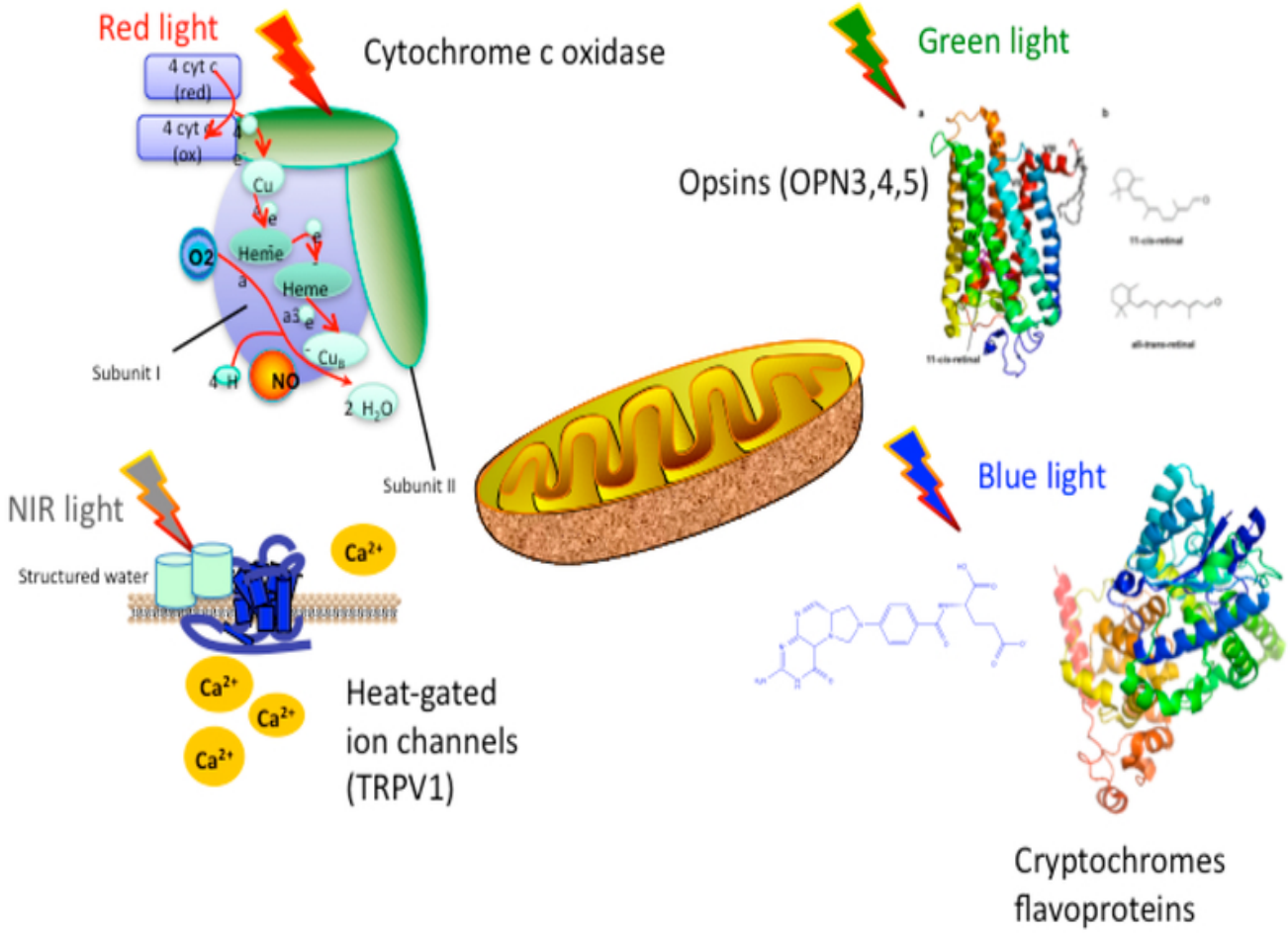


Figure 1.

Proposed chromophores for PBM that can absorb different wavelengths of light. It should be noted that there is considerable overlap between the chromophores, and that the NIR absorbed by structured water is likely to be longer wavelength (>950 nm).

Cytochrome C oxidase (CCO) is the terminal enzyme (unit IV) in the electron transport chain situated in the outer mitochondrial membrane. The electron transport chain, through a series of redox reactions, facilitates the transfer of electrons across the inner membrane of the

mitochondria. The net result of these electron transfer steps is to produce a proton gradient across the mitochondrial membrane that drives the activity of ATP synthase (sometimes called unit V) that produces the high-energy adenosine triphosphate (ATP) from ADP. CCO mediates the transfer of electrons from cytochrome C to molecular oxygen. CCO is a complex protein, composed of thirteen different polypeptide sub-units, and also contains two heme centers and two copper centers. Each of these heme and copper centers can be either oxidized or reduced, giving sixteen different oxidation states. Each of these oxidation states has a slightly different absorption spectrum, but CCO is almost unique amongst biological molecules in having a significant absorption in the near-infrared spectrum. In fact, Britton Chance estimated that over 50% of the absorption of NIR light by biological tissue could be attributed to this single enzyme as a chromophore [5].

In many publications, CCO has been shown to be a biological photoacceptor and transducer of signals activated by light in the red and NIR regions of the spectrum [6,7]. Specifically, absorption of the photons delivered in PBM, seems to promote an increase in the availability of electrons for the reduction of molecular oxygen in the catalytic center of CCO, increasing mitochondrial membrane potential (MMP), and increasing levels of ATP, cyclic adenosine monophosphate (cAMP), and reactive oxygen species (ROS), all of which indicate increased mitochondrial function, and can trigger initiation of cellular signaling pathways [8]. However recently, the CCO hypothesis has been brought into question. Lima et al. [9] genetically engineered two different kinds of cells to not express any active CCO, and found they responded equally well to 660 nm light, compared to wild type cells. Although other units in the electron transfer chain, such as complexes I-IV and succinate dehydrogenase also show increased activity as a result of PBM, CCO is still believed to be one of the primary photoacceptors. This notion is supported by the fact that low-level light irradiation such as PBM causes increased oxygen consumption, and is bolstered by the fact that the majority of oxygen consumption occurs at complex IV, and moreover that the addition of sodium azide, a CCO inhibitor, abrogates the effects of PBM [10,11]. Moreover, rho-zero cells that lack functional mitochondria do not respond to PBM, in the same way as their wild-type counterparts [12].

Nevertheless, despite the amount of évidence in favor of CCO being a major chromophore for red and NIR light, mounting evidence is suggesting that this is not the whole story. Lima et al. [9] investigated two cell lines lacking CCO, one mouse line with the Cox10 knocked out (that could not synthesise the heme a cofactor) and a second human line with a mutation in the mtDNA gene coding for tRNA lysine (that lacked three critical CCO subunits). PBM (660 nm) caused increased cell proliferation in both wild type and CCO knock out cells, together with increased ATP and citrate synthase levels. These results showed that functional CCO was not required for its ability to enhance metabolism and cell proliferation.

A recent editorial [13] from Sommer in Ulm, Germany suggested that the effects of red and NIR light (especially pulsed at low frequency such as 1 Hz) on the interfacial water layers (IWL) inside cells could be an alternative explanation. If these IWL were inside the mitochondria, then the lowering of viscosity as a result of the energy absorption, could allow the molecular rotor, which is ATP synthase, to rotate faster and produce more ATP. On the other hand if the IWL were localized within the plasma membrane, light absorption could increase the uptake of nutrients accounting for increased proliferation.

Regardless of the actual chromophore, PBM can trigger retrograde mitochondrial signaling [14]. This refers to signals and communications passing from the mitochondria to the nucleus of a cell, rather than vice versa. The aforementioned mitochondrial changes result in an altered mitochondrial ultrastructure, and triggering of mitochondrial biogenesis [15]. As a result, membrane permeability and ion flux at the cell membrane are altered, in turn leading to the altered activity of activator protein-1 (AP1) and NFκB [16].

There is emerging evidence that other primary chromophores such as opsins, flavins and cryptochomes, may mediate the biological absorption of light, particularly at shorter wavelengths (blue and green). Opsins contain a *cis*-retinaldehyde molecule as a chromophore that is photo-isomerized to the all-trans isomer, thus producing a change in protein conformation and initiating a signaling cascade [17]. Flavins and flavoproteins contain a chromophore such as riboflavin, flavin mononucleotiode, or flavin adenine dinucleotide and can carry out redox reactions when excited by light [18]. Cryptochromes are a special sub-class of flavoproteins that act as blue–light receptors in plants, animals and even humans [19].

Although evidence proving that light-gated ion channels can be cited as mechanisms of action in PBM is sparse at the present time, it is gradually increasing. PBM is most likely to affect transient receptor potential (TRP) channels. First discovered in a Drosophila mutant as the mechanism responsible for the vision of insects, they are now known to be sensitive to light [20], in addition to a wide variety of other stimuli. TRP channels are calcium channels, and are modulated by phosphoinositides [21]. Light-gated ion channels have attracted immense attention in the field of optogenetics [22]. However the majority of these studies employ ion channels similar to bacterially derived channelrhodopsin [22]. The majority of research relating PBM to light-gated ion channels has been done by testing the TRPV "Vanilloid" subfamily of TRP species. Evidence from studies done by various groups [23–26] have led to the general consensus that TRP channels are most likely to be activated by green light. However, because green light lacks the same penetrating ability of infrared or near-infrared light, it lacks practical clinical application. However, Ryu et al. found that exposure to infrared (2780 nm) wavelength light attenuated TRPV1 activation, causing a decrease in generation of pain stimuli [24]. A similar, but far less dramatic antinociceptive effect was also observed when TRPV4 was exposed to light of the same wavelength. TRPV4 was also shown to be responsive to 1875 nm pulsed light, although it cannot be ruled out that the results were due to thermal stimuli rather than light stimuli [25], as water is the primary absorber of infrared in this region.

It is clear that water must be by far the most important chromophore at infrared wavelengths (>900 nm), considering its molecular absorption coefficient and its relative abundance in cells and tissues. Nevertheless PBM as usually carried out, does not produce excessive heating of the tissues, especially within the brain. In fact the most noticeable heating effect (if any) is felt on the skin of the scalp. How then can we explain that PBM can have powerful effects on the brain at wavelengths as long as 1064 nm [27,28]? One answer may lie in the concept of 'nanostructured water' or 'interfacial water' elaborated by Pollack [29–31]. This exclusion zone (EZ) water (which may be the same as the IWL discussed above [13] absorbs optical radiation which produces distinct physical changes in parameters such as viscosity and pH. Since the EZ water layers occur on intracellular membranes, it is reasonable to suggest that ion channels embedded within these membranes (for instance in mitochondria), may be triggered by these

physical changes. Since bulk water does not absorb IR light to the same degree as EZ water, this would explain why biochemical changes can take place within the cells, while there is no detectable bulk heating of the tissue, as would have been expected if the IR energy was absorbed by all water molecules.

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## 2. Alzheimer's Disease and Dementia

Dementia is the clinical term used to describe a broad range of brain disorders that affect cognitive and executive functioning and memory [32]. The diagnosis of dementia requires a change in mental function with a more pronounced decline than one would expect due to the normal aging process [33]. In 2015, 46.8 million people throughout the world were estimated to be suffering from dementia, with 58% living in low and middle income countries and this number is expected to double every 20 years [34].

Alzheimer's disease (AD) is the most common type of dementia (60% to 70% of cases) followed by vascular dementia (25%), and Lewy body dementia (15%) [35]. AD was first described by Alois Alzheimer (1864–1915) who published his report in 1911 [36]. About 70% of the risk is probably genetic, with many genes proposed to be involved [37]. Other risk factors include a history of head injury, depression, and hypertension. AD is characterized by diffuse atrophy of the entire brain (especially of the cortex), accompanied by extracellular beta-amyloid plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau protein [38]. The precise mechanisms of AD remain a subject of hot debate [39]. A wide variety of other investigational drugs have been tested in clinical trials, but so far without much success.

The following section will summarize some of the hypotheses. The amyloid hypothesis has been the predominant explanation for decades. Aβ peptides (40 or 42 amino acids) are formed by sequential enzymatic cleavage of amyloid precursor protein (APP) by beta and gamma secretases. An increase in the level of Aβ 42 leads to amyloid fibril formation, which eventually develop into senile plaques. However the failure of several drug trials that have targeted the amyloid peptides (beta and gamma secretase inhibitors) and amyloid plaques (immunotherapy approaches using monoclonal antibodies) has led to the concept that the amyloid plaques may be markers rather than causes of the brain deterioration [40].

An alternative hypothesis focuses on tau [41]. Tau is a microtubule-associated protein involved in microtubule assembly. There are two isoforms expressed in the adult human brain (4R and 3R) mainly in axons of neurons. In AD brains, 3R and 4R tau is accumulated in a hyperphosphorylated state that forms neurofibrillary tangles (NFTs) in cell bodies, or threads if they are formed in dendrites or axons. Many different brain disorders are characterized by tau pathology and are known as "tauopathies" [42]. These include frontotemporal dementia, corticobasal degeneration, Richardson syndrome, Parkinson's disease, chronic traumatic encephalopathy, and age-related tau astrogliopathy.

Neuroinflammation and reactive gliosis are hallmarks of AD [43]. Accumulating evidence suggests that that microglia with the M1 phenotype are important players in AD [44]. Not only

do the M1 microglia pump out pro-inflammatory cytokines, but these cells down-regulate their phagocytic functionality, and therefore fail to clear the amyloid plaques. Any therapy (such as PBM) that can switch the microglial phenotype from M1 to M2 may be helpful for AD.

The increased incidence of AD in patients suffering from hypertension and irregular heartbeat, gave rise to the hypothesis of "micron strokes" [45]. Micro-strokes caused by fibrous eythrocyte emboli or micron-sized cholesterol crystals could act as "seeding points" for the growth of amyloid plaques as a healing response. A related hypothesis concerns the influence of vascular dysfunction and micro-hemorrhages [46]. Vascular dysfunction is often described as causing vascular dementia, but there is increasing evidence that it plays a role in AD as well [47]. These micro-hemorrhages have been correlated with plaque formation [48]. These micro-hemorrhages in cerebral vessels, could act as triggers to activate the innate immune system. They could also be indicative of sites of breakdown of the blood-brain barrier, which is considered as one of the early markers of cognitive dysfunction [49].

Oxidative stress has been implicated in the pathogenesis of AD [50]. The evidence includes increased levels of certain metals in AD brains such as iron, aluminum, and mercury that can generate free radicals. Increased lipid peroxidation, 4-hydroxynonenal, oxidative damage to protein and DNA, advanced glycation end products (AGE), malondialdehyde, carbonyls, peroxynitrite, heme oxygenase-1 and SOD-1 in neurofibrillary tangles and amyloid plaques. However although a diet high in antioxidants offers some protection, supplementation with antioxidants has largely failed to show any benefits [51].

Reductions in mitochondrial activity and glucose metabolism are widely seen in AD [52]. Changes in cytochrome c oxidase and morphological changes in mitochondria have been found. Activation of the integrated stress response and the transcription factor ATF4 may be caused by mitochondrial dysfunction.

Finally, another hypothesis implicates changes in the gut microbiome [53]. The bacteria themselves may secrete bacterial amyloid that may trigger cross-seeding of amyloid plaques, or else the bacteria may over-stimulate the innate immune response [54]. Bacteria themselves, such as *Porphyromonas gingivalis*, have been found in AD brains [55]. Other pathogens such as viruses and spirochetes may be involved in the brain, and Aβ peptide may function as an antimicrobial defense peptide [56].

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# 3. Mechanisms of PBM in the Brain

As will be seen in the following section, a bewildering array of different mechanisms have been proposed to account for the benefits of transcranial PBM (tPBM) on the brain. These are schematically shown in Figure 2.