The theory of brain cell activation

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Abstract

Parkinson's disease, Alzheimer's disease, and other neurodegenerative disorders are intimately associated with physical-gated ion channels and can be treated via physical modalities. Activation of neurotransmitter-related neurons constitutes a critical component of such therapeutic approaches, wherein voltage-gated Ca2+ channels represent the optimal target for physical activation, aiming to induce Ca2+ influx and thereby trigger neurotransmitter release from synaptic vesicles at neuronal axon terminals. The theory of brain cell activation expounds the principles, methodologies, and therapeutic objectives for treating physical-gated ion channel diseases such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative conditions, while also suggesting that exclusive reliance on pharmaceutical and chemical therapeutic strategies may undermine our confidence in conquering these diseases. Consequently, the application of physical approaches, or the combined utilization of physical and chemical modalities, in treating certain major encephalopathies may constitute our primary research trajectory for the future.

Full Text

The Theory of Brain Cell Activation

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Abstract

This paper presents a novel hypothesis derived from effective treatment of Parkinson' s disease (PD) and Alzheimer' s disease (AD) using transcranial magnetoelectric (TME) stimulation technology. The central premise is that voltage-gated Ca2+ channels represent the optimal target for physical activation. The fundamental content posits that neurodegenerative diseases such as PD and AD are closely associated with physically-gated ion channels that can be

modulated through physical means. Activating neurotransmitter-specific neurons plays a crucial role in treatment, with voltage-gated Ca2+ channels serving as the best target for physical intervention. The therapeutic objective is to induce Ca2+ influx that triggers neurotransmitter release from synaptic vesicles at neuronal axon terminals.

The theory of brain cell activation establishes the principles, methodologies, and therapeutic goals for treating physical-gated ion channel diseases including AD, PD, and other neurodegenerative disorders. It suggests that reliance on pharmaceutical and chemical approaches alone may undermine our confidence in conquering these diseases, and that the application of physical methods—or combined physical and chemical approaches—may represent the primary research direction for future treatment of major encephalopathies.

Keywords: neuronal degeneration; physical means; transcranial magnetoelectric; voltage-gated Ca2+ channels; best target

Introduction

Parkinson' s disease and Alzheimer' s disease are neurodegenerative disorders of the nervous system. The primary pathological changes in PD involve degeneration and death of dopaminergic neurons in the substantia nigra, resulting in decreased striatal dopamine levels that produce tremor, muscle rigidity, bradykinesia, postural instability, and related syndromes. Clinical treatment employs the dopamine precursor levodopa as replacement therapy to compensate for reduced brain dopamine. While this approach can significantly improve symptoms for several years, long-term use produces more serious side effects, including the "on-off" phenomenon, and continued levodopa administration cannot halt PD progression [**?**]. The pathological features of AD include massive senile plaques (SP) composed primarily of A , neurofibrillary tangles (NFTs) formed by aggregated microtubule-associated tau proteins, and neuronal loss leading to brain atrophy. The correlations among these features remain unclear, and currently no pharmacological treatment can prevent or delay AD progression [**?**]. The more widely accepted pathogenesis hypothesis for AD is the cholinergic hypothesis, which proposes that selective degeneration of cholinergic neurons reduces acetylcholine (ACh) synthesis, storage, and release, producing clinical manifestations dominated by memory and cognitive dysfunction. ACh represents a crucial neurotransmitter in brain tissue.

This article presents a novel viewpoint based on effective PD and AD treatment using transcranial magnetoelectric stimulation technology. The hypothesis proposes that voltage-gated Ca2+ channels constitute the optimal activation target, suggesting that basic metabolic processes in degenerating dopaminergic and cholinergic neurons are maintained by basal exocytosis before cell death, and that a reversible process exists between degenerative and normal neuronal states. Physical means (TME) can activate dopaminergic neurons, cholinergic neurons, and other cell types, with voltage-gated Ca2+ channels serving as the best tar-

get for physical intervention. This view supports both the vesicle hypothesis [**?**] and the cholinergic hypothesis [**?**]. The author proposes naming this viewpoint the "theory of brain cell activation," which applies to encephalopathies but is not limited to them.

This article focuses specifically on degenerating dopaminergic and cholinergic neurons, excluding upstream events that may cause neuronal degeneration (such as A and tau protein) and downstream consequences of neuronal degeneration.

Ion channels on cell membranes are specialized integrins with ion selectivity and gating characteristics. The process of ion channel opening and closing is called gating. Currently, gated ion channels are subdivided into chemical, voltage-gated, and mechanical gating categories [**?**]. Since sound, light, electricity, magnetism, force, and heat possess physical properties, voltage and mechanical gating are categorized as physical gating, distinct from chemical gating. Voltage-gated Ca2+ channels belong to the family of physically-gated ion channels.

2. Basic Content

Neurodegenerative diseases such as PD and AD are closely related to voltage-gated Ca2+ channels and can be treated with physical means. Activating neurotransmitter-specific neurons plays a key role in treatment, with voltage-gated Ca2+ channels representing the optimal target for physical intervention. The therapeutic purpose is to induce Ca2+ influx that triggers neurotransmitter release from synaptic vesicles at neuronal axon terminals.

3. Validation Methods

Validation relies on two approaches: animal studies demonstrating positive correlation between TME stimulation and endogenous dopamine/acetylcholine generation, and clinical studies showing TME stimulation improves symptoms in PD and AD patients.

3.1 Animal Studies

The relationship between PD and decreased brain dopamine levels has been repeatedly confirmed over the past half-century [**?**, **?**]. Numerous studies have demonstrated a positive correlation between TME stimulation and endogenous dopamine generation. Using intracerebral microdialysis techniques, investigators examined transcranial magnetic stimulation effects on dopamine release in the hippocampus, nucleus accumbens, and striatum of adult male Wistar rats. Results indicated that transcranial magnetic stimulation significantly increased dopamine concentrations in these regions [**?**]. Other research activated dopaminergic neurons in PD rat models through transcranial magnetic stimulation, promoting endogenous dopamine release in the ventral striatum [**?**]. Studies in adult monkeys with PD who had stimulating electrodes successfully

implanted found that electrical stimulation effectively improved symptoms in hemiparkinsonian models, with microdialysis combined with HPLC methods showing increased striatal extracellular dopamine and its metabolites [?]. Additional findings demonstrated that subthalamic nucleus stimulation could increase dopamine release in rat striatal cells and activate dopaminergic neurons [?], while electrical stimulation promoted release of endogenous opioid peptides in the central nervous system [?]. These results collectively suggest that electrical stimulation can promote neurotransmitter release. Neurotransmitters and neuropeptides coexist within neurons [?], and TME appears superior to pure transcranial magnetic or electric stimulation alone.

3.2 Clinical Confirmation

Since 1994, the concept that "activation of brain cells is key to treating various difficult encephalopathies" has been presented [?]. The author has continuously verified and refined the "theory of brain cell activation" for nearly two decades, moving iteratively between theory and practice. Guided by this theory, we successfully developed specialized encephalopathy treatment equipment including brain function rehabilitation instruments [?, ?] (for cerebral apoplexy sequelae, vascular dementia, and brain atrophy) and treatment instruments for Parkinson' s disease [?], depression [?, ?], and Alzheimer' s disease [?, ?] using non-intrusive TME and other physical means. These devices have undergone clinical verification at national clinical trial sites and received medical device registration certificates from the People' s Republic of China in 1996, 2011, 2011, and 2014. These apparatuses are safe for home use by patients without clinician supervision. Their merit speaks for itself, yet our contributions have remained largely unnoticed in clinical medicine. Nevertheless, from 1996 to the date of submission, over 50 million encephalopathy patients have benefited from this technology with exciting feedback. The mechanism involves activation of peptide neurons, dopaminergic neurons, serotonergic neurons, and cholinergic neurons.

In randomized, multicenter, double-blind, self-crossover controlled trials for PD using non-intrusive TME stimulation, Parkinson' s patients meeting inclusion criteria showed significant improvement in resting tremor, rigidity, bradykinesia, and other symptoms, with primary applicability for mild to moderate PD [?]. In multicenter, randomized, double-blind, placebo-parallel controlled trials for AD and vascular dementia using non-intrusive TME stimulation, Alzheimer' s patients meeting inclusion criteria demonstrated significantly improved memory, cognitive function, mental state, and daily operational abilities, with primary applicability for mild to moderate AD and vascular dementia [?]. These results were recognized by the China Food and Drug Administration (CFDA) as part of the clinical registration basis for Parkinson' s and Alzheimer' s therapy devices.

4.1 Cellular and Molecular Mechanisms of Neuronal Degeneration

PD is closely related to dopaminergic neuronal degeneration and death in the substantia nigra, resulting in decreased striatal dopamine levels. Tyrosine derived from food is converted to dopa by tyrosine hydroxylase (TH) in neurons, then to dopamine by dopa decarboxylase. Dopamine is packaged into synaptic vesicles at dopaminergic neuron axon terminals, with release completed through rapid Ca2+-dependent vesicle exocytosis [**?**, **?**], as shown in Fig. 1 [Figure 1: see original paper]. When intracellular Ca2+ concentration increases to a certain level, dopamine vesicle release is triggered. Ca2+ influx is controlled by voltage-gated Ca2+ channel opening induced by membrane depolarization. Vesicle exocytosis includes both Ca2+-dependent rapid regulation exocytosis and basal state exocytosis, with the latter being independent of action potentials and Ca2+ [**?**]. Intracellular Ca2+ originates from both extracellular influx and synaptic calcium stores [**?**], with these sources playing complementary roles. If neurons release neurotransmitters at sustained high frequency, accompanied by neurotransmitter release into the presynaptic space and Ca2+ increase, this enhances TH catalytic activity and TH mRNA transcription and synthesis enzyme gene expression [**?**].

Conversely, if dopaminergic neurons cannot release dopamine at normal rates in a timely manner, neuronal degeneration occurs. Increased dopamine in the axoplasm can inhibit TH activity, leading to time-dependent inhibition of dopamine synthesis through feedback regulation, potentially related to the "on-off" effect observed clinically with levodopa treatment [**?**]. Degenerating dopaminergic neurons gradually lose function and die, though basal state exocytosis maintains basic metabolism before death. Exogenous dopamine, while relieving symptoms, further reduces TH activity, lowering the vesicle fusion rate of basal state exocytosis (which is independent of action potential and Ca2+ control). This replacement therapy effectively abandons efforts to rescue degenerating dopaminergic neurons. The regulated neuronal death signaling pathway disrupts the balance between survival and death signals, initiating the apoptotic program [**?**]. This may explain why PD patients taking levodopa for 2-5 years develop serious dysfunction, supporting the vesicle hypothesis.

Although AD pathogenesis is complex and difficult to fully explain with a single hypothesis, the selective degeneration of cholinergic neurons represents an important biological basis for learning and memory. Acetylcholine is synthesized from acetyl-CoA (produced during choline and glucose decomposition) via choline acetyltransferase (ChAT) catalysis in axoplasm at axon terminals, then transported into synaptic vesicles via acetylcholine transporters. If cholinergic neurons cannot release acetylcholine at normal rates in a timely manner, cholinergic neuronal degeneration occurs, while increased acetylcholine in the axoplasm inhibits ChAT activity. A 50% decrease in enzyme activity affects acetylcholine synthesis [**?**]. Similarly, degenerating cholinergic neurons upregulate death signaling pathways and initiate apoptotic programs. Existing

drugs such as cholinesterase inhibitors and NMDA receptor antagonists target non-degenerating cholinergic neurons, which may explain why these treatments cannot significantly prevent or delay disease progression. Much AD treatment research focuses on upstream or downstream events of cholinergic neuronal degeneration rather than the degeneration itself. This explanation supports the cholinergic hypothesis.

4.2 The Mechanism of TME on Ca2+ Channels

Voltage-gated calcium channels belong to an oversized family of ion channels, with the 1 subunit serving as the main functional unit. Experimental evidence shows that subunits of voltage-gated calcium channels share common characteristics: the S4 fragment contains positively charged amino acids that play a leading role in membrane activation and potential changes, while the S6 fragment contains specific amino acid residues that play a key role in voltage-dependent calcium channel inactivation, as shown in Fig. 2 [Figure 2: see original paper]. Channel activation requires charged amino acids or strong bipolar ions in the phospholipid bilayer membrane electric field. Movement of these gate charges or voltage receptors under electric field influence causes channel protein conformational changes that lead to channel activation and opening [**?**]. As a physical factor, magnetic fields exert Lorentz force on moving charged species and affect ion permeability and transmembrane potential, potentially causing configuration changes in membrane ion channels. Experimental results suggest that moderate-intensity constant magnetic field effects on ion channels may be associated with movement of ion channel-related charges in the cell membrane [**?**]. Based on electrophysiological characteristics, voltage-gated Ca2+ channels are divided into six subtypes: L, N, P, Q, R, and T. Different subtypes have different activation potentials; for example, L-type calcium channels activate at -10mV while T-type channels activate at -70mV. In fact, when membrane potential approaches -40mV, the open probability of Ca2+ channels begins to increase significantly [**?**]. Under normal conditions, intracellular calcium ion pumps maintain environmental stability by extruding Ca2+ from cells. In AD, this function is impaired, causing intracellular calcium ion overload and reducing the gradient between intracellular and extracellular calcium ions. TME can induce Ca2+ influx and also prompt rapid Ca2+ outflow from calcium stores. Because the stimulation is rhythmic, it causes bidirectional Ca2+ concentration oscillations [**?**].

The most direct route for activating voltage-gated channels is electricity. Non-intrusive TME ultimately acts primarily in electrical form, simultaneously activating key neural populations while accommodating the facts of whole-brain neuronal distribution and high skull impedance. Its safety and effectiveness are simpler to achieve than deep brain stimulation, and its high-strength transcranial magnetic stimulation is difficult to realize through other means.

4.3 The Optimal Target of TME Effects

Voltage-gated calcium channels are the optimal but not the only targets for physical activation. Voltage-gated sodium channels provide the material basis for action potential generation and propagation, while voltage-gated calcium channels open during membrane depolarization to cause calcium influx. TME stimulation can directly activate calcium channels, leading to action potential backpropagation and sodium channel activation; alternatively, it can first activate sodium channels, causing action potentials to conduct along the axon to its terminal and subsequently activate calcium channels. Only calcium channel activation achieves the purpose of triggering neurotransmitter vesicle release through calcium influx.

Because new technologies can simultaneously record neuronal information from multiple locations, the concept of action potential backpropagation has been proven. Ca2+ influx does not cause uncontrolled neurotransmitter release, even with intense external physical stimulation. No linear relationship exists between vesicle fusion rate and free calcium concentration [**?**]. This non-linear relationship makes synaptic vesicle fusion extremely sensitive to Ca2+ concentration changes, limited to a very narrow Ca2+ concentration range and a very brief time period. Regeneration of endogenous neurotransmitters, including vesicle loading, transport, and anchoring, all require time and processing [**?**, **?**]. During rapid vesicle exocytosis, vesicles can become rapidly depleted, with release rate exponentially attenuating over time [**?**]. Neurotransmitter release into the synaptic cleft also follows a constant internal environment doctrine, which is not static but rather constant based on rhythmic activities.

Furthermore, TME targets are not limited to voltage-gated ion channels. In AD, for example, specific external electromagnetic fields can eliminate electric charges from -amyloid polypeptide (A) nuclei (the main component of senile plaques), deacidify Tau protein, remove A or prevent A polymerization, and protect microtubule assembly and axonal transport systems.

5. Discussions

The views presented in this article serve both as a deduced assertion based on existing biochemical results and as a pathogenesis explanation for PD and AD, thereby driving exploration of safe and effective treatments and providing a theoretical platform. The theory of brain cell activation applies to encephalopathies but is not limited to them, and may serve as the theoretical basis for establishing "physical nosography." All neurotransmitter-specific neuronal degenerative diseases are closely related to voltage-gated Ca2+ channels and may be amenable to physical intervention. In fact, we have also applied TME clinically in epilepsy with astonishing effects, while TME shows good performance in pediatric cerebral palsy and awakening persistent coma patients.

Brain activity is extremely complex, and the authors clearly recognize that this new viewpoint requires more reliable supporting evidence. Both patch clamp

recording and intracellular detection may cause varying degrees of neuronal damage, removing cells from their original authentic state. We are currently seeking direct authentication technology for tracking living individual neurons during TME stimulation. TME stimulation' s relationship to membrane ion channel biological properties and channel configuration changes requires further theoretical and experimental validation at molecular and cellular signal transduction levels.

For neurodegenerative diseases, we seem more accustomed to seeking solutions through pharmaceutical or chemical means, which may not represent the optimal approach. The blood-brain barrier (BBB) constitutes the first barrier that chemical approaches must overcome. The BBB functions like a defensive perimeter for the central nervous system, preventing brain damage from external chemical agents while also excluding many beneficial substances [**?**]. Physical-gated ion channels constitute the second barrier for chemical approaches. Attempting to push open physically abnormal gated ion channels through action potentials generated by chemical means may be so difficult as to shake our confidence in overcoming these diseases. The frustration in Alzheimer' s disease drug research and development [**?**] may already prove this point.

PD and AD represent global challenges. Although scientists worldwide have attacked these problems for over a century and produced some research results in chemical drug development, substantial improvements remain elusive. Both TME and voltage-gated Ca2+ channels possess significant physical properties, and TME stimulation applications have achieved remarkable clinical results in PD and AD treatment. This suggests that physical means alone or combined physical-chemical approaches may represent the main research direction for conquering PD and AD in the future. For example, in late-stage severe PD patients where excessive dopaminergic neuron death has occurred, combined application of TME and levodopa drugs may be more scientifically appropriate.

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Figure Legends

Fig. 1 Neurotransmitters are released by exocytosis [**?**]
Fig. 2 Molecular Mechanism for calcium gated channels [**?**]

Note: Figure translations are in progress. See original paper for figures.