Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2022.45.007226

Light Therapy in Parkinson's Disease

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ARTICLE INFO

Received: July 29, 2022

Published: August 09, 2022

Citation: Michael Besser AM. Light Therapy in Parkinson's Disease. Biomed J Sci & Tech Res 45(4)-2022. BJSTR. MS.ID.007226.

ABSTRACT

The neurodegenerative Parkinson's disease, associated with dopamine deficient neurons in the basal ganglia, has defied medical attempts to stop disease progression. Light therapy applied either directly to the brain or indirectly via its effect on the gut microbiome, offers a potential novel treatment approach which both protects healthy neurons and rescues damaged ones. As well as aiding symptomatic relief light therapy either alone or as an adjunct, may stop progression to dementia and early death.

Keywords: Dopamine; Neuroprotection; Photobiomodulation; Microbiome; Vagus Nerve

Abbreviations: MTPT: Mammalian Mitochondrial Permeability Transition Pore

Introduction

Parkinson's disease is a movement disorder resulting from the loss of dopaminergic neurons of the midbrain. This causes resting tremor, akinesia and rigidity often associated with cognitive decline and early death. The current medical treatment with L-Dopa is very effective in attenuating the motor signs, at least initially but eventually neurosurgery can be needed with implantation of electrodes and deep brain stimulation. These treatments however do not reliably alter the slow progression of the disease and neurons continue to die. Despite an intense search for the specific cause of this neurodegenerative disease there is also a need to look towards developing an approach that will regulate the self repair mechanisms of neurons. This will potentially alleviate, or at least slow, the progression of Parkinson's and perhaps other neurodegenerative disease. Red to infrared light therapy (600-1070 wavelength) is emerging as an effective, repair orientated therapy that may be capable of regulating specific neuronal functions, as well as being neuroprotective and stabilising dying neurons (Johnstone, et al. [1]). In Parkinson's disease light therapy can be applied directly or indirectly to the substantia nigra pars compacta (SNc) of the midbrain. More recently there have been anecdotal reports of the benefits of light therapy by its affect on the gut microbiome ("photobiomodulation") via the vagus nerve (Liebert, 2019).

Parkinson's Disease

Parkinson's disease is a slow, progressive neurodegenerative disease of insidious onset causing resting tremor, rigidity, akinesia and bradykinesia (Jancovic, et al. [2]). This is due to loss of pigmented dopaminergic neurons in the SNc and other nuclei of the basal ganglia causing abnormal neuronal activity (Blandini, et al. [3]). In a small number of cases defective genes contribute to the development of Parkinson's disease. It may also be caused by exposure to a neurotoxin occurring many years prior to the onset of clinical signs (Bove, et al. [4]). Mitochondrial dysfunction however plays the central role underpinning the degeneration of dopaminergic neurons, whether by toxic insult or genetic defect, with progressive accumulation of mutations in mitochondrial DNA (Exner, et al. [5]). Neurodegeneration leads to the accumulation of abnormal proteins (Lewy bodies) within the neurons (Goedert, et al. [6]) together with glutamate excitotoxicity and local inflammation in the SNc (Whitton, et al. [7]).

Management of Parkinson's Disease

Current treatment for most patients is replacement dopamine drug therapy. In some patients surgery is needed to correct the abnormal function of the basal ganglia circuitry caused by the loss of dopamine. This occurs when medication becomes ineffective or with progressive disease where further symptomatic relief is needed. Three types of drug therapy are used to enhance the defective dopamine pathway (Shapira, et al. [8]). First line treatment is usually L-Dopa (levodopa), a precursor to dopamine, which quickly reduces the motor signs but its efficacy reduces over time. Within several years involuntary movements (dyskinesia) appear, especially in the upper limbs, due to dysregulation of the dopaminergic receptors. Second line drug therapy uses dopamine agonists which mimic the action of dopamine and activate the dopamine receptors of neurons directly. These have fewer motor complications and are often the treatment choice in younger patients.

The final group of drugs are monoamine oxidase inhibitors which help to stop the breakdown of dopamine at the synapse, thereby increasing availability to the postsynaptic neurons (Worth, 2013). Drug treatments give early good symptomatic relief but there is little evidence they are neuroprotective, and they do not slow the pathology of the disease or stop neuronal death (Hart, et al. [9]). Surgical treatment is reserved after drug treatments fail to relieve symptoms and dyskinesia develops. The basic surgical principle is to target and correct the abnormal motor activity of basal ganglia nuclei and thalamus due to reduction of dopamine levels. The nuclei targeted are usually the motor nuclei of the thalamus, the globus pallidus and the subthalamic nucleus with the aim of reducing tremor, akinesia and rigidity. Initial surgical efforts were directed at destructive lesions but more recently deep brain stimulation using implanted electrodes at high frequency is used to dampen the abnormal activity in these nuclei (Ashkan, et al. [10]). This has low morbidity with effective long term management of motor signs but little evidence of slowing of the pathological process (Charles, et al. [11]) and prevention of neuronal death (Wallace, et al. [12]).

Neuroprotection Using Light Therapy

There is both basic science and clinical evidence for neuroprotection in Parkinson's disease by light therapy using low level laser red to infrared light of 600-1,070nm. The process may have evolved in epithelial tissues and remain inducible in the neuroepithelium. This common mechanism is suggested by light therapy success in many different models of disease in a range of neural systems such as depression (Schiffer, et al. [13]) and age related macular degeneration (Rojas, et al. [14]). The mechanisms involved are not entirely clear but the most compelling evidence suggests direct stimulation of the mitochondria boosting their function via an increase in ATP production (Rojas, et al. [14]). This primary mechanism is supported by the indirect stimulation of the immune system and stem cells (Byrnes, 2005). These stimulated cells may release trophic factors such as nerve growth factor and vascular endothelial growth factor that improve the function of dying cells with a reduction in apoptosis (Hou, et al. [15]). There have been promising experimental results in animal models indicating that light therapy both protects healthy neurons and also rescues damaged neurons by increasing ATP levels (Peoples, et al. [16]). Neuroprotection studies show far better outcomes when therapy is started earlier in the disease process with less prior neuronal degeneration (Ashkan, et al. [17]). Light therapy also appears to restore function to salvaged neurons (Shaw, et al. [18]) but it is not clear how much light is required and how it should be administered to achieve neuronal survival (Rojas, 2017). Light applied in bursts may be more effective in short pulses rather than being applied continuously (Oron, et al. [19]).

Human Studies

Despite promising experimental results in animal models there have been no major clinical trials of light therapy in patients with Parkinson's disease, only anecdotal reports and non randomised studies (Maloney, et al. [20]). An obvious problem is delivery of light applied from an external source to deeper brain structures in humans. Attempts are currently underway to develop an intracranial light optical fibre device to deliver a strong light signal deep into the brain near the SNc (Johnstone, et al. [21]). Clearly there are many advantages in using light therapy for Parkinson's disease, especially its potential to be neuroprotective. Also, it appears to be free of any side effects with a large safety margin (Mc Carthy, et al. [22]). Treatment with light therapy is also relatively uncomplicated. The patient would require a minimally invasive surgical stereotactic procedure for the insertion of a light optical device into the brain linked to a pacemaker and battery. (McGeer PL, et al. [23]). The light is applied to the SNc as required, similar to single electrode deep brain stimulation currently being used with comparable procedural risks (Benabid, et al. [24]).

The Gut Microbiome and Parkinson's Disease

There is a particularly strong link between the microbiome and Parkinson's disease. Constipation affects over 90 per cent of patients with Parkinson's disease often preceding the diagnosis by many years (Perez-Pardoa, et al. [25]). The disease is also more common in those who have irritable bowel disease (Jankovic, et al. [26]) and the gut microbiome in Parkinson's patients has been shown to be altered compared to the general population (Parashar, et al. [27]). The current hypothesis suggests that local inflammation in the gut excites an inflammatory response with increased production and excess accumulation of a protein, alpha synuclein. Some of this excess may be transported to the brain via the vagus nerve (Bravo, et al. [28]). Abnormal accumulation of this protein in nerve cells

produce Lewy bodies which are present in high numbers in the brain of patients with Parkinson's disease and have been detected in the gastrointestinal tract of these patients many years prior to their diagnosis (Derkinderen, et al. [29]).

The vagus nerve begins from a number of nuclei in the lower brain stem and supplies the gastrointestinal tract down to the first half of the large intestine. Patients who have undergone surgical transaction of the vagus are known to be less likely to develop Parkinson's disease (Klingelhoefer, et al. [30]). Direct communication between the microbiome and the brain is theoretically possible through the vagus nerve which provides a direct link to the enteric, or autonomic, nervous system (Pavlov, et al. [31]). The latter communicates directly with the gut lumen and is exposed to microbially produced neurotransmitters (Bravo, et al. [28]). Endocrine cells in the gastrointestinal tract have been shown to synapse with the vagus nerve and transmit signals directly from the gut to the brain in a single synapse (Kaelberer, et al. [32]). The vagus nerve can influence gut motility and mucin secretion both of which will affect the microbiome (Mayer, et al. [33]). As well short chain fatty acids produced by the microbiome can directly influence the sympathetic nervous system (Kimura, et al. [34]).

Improvement in the gut microbiome may reduce gastrointestinal tract inflammation and permeability which should reduce alpha synuclein production and transportation to the brain (Sherwin, et al. [35,36]). Theoretically the risk of Parkinson's disease is also reduced by the anticipated increase in beneficial microbial metabolic by-products including serotonin, gamma amino butyric acid and dopamine (Sun, et al. [37]), and symptoms should improve in those who already have the disease. A recent study (Bicknell, et al. [38]) has shown that infrared light delivered as low level laser to the abdomen of healthy mice can produce a significant change in the gut microbiome. It is uncertain whether the light is primarily absorbed by the microbial cells themselves or by the host cells surrounding the microbes or a combination of both. (Willis GL, et al. [39]). The alteration in the microbiome may also be a secondary effect of light affecting the mouse inflammatory response (Hamblin, et al. [40]). A series of experiments on Parkinson's disease in a mouse model has shown neuroprotection can also be achieved by infrared light delivered to areas of the body remote from the brain (Sampson, et al. [41]). This is postulated to be due to activation of stem and immune cells or a mediator linked to changes in the microbiome (Kim, et al. [42]).

There have been anecdotal reports of improvements in the symptoms of Parkinson's disease patients including gait disturbance, balance, cognition issues and fine motor skills after receiving infra red light therapy to the abdomen (Bicknell, et al. [2]). These patients showed changes in their gut microbiome with a decrease in some genera of microorganisms that are increased in Parkinsonian patients, and an increase in others that are deficient in these patients (Parashar, et al. [27]) & Liebert, et al. [49]). One of these deficient bacteria (prevotella) is so strongly associated with a more severe form of Parkinson's disease that it has been proposed as a biomarker for the disease Liebert, et al. [49]). (Imhann F, et al. [43]). The bacteroids in the gut that increased with light therapy are considered beneficial to the microbiome through their anti-inflammatory properties and production of healthy short chain fatty acids (Inhann, et al. [43]). Light therapy potentially could act as an adjunct to traditional treatments to rebalance the microbiome, especially dopamine and neurotransmitter production, (Johnstone, et al. [44]) and positively affect the outcome of some difficult to treat patients with Parkinson's disease (Jenkins, et al. [45-48]).

Conclusion

The discussion of the possible mechanism of action of the effect of light therapy on the human brain either directly or via the microbiome is highly speculative and in its infancy. Early experimental results in animal models however have shown promise that light therapy both protects healthy neurons as well as rescuing damaged dopaminergic neurons. Anecdotal human studies suggest a beneficial neuroprotective outcome of photobiomodulation in patients with neurodegenerative disease. Obviously further research is needed but it is also clear that red to infra red light therapy has the potential to develop into a viable treatment option, or at least an adjunct, for patients with Parkinson's disease. It offers the potential of neuroprotection and prevention of disease progression to cognitive decline and early death.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2022.45.007226

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