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Alzheimer's Pathogenesis and Treatment by Transcranial Pulse Stimulation

Christiyan Naydenov*, Teodora Manolova, Ivan Mindov

Department of Neurology and Psychiatry, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

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***Correspondence:** Christiyan Naydenov, Department of neurology and psychiatry at the Medical faculty of Trakia university, Armeyska 11 str., Stara Zagora 6000 city, Bulgaria. E-mail: christiyan_naydenov@abv.bg
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Abstract

The article discusses the use of transcranial pulse stimulation (TPS), a treatment method that uses ultrasound to penetrate the brain up to 8 cm. The article aims to review published studies on the effects of TPS on Alzheimer's disease and to link the mechanism of the treatment with the pathophysiology of the disease. The discussion highlights the pathological triad of senile plaques, neurofibrillary tangles, and granular degeneration that causes Alzheimer's disease. Patients with diabetes mellitus are predisposed to degenerative diseases, and the overlap between Alzheimer's disease and obesity may be explained by the use of streptozotocin, which generates reactive oxygen species leading to DNA damage and cell death. The accumulation of beta-amyloid in the brain, mitochondrial malfunction, decreased production of ATP, and energy insufficiency is also discussed. The article concludes that TPS is a potential treatment for Alzheimer's disease and that it can boost the expression of growth factors, enhance the flow of blood to the brain, trigger the creation of novel blood vessels, and promote the regeneration of nerves.

Introduction

TPS is a modern additional treatment method using ultrasound (shock waves). The pulse stimulation can penetrate to depths of 8 cm in the brain. The system represents an incomparable progress in the realm of transcranial stimulation. Every pressure pulse is generated when the driving level reaches 0.25 mJ/mm^2 and the pulse repetition frequency is set to 2 Hz. The usual outcome of TPS is the transmission of mechanical signals, which boosts the expression of growth factors, predominantly enhances the flow of blood to the brain, triggers the creation of novel blood vessels (angiogenesis), and promotes the regeneration of nerves [1], [2]. Another consequence is the discharge of nitric oxide (NO), which results in the direct dilation of blood vessels (vasodilation), leading to increased blood flow [1], [2], [3], [4], [5], [6].

Aim

The aim of this study was to do overview of published results on TPS effects on Alzheimer's and make a link between the mechanism of the treatment and pathophysiology of the disease.

Alzheimer's and TPS

Pronounced atrophy in the frontal and parietal lobes represents the pathomorphological triad of senile plaques, neurofibrillary tangles, and granular degeneration. This finding determines the manifestation of progressive dementia, speech, and praxis disorders. Parkinsonian symptoms, severe intellectual decline, and movement disorders are observed. It is known that patients with diabetes mellitus are predisposed to degenerative diseases, and recent data suggest that this predisposition may be genetically determined. Alzheimer's disease (AD) is a metabolic disorder characterized by significant and gradual impairments in the utilization of glucose by the brain, as well as the response to stimulation by insulin and insulin-like growth factor [7]. In the past decade, epidemiological data suggest the real existence of this relationship. Streptozotocin (STZ) is a synthetic compound used in research to induce diabetes in laboratory animals. It may explain the overlap between AD and obesity [8]. Once metabolized, it generates reactive oxygen species leading to DNA damage and cell death. Intracerebral injection of STZ inhibits cerebral glucose utilization, oxidative metabolism, insulin receptor function, spatial memory, and cognitive and behavioral responses [9].

In aging, obesity and diabetes mellitus, the clearance of amyloid is reduced, which increases its toxicity [10]. Accumulated beta-amyloid (ADDLs-amyloid beta-derived diffusible ligands) disrupts the signaling mechanism by binding to synapses and changing its shape. As a result of diminished insulin levels and decreased activity of insulin receptors in AD, neuronal insulin receptors (GLUT3) become less responsive. This results in impaired utilization of glucose, mitochondrial malfunction, decreased production of ATP, and energy insufficiency [9]. These changes are identical to the changes in diabetes mellitus and induce its neurological form [8], [7]. The current hypothesis for the pathogenesis of Alzheimer's disease focuses on the deposition of amyloid and tau protein, which lead to degeneration [11]. Within the brain, the synaptic membrane protein amyloid precursor protein (APP) is metabolized to produce a polypeptide consisting of 37–49 amino acids, known as amyloid-β (Aβ). The principal constituent of amyloid plaques observed in the brains of Alzheimer's disease patients is the fibrillary form of Aβ, which primarily consists of the 42-amino-acid variation (Aβ42). A soluble version of Aβ42 can be identified in both the cerebrospinal fluid and plasma and can produce soluble oligomers, which are believed to be the harmful manifestation of Aβ [11]. The initial stage in the onset of AD seems to be the accumulation of Aβ in the medial parietal cortex, even though the clustering of tau in the medial temporal lobe (MTL) is observed before Aβ accumulation in older individuals without cognitive impairment. Whether tau accumulation in the MTL is the primary stage in AD or a relatively innocuous occurrence is a significant unresolved question. It is possible that tau accumulation becomes pathological and spreads when exposed to Aβ. Even though there is a strong correlation between Aβ and tau, the connection between Aβ and neurodegeneration is tenuous. On the contrary, it is tau that is linked with brain atrophy and hypometabolism, which, in turn, have an impact on cognition, although there is evidence of an interaction between Aβ and tau resulting in neurodegeneration leading to dementia [12]. The typical function of tau protein is to sustain the steadiness of microtubules within axons. When tau hyperphosphorylated, it leads to an axonal and synaptic dysfunction (neurofibrillary tangles) as part of the pathomorphological triad [11]. There is still no drug that shows a clinically significant effect on the course of the disease [13]. The presence of transient ultrasonic mechanical waves induces various sonochemical and sonomechanical effects on the side chains of protein amino acids. This ultimately leads to a change in the quaternary structural organization of proteins. This can affect the properties of proteins by changing the internal hydrophobic residues of the protein and causing it to unfold into an irreversible denatured state. The final result is emulsification which changes the functionality of the protein. *In vivo* enzymes are protected from this process [14], but the introduced ultrasound catalyzes this change. In general, emulsions in nano- or micro-scale are not stable which could turn into two or more phases [15]. The protein microspheres are formed due to high mechanical energy, inducing of protein re-conformation at oil–water interface [16].

Discussion

It is imperative to comprehend how a concentrated ultrasound surgical beam interacts with healthy and cancerous tissues, and to analyze the histological reaction of diverse tissues to the ultrasonic impact [17], particularly in the context of oncology [18]. Research has shown a significant improvement in the cognition of Alzheimer's patients after 2 weeks of treatment by TPS [19]. The impact of TPS extends beyond the spatial and temporal stimulation settings, fostering additional clinical applications, as it enhances the functional and structural interconnection between the stimulated left primary somatosensory cortex and neighboring sensorimotor regions for up to 7 days after the final stimulation. These observations imply that TPS elicits neuroplastic alterations [20]. Activation of regions linked to depression, such as the extended dorsolateral prefrontal cortex, seems to mitigate depressive symptoms in AD patients. Therefore, TPS could potentially serve as an innovative supplementary treatment for depression in AD and other neuropsychiatric disorders [21]. Furthermore, blood–brain barrier disruption for drug delivery effect is known [18]. Side effects were rare (in 4% of sessions) with moderate subjective severity and only transient [22]. To ensure safety, monitoring before, during and after treatment is recommended. This can be achieved through MRI measurements immediately before treatment for exclusion of dangerous pathologies, EEG and fMRI recordings alongside therapy, and questionnaires for patients about the occurrence of side effects. To further advance the field, it is important to increase understanding of physical parameters and their influence on bioeffects in humans and clinical populations [23]. Although statistical significance was lacking, we observed an increase in power across various frequency bands and channels. However, the results were restricted by a high degree of variability and possibly an inadequate sample size.

Conclusion

The article describes the use of transcranial pulse stimulation (TPS), a treatment method that uses ultrasound to stimulate the brain. TPS can

improve the expression of growth factors, increase blood flow to the brain, and promote the regeneration of nerves. The article also discusses Alzheimer's disease (AD) and its pathophysiology, which involves the deposition of amyloid and tau protein leading to degeneration. TPS may have potential benefits for AD, as it can improve blood flow to the brain and promote nerve regeneration. The article also discusses how ultrasound can affect protein structure, potentially leading to changes in protein functionality. Overall, the article provides an overview of TPS and its potential benefits for AD, as well as a detailed discussion of the pathophysiology of AD.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

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