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Opinion

Photobiomodulation Therapy: A Novel Therapeutic Approach to Alzheimer's Disease Made Possible by the Evidence of a Brain–Gut Interconnection

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Abstract

The evidence of brain–gut interconnections in Alzheimer's disease (AD) opens novel avenues for the treatment of a pathology for which no definitive treatment exists. Gut microbiota and bacterial translocation may produce peripheral inflammation and immune modulation, contributing to brain amyloidosis, neurodegeneration, and cognitive deficits in AD. The gut microbiota can be used as a potential therapeutic target in AD. In particular, photobiomodulation (PBM) can affect the interaction between the microbiota and the immune system, providing a potential explanation for its restorative properties in AD-associated dysbiosis. PBM is a safe, non-invasive, non-ionizing, and non-thermal therapy that uses red or near-infrared light to stimulate the cytochrome *c* oxidase (CCO, complex IV), the terminal enzyme of the mitochondrial electron transport chain, resulting in adenosine triphosphate synthesis. The association of the direct application of PBM to the head with an abscopal and a systemic treatment through simultaneous application to the abdomen provides an innovative therapeutic approach to AD by targeting various components of this highly complex pathology. As a hypothesis, PBM might have a significant role in the therapeutic options available for the treatment of AD.

Keywords: Alzheimer's disease; neurodegeneration; neuroinflammation; brain–gut axis; microbiota; microbiome; photobiomodulation; low-level laser therapy (LLLT); oxidative stress; mitochondria

1. Introduction

Recent treatments such as Food and Drug Administration (FDA)-approved anti-amyloid-β monoclonal antibodies have been shown to slow the progression of Alzheimer's disease (AD) in patients. However, this benefit comes with an increased risk of adverse effects [1,2]. There is a pressing need for novel treatments for AD ideally offering reduced adverse effects and increased cost-effectiveness. In recent decades, human microbiota have attracted more research attention, and the gut–microbiome–brain axis has been demonstrated to regulate multiple neurophysiological responses [3–5] through interactions among the autonomic nervous system, enteric neural system, central nervous system (CNS), immune system, and endocrine system. Probiotic supplementation has been used in the treatment of multiple CNS-related diseases and has demonstrated the modulation of numerous genes in the brain [6] with consequences for inflammatory and neuronal processes.

In AD, patients display altered microbial diversity and composition, as indicated by fecal analysis compared with controls [7]. The observed shifts in the composition of the microbiome may lead to an inflammatory condition in the intestine that degrades the epithelial barrier [8]. This could result in an increased translocation of proinflammatory products and bacterial molecules triggering autoimmunity, such as liposaccharides, amyloids, DNA, proteins, and polysaccharides. The systemic inflammation leads to microglia activation, neuroinflammation, and blood–brain barrier impairment [9]. Photobiomodulation (PBM) allows simultaneous transcranial and abdominal application, reaching several important targets for the treatment of such a complex pathology. Transcranial PBM, acting via the cytochrome *c* oxidase (CCO), could increase adenosine triphosphate (ATP) and influence downstream cellular signaling to reduce oxidative stress and neuroinflammation as well as upregulate synaptogenesis and neurogenesis [10]. Abdominal PBM application could restore mitochondrial normal function in gut neurons. Its potential restorative effects on the gut–microbiome–brain axis may have a significant effect on immune modulation through a reduction of oxidative stress, a decrease in proinflammatory cytokines, and changes in macrophage phenotype [11]. The local effect of PBM on inflammatory pathways most likely has systemic consequences. Circulating immune cells (mast cells, macrophages, etc.), stimulated by PBM [12–15], could

transduce protective signals from distal tissues such as the gut to sites in need of protection such as the brain.

The mechanisms considered in this opinion paper are involved in brain–gut interconnections, evidencing PBM as a potential treatment of AD and allowing synergies through multitarget approaches to this multifactorial disease.

2. The Brain–Microbiome–Gut Axis and AD

There is increasing evidence for the contribution of gut microbiota (GM) to the pathogenesis of AD, and it has already been found that AD patients have altered microbiota diversity [16]. Furthermore, GM have been demonstrated as an important player in insulin resistance and type 2 diabetes mellitus [17,18], which are known to be more frequent in AD patients [19].

Bacterial byproducts such as short-chain fatty acids (SCFAs) exert numerous neuromodulation effects and act directly on gastrointestinal cells, stimulating the synthesis of hormones such as leptin, ghrelin, and glucagon-like peptide 1, peptide YY [20]. These hormones have been shown to exhibit neuroprotective effects [21]. The microbiome has a role in tryptophan metabolism, producing tryptophan catabolites and also other metabolites including neurotransmitters and hormones able to leave the gut lumen and be detected in the circulation to serve as signaling molecules such as catecholamines, serotonin, gamma aminobutyric acid, dopamine, acetylcholine α-melanocyte stimulation hormone (α-MSH), norepinephrine, and melatonin [22–24]. The afferent neurons of the enteric nervous system can be activated or stimulated by bacteria. The vagal nerve plays a crucial role in facilitating direct neural communication between the gut and the brain [25].

As the source of a large amount of bacterial product, GM may contribute through the disruption of physiological barriers to systemic inflammation and autoimmunity [26]. Bacteria or their products can translocate from the gastrointestinal tract to the CNS. Bacterial amyloids [27] may act as prion protein cross-seeding of misfolding and enhance native amyloid aggregation. Moreover, GM products may prime microglia, enhancing the inflammatory response in the CNS, which, in turn, results in pathologic microglial function, increased neurotoxicity, and impaired amyloid clearance [28].

GM may promote brain inflammation in AD brains and be responsible for the inflammatory reaction featured around amyloid plaques. The possible role of GM was investigated in cognitively impaired AD patients by studying the association of brain amyloidosis, GM taxa with pro-inflammatory or anti-inflammatory properties, and peripheral inflammation [29]. Cognitively impaired patients with amyloidosis revealed higher expression levels of blood pro-inflammatory cytokines such as interleukine-6 (IL-6), chemokine ligand 2 (CXCL2), nucleotide oligomerization domain (NOD)-like receptor protein 3 (NLRP3), and interleukin-1β (IL-1β) and a reduction of the anti-inflammatory cytokine interleukin-10 (IL-10) compared with both controls and cognitively impaired patients without amyloidosis. The pro-inflammatory cytokines IL-1β, NLRP3, and CXCL2 were positively correlated to the relative abundance of the *Escherichia-Shigella genus*, which includes mostly species known for their pro-inflammatory properties, but negatively correlated to *Eubacterium rectale* species, known for its anti-inflammatory properties. This indicates a possible association of a peripheral inflammatory state in patients with cognitive impairment and brain amyloidosis. Thus, GM may be responsible for peripheral inflammation, favoring brain amyloidosis and, as a possible consequence, neurodegeneration and cognitive impairment in AD.

3. Gut Microbiome Modification as a Therapeutic Approach for the Treatment of AD

Modifying the gut microbiome exhibits promise in treating AD and other neurological conditions [30,31]. While interventions like diet, probiotics, and fecal microbiota transplantation (FMT) have had some success, they may not be sufficient for a complete treatment. Recently, it has been demonstrated in aged rats that the mixture VSL#3 containing eight strains of probiotics modulates the expression of several genes in the brain cortex, with positive inflammatory and neuronal consequences [6]. A recent clinical phase-3 trial [32] has shown that GV-971, a sodium oligomannate that is able to remodel gut microbiota, suppressing gut dysbiosis and the associated phenylalanine/isoleucine accumulation, reverses cognition impairment in patients with mild cognitive impairment due to AD [33]. FMT, approved for certain intestinal diseases including recurrent *Clostridium difficile* infection [34], is being explored for neurodegenerative diseases such as Parkinson's and other non-intestinal disorders [35]. Studies suggest FMT can improve cognitive symptoms in AD patients [36,37]. Achieving a healthy microbiome seems crucial for balancing key compounds and influencing the progression of neurodegenerative diseases. However, clinical trials are still lacking and are essential for more conclusive results.

4. PBM Effects on the Brain and Microbiome

The mechanisms involved in PBM exposure to produce its positive effects on AD symptoms are not fully understood. Transcranial PBM for stimulation of the brain in AD patients has shown improvement of cognitive functions [38–40], quality of life and patient independence [41], and enhancement of prefrontal oxygenation [39,42].

However, the exact mechanism by which light interacts with the microbiome remains to be elucidated. Beyond the chromophores located in mammalian cells, which could respond to PBM, there is also a diverse range of bacterial species (both Gram-positive and Gram-negative) and fungal (including yeast) cells that have been demonstrated to

respond to PBM [43,44]. In general, an increased proliferation of the microbial cells was observed, but at higher doses, inhibition was also seen, resulting from a biphasic dose-response curve of the PBM [45,46]. *In vitro* study [47] has indicated that PBM inhibits the growth of *Pseudomonas aeruginosa* and *Escherichia coli*, two Gram-negative bacteria that infect skin ulcers. However, the changes in the microbiome composition observed in the mouse experiments [48] may be due to other effects of PBM on the murine inflammatory system. Indeed, PBM has well-known anti-inflammatory and redox signaling effects, thus reducing the level of pro-inflammatory cytokines such as IL-6, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) [49] and changing the activity of macrophages and neutrophils [11]. Importantly, PBM can alter the polarization state of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 lineage [50].

It has been posited that PBM delivered to the abdomen of healthy mice can significantly modify the gut microbiome composition [51]. Recent data has signified that an Amyloid β (Aβ_{25-35}) peptide central injection in mice produces significant changes in the gut microbiome [48], and the dysbiosis observed in this AD murine model is similar to what has been reported in AD patients [52]. Abdominal PBM application reversed the decline of Firmicutes phylum (Gram-positive), reversed the increase of *Tenericutes* (Gram-negative) and *Bacteroidetes* (Gram-negative) phyla [53], and reduced the expression of *Deferribacteres* produced by Aβ_{25-35} peptide injections. These results suggest that PBM could reduce the overexpression of Gram-negative bacteria that have been shown responsible for the inflammatory processes occurring in AD [28]. The findings were confirmed in the same mouse model with red and near-infrared light directed to the abdomen [54], resulting in a decrease of the relative abundance of *Helicobacter*, a genus previously identified as a risk factor for AD [55]. In APP/PS1 mice, a restoration of the microbiome composition was observed after mid-infrared light was directed to the entire body, producing an increase in *Akkermansia* [56], which is known for its protective effects on amyloid pathology [57].

5. Discussion

During the last several years, more evidence has been accumulated demonstrating the involvement of microbiota in various diseases such as cancer [58], diabetes [59], neurological disorders, and gastrointestinal disorders [60]. Furthermore, the manipulation of the microbiota in the human body can be a strategy for disease treatment. In view of the complexity of AD, the discovery of a single, unique molecule with an unambiguous mechanism of action able to prevent or cure this pathology as found in other cases of drug discovery becomes increasingly elusive. As a result, novel clinical trials are being designed by combining the action of several pathways to obtain stronger effects with fewer side effects [61], and this type of drug development is promoted by the US FDA [62]. In this context, PBM emerges as a therapeutic opportunity because it can target the CNS through transcranial application concomitantly with abscopal effects through abdominal application.

The direct effect of PBM on mitochondria to activate CCO is of importance as a possibility of information exchange exists between the GM and neural mitochondria [18,63]. Furthermore, there is an increasing amount of data demonstrating the involvement of an aberrant metabolism and defective mitochondrial bioenergetics [64–68] in AD onset and progression. These mitochondrial dysfunctions trigger impaired synaptic activities in AD such as calcium signaling, synaptic energy, and neurotransmission [69,70]. Maintaining optimal neuronal and synaptic function is crucial in AD and is closely linked to mitochondria [67,69,70].Thus, the suggestion emerges that targeting mitochondria could be a promising approach for developing new treatments. As PBM is strongly hypothesized to target mitochondria function, it may be considered as a novel promising therapeutic tool for treating AD.

Preclinical data obtained in mice in the Aβ_{25-35}model of AD has signaled that daily concomitant application of PBM at a pulsed-wave mode both on the head and abdomen for 10 minutes produced a neuroprotective impact on the neurotoxic effects of Aβ_{25-35} peptide injection by normalizing all the modified behavioral and biochemical parameters [71]. The efficacy observed with this PBM exposure was not seen when the head or abdomen alone was exposed in similar experimental conditions. GM composition induced by toxic peptide injection was also restored by PBM application to the head and abdomen [48]. A pilot clinical study proved that the therapy is safe and well tolerated and confirmed that dual application of PBM therapy to both the head and the abdomen led to an improvement of cognitive functions in patients with mild to moderate AD [72]. In another clinical study, significant changes in microbiome diversity were observed in a patient after PBM abdominal treatment [73]. A multicentric, double-blind, randomized, sham-controlled, pivotal clinical trial was initiated in June 2023 at the Toulouse University Hospital Gerontopole, which included 108 patients with the National Institute on Aging–Alzheimer's Association (NIA-AA) clinical diagnosis of AD [74]. The primary endpoint of this ongoing pivotal clinical trial is the evolution of patients' cognition after 26 weeks of brain–gut PBM therapy, as measured by the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog).

Transcranial PBM is emerging as a potential treatment and cognitive enhancement method for various neurodegenerative pathologies. It has also been shown to help increase the potential of pharmacological therapies by modulating the blood–brain barrier permeability, opening innovative avenues for non-invasive therapeutic interventions in the CNS [75]. The evidence that abdominal PBM is able

to activate mechanisms of brain neuronal rescue by means of the brain–microbiome–gut axis confirms the interest in associating transcranial to abdominal PBM in clinical practice.

6. Conclusion

PBM appears to be a promising non-invasive, non-pharmacological therapeutic strategy for AD, able to mobilize multiple mechanisms in synergy through the association of transcranial and transabdominal application for optimal treatment efficacy. Due to its affordability, safety profile, and ability to be administered both at home and in hospitals, brain–gut PBM has the potential to become widely accessible and integrated into the treatment of AD.

Author Contributions

FJR and GB performed the literature searches, designed and wrote the paper and contributed to the editorial changes in the manuscript. BL, CR, and JT contributed to its analysis, its critical review, and its final version approval. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

GB is an employee of REGEnLIFE and owns equity in the company. FJR is the director of FR Consulting. BL and CR are employees of Vaiomer. BL is a shareholder of Vaiomer. The authors declare no conflict of interest and the writing is not influenced by this relationship.

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