The theory of brain cell activation

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Abstract

This is a new idea that based on effective treatment of Parkinson's disease and Alzheimer's disease with transcranial magnetoelectric stimulation technology, it can understand a hypothesis about voltage-gated Ca2+ channels is the best target for activation by physical means, basic content： Parkinson's disease , Alzheimer's disease etc. neuronal degeneration diseases, that closely related to physical-gated ion channels, which can be treated with physical means, activating neurotransmitters-energic neurons plays key roles in the treatment, and voltage-gated Ca2+ channels is the best target for physical means, the purpose is to induce Ca2+ inflowing and triggers neuronal axon terminals synaptic vesicles releasing neurotransmitters. The theory of brain cell activation sets forth the principle, method and purpose of treatment of the physical gated ion channel diseases such as Alzheimer's disease, Parkinson's disease and other neural degeneration diseases, and indicates that the attempt to treat these diseases using pharmaceutical and chemical approaches could shake our confidence in conquering the diseases, and the application of physical approaches or combined application of physical and chemical approaches in the treatment of some major encephalopathy may be our main research direction in the future.

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

1. Introduction

Parkinson's disease (PD) and Alzheimer's disease (AD) are nervous system degenerative disease. The major pathological changes in PD are dopaminergic neuronal degeneration and death in the substantia nigra which results into striatal dopamine levels decreasing, leading to tremor, muscle rigidity, bradykinesia and postural instability etc. a series of syndrome. The application of DA precursor levodopa to compensate for the brain to reduce DA in the clinical. It is a replacement therapy, although which can obviously improve the symptoms a few years, but there will be more serious side effects after longer-term use of the drug, even can appear "open-close" effect, continue taking levodopa can't stop the progress of PD [1]. The pathological features in AD are massive senile plaques (SP) in the brain (major ingredient is Aβ), neurofibrillary tangles (NFTs) formed via aggregation of microtubule-associated tau proteins, and neuron loss, which will cause atrophy of brain tissue, correlations between these characteristics are unclear. At present, there is no medicines treatment for prevent and delay AD development[2].The more recognized pathogenesis of AD is as hypothesis cholinergic, namely the reduction of cholinergic neurons in the brain, lead to acetylcholine (ACh) synthesis, storage, release and decrease and produce a series of clinical manifestations, with memory and identify dysfunction as the main symptom, moreover ACh is a kind of important neurotransmitters in brain tissue.

The view point of the article is a new idea that based on effective treatment of PD and AD with transcranial magnetoelectric (TME) stimulation technology, it can understand a hypothesis about voltage-gated Ca^{2+} channels is the best target, it suggests that the basis of exocytosis maintains basic metabolic processes of degenerative dopaminergic neurons, cholinergic neurons before death, and there is a reversible process between degenerative and normal neurons, which can be used with physical means(TME) for activating dopaminergic neurons, cholinergic neurons and so on, and the voltage-gated Ca^{2+} channels is the best target for physical means(TME). This view supports hypothesis vesicles [3] and hypothesis cholinergic [3]. The author made bold to name this viewpoint as “theory of brain cell activation”, which is applicable to encephalopathy but not limited in encephalopathy.

This article is only aimed at degenerative dopaminergic neurons, cholinergic neurons, not including upstream events which may cause neuronal degeneration and downstream events which be leded to the degeneration of neurons, such as: Aβ, tau protein, etc.

Ion channels on the cell membrane are particular integrin which have ion selectivity and gating characteristics. The process of ion channels opening and closing its gate is called gating. Currently, the gated ion channels are subdivided into chemical, voltage-gated, and mechanical gating [4] etc. Because sound, light, electricity, magnetism, force and heat have physical properties, in addition to the chemical gating, the voltage, and mechanical gating are categorized as physical gating etc. Voltage-gated Ca^{2+} channels belong to the physical-gated ion channels.

2. Basic content

PD, AD etc. neuronal degeneration diseases, that closely related to voltage-gated Ca^{2+} channels, which can be treated with physical means, activating neurotransmitters-energic neurons plays key roles in the treatment, and voltage-gated Ca^{2+} channels is the best target for physical means, the purpose is to induce Ca^{2+} inflowing and triggers neuronal axon terminals synaptic vesicles releasing neurotransmitters.

3. Validation methods

By means of animal study test, it is a positive correlation between TME stimulation and endogenous dopamine, acetylcholine generation, and by clinical study of TME stimulation for improvement in symptoms of PD, AD patients.

3.1 Animal study

PD is closely related to decrease of brain dopamine levels, which has been repeatedly confirmed [5, 6] in the past half century. The large number of stduies have proved that there is a positive correlation between TME stimulation and endogenous dopamine generation. Investigated the impact of transcranial magnetic stimulation on the dopamine release of hippocampus, nucleus accumbens and striatum of adult male Wistar rats using intracerebral microdialysis technique. The results suggested tnat transcranial magnetic stimulation can significantly increased dopamine concentrations in the hippocampus, nucleus accumbens, and striatum [7]. Activated the dopaminergic neurons of the rat model of PD by transcranial magnetic stimulation, prompting endogenous dopamine release in the ventral striatum[8]. Selected the adult monkeys of PD that has been successfully installed stimulating electrode in the study, and found that the electrical stimulation could effectively improve the symptoms of partial side monkey model of PD. The effective electrical stimulation can increase the striatal extracellular dopamine and its metabolites with microdialysis sampling techniques combined with HPLC method [9]. Research findings that subthalamic nucleus stimulation could increase dopamine release in rat striatal cells and activate dopaminergic neurons [10]. Someone demonstrated [11-13] that electrical stimulation could promote the release of endogenous opioid peptides in the central never system. Thus it could be inferred that electrical stimulation can promote the release of neurotransmitters. Neurotransmitters and neuropeptides are coexisted within neurons [14-16]. The role of TME is far superior to pure transcranial magnetic or transcranial electric.

3.2 Clinical confirmation

Since 1994, the concept that, "activation of brain cell is a key treatment of a variety of difficult encephalopathy [17]" was presented. The author continuously repeated to verify and improve the "the theory of brain cell activation" nearly two decades from theory to practice and then the other. Under the guidance of this theory, we successfully developed encephalopathy professional equipments, such as brain function rehabilitation instrument [18,19] (Suitable for cerebral apoplexy sequela, vascular dementia, and brain atrophy), treatment instrument for Parkinson[20-22], depression[23,24], and Alzheimer[20,25] using a non-intrusive TME etc.

physical means, which have got through the clinical verifications in the national clinical trial sites. It has been eligible for People's Republic of China medical Device Registration Certificate and industrialization in 1996, 2011, 2011, and 2014. Beause these apparatuses are perfectly safe to use in ordinary households by the patients themselves saving the instructions from clinicians. The merit speaks for itself, and yet it contributes much to the cause of our work remaining unnoticed in the field of clinical medicine. But the truth is that, from the year of 1996 to the date of my submission, the number of encephalopathy patients benefited from it is more than 50 million and the effect of feedback is exciting. One explanation for its mechanism is that the peptide neurons, dopaminergic neurons, serotonergic neurons, and cholinergic neurons are all mainly activated accordingly.

We use a non-intrusive TME stimulation technology in the clinical of PD, in the randomized, multicenter, double blind, self crossover control trial was carried study, the Parkinson's patients complied with the inclusion criteria, conducted the clinical trials, the results shows TME stimulation could significantly improve the resting tremor, rigidity, bradykinesia and other symptoms of PD, main treatment for the mild to moderate Parkinson's disease [26]. By using a non-intrusive TME stimulation technology in the clinical of AD and vascular dementia, in the multicenter, randomized, double blind, placebo parallel controlled trial was carried study, the Alzheimer's patients complied with the inclusion criteria, the results shows TME stimulation could significantly improve memory, cognitive function, mental state and operational abilities in everyday life of Alzheimer's patients, main treatment for the mild to moderate Alzheimer's disease, vascular dementia[25]. The above result was also recognized by CFDA and as a part of clinical registration basis about Parkinson therapy device and Alzheimer therapy device.

4. Explanation

4.1 Cellular and molecular mechanisms of degeneration of neurons

PD is closely related to dopaminergic neuronal degeneration and death in the substantia nigra which results into striatal dopamine levels decreasing, Tyrosine comes from food directly or indirectly will be transferred into dopa in neurons under the roles of Tyrosine hydroxylase (TH). Dopa would be transferred into dopamine by the dopa decarboxylase. Dopamine was packaged into the terminal synaptic vesicles of dopaminergic neuron axons, whereas dopamine release of vesicles is completed by quick regulation process of Ca^{2+}-dependent vesicle exocytosis [27, 28], as shown in Fig. 1.When the concentration of the intracellular flow of Ca^{2+} increases to a certain extent, the release of vesicles dopamine will be triggered. Ca^{2+} influx is controlled by the voltage-gated Ca^{2+} channels open induced by the membrane depolarization. Vesicle exocytosis are divided into Ca^{2+}-dependent rapid adjustment exocytosis and the basic state exocytosis, in which basic state exocytosis is beyond control of action potentials and Ca^{2+} [3]. Intracellular Ca^{2+} comes from not only the extracellular influx of Ca^{2+}, but also comes from the synaptic calcium depot [30]. Influx superposition of Ca^{2+} and basic state of Ca^{2+} play their roles each other. If neuron releases neurotransmitters with sustained high-frequency, and accompanied by neurotransmitter releasing into the presynaptic and Ca^{2+} increase, which will increase the catalytic activity of TH, and the mRNA transcription of TH and its synthesis enzymes gene expressions [29].

Instead, if the dopaminergic neurons can not release dopamine timely at normal rate, degeneration neurons would occur. While increased dopamine in the shaft plasma can inhibit the activity of TH. The feedback regulation can lead to time-dependent inhibition of dopamine synthesis, which may be related to "open-close" effect [31] appeared in the clinical use of levodopa treatment of PD. Degenerative dopaminergic neurons will gradually lose their function and become death. The basis of state exocytosis maintain its basic metabolism before death. Exogenous dopamine, relieving the patient's symptoms at the same time, will further reduce the activity of TH. Then the vesicle fusion rate of the basis state exocytosis, which is not controlled by action potential and Ca^{2+}, becomes lower. This replacement therapy is equivalent to abandon rescuing the degenerative dopaminergic neurons. The regulated neuronal death signaling pathway leads to destroying the balance between survival and death signal and the apoptotic program starting [32]. This seems to be an explanation for the condition those patients with PD taking levodopa for 2~5 years would lead to serious dysfunction. This explanation supports hypothesis vesicles.

Although the pathogenesis of AD is complex, it is difficult to use a hypothesis fully explained, but the truth that brain cholinergic neurons occur selective degeneration, and cholinergic neurons is a important biological basis of learning and memory. Acetylcholine is generated from AcetyL-CoA, which is produced during decomposition of choline and sugar, with choline acetyltransferare (ChAT) as the catalyst. Acetylcholine is synthesized in the axoplasm for axon terminals, then through acetylcholine transporter transferred to synaptic vesicles for storage. If the cholinergic neurons can not release acetylcholine timely at normal rate, degeneration of cholinergic neurons would occur, while increased acetylcholine in the shaft plasma can inhibit the activity of ChAT. Enzyme activity decreases about 50% will effect on synthetic for acetylcholine [3]. As the same, degenerative cholinergic neurons death signaling pathway upregulates and the apoptotic program starting. Existing drugs such as cholinesterase inhibitors, NMDA receptor antagonist for the treatment of AD, which be aimed at not have taken place in degeneration of cholinergic neurons, this is one explanation of these drugs, that cannot prevent or delay the progression of the disease was significantly, and the research for the treatment of AD drugs also have taken place in many points to the degeneration of cholinergic neurons of the upstream or downstream events. This explanation supports hypothesis cholinergic.

4.2 The mechanism of TME on Ca2+ channel

Voltage-gated calcium channels belong to oversized family members of ion channels. Among of them, α1 subunit of Ca^{2+} channel is the main functional units. Experiments show that the common characteristics of α subunit of voltage-gated calcium channel are as follow: S4 fragment containing positive charged amino acids, plays a leading role in the activation of membrane and potential changes; S6 fragment containing certain amino acid residues, plays a key role in the inactivation of voltage-dependent calcium channels, as shown in Fig. 2 . Channel activation requires the condition that there have charged amino acids or strong bipolar ion in the phospholipid bilayer membrane electric field. These gates charge or voltage receptors movement under the effect of electric field cause the channel protein conformational change, which leads to channel activation and open [33]. As a physical factor, the magnetic field has the Lorentz force on the moving charged species, and has

an impact on the permeability of ions and the cell membrane potential across the membrane, which could result in configuration changes of membrane ion channel. Experimental results suggest that the impact of moderate-intensity constant magnetic field on the ion channel may be associated with movement of ion channels related charges in the cell membrane [34]. According electrophysiological characteristics, the voltage-gated Ca^{2+} channels are divided into L, N, P, Q, R and T other six subtypes. Different subtypes of Ca^{2+} channels have different activation potential, such as activation potential of the L-type calcium channel is -10mV, and activation potential of T-type calcium channel is -70mV. In fact, when the membrane potential is near to -40mV, open probability of Ca^{2+} channel begins to significantly increase [3] .Under normal circumstances, the cell membrane has the intracellular calcium ion pump out of cell function, maintain the stability of internal environment. When suffer from AD, this function is impaired, intracellular calcium ion overload, causing the cells inside and outside calcium ions are relatively close to the static. TME can induce Ca^{2+} inflowing, so will also be prompted Ca^{2+} outflow rapidly of the Ca^{2+} depot, because the stimulation is rhythmic, will cause Ca^{2+} concentration of two-way oscillation [37].

The easiest route for Voltage-gated is electricity, and non-intrusive TME mainly is the ultimate role in the form of electricity, at the same time of activation key neural population, catered to give mass to the facts of whole brain neurons distribution and skull high impedance, its safety and effectiveness is simple deep brain stimulation, high strength of transcranial magnetic stimulation is difficult to realized or some other way.

4.3 The best target of TME effect

Voltage-gated calcium channels are the best targets for physical activation, but not the only target. Voltage-gated sodium channels are the material basis for generation and propagation of action potential. While the voltage-gated calcium channels will open at the cell membrane depolarization and cause calcium influx. TME stimulation not only directly activate the calcium channels, resulting in action potential backpropagation and the sodium ion channel activation; but also can firstly activate sodium ion channels, resulting in action potential conducting along the axon to its final end and activate the calcium channels. Only activation of calcium channels can achieve the purpose that calcium influx triggers the release of vesicles neurotransmitter. Because the new technology can record the information of neurons simultaneously in multiple locations, this concept has been proved: there is back propagation in the action potential.

Ca^{2+} influx does not result in the uncontrolled release of neurotransmitters, even there is intense physical stimulation from the outside. There is no linear relationship between the rate of vesicle fusion and free calcium concentration [3]. This non-linear relationship makes synaptic vesicle fusion to be extremely sensitive changes for Ca^{2+} concentration, and which is limited to a very narrow range of Ca^{2+} concentration and a very short period. Regeneration of endogenous neurotransmitters including vesicle loading, transshipment and anchoring all need time and process [36, 37]. In the process of rapid vesicle exocytosis, vesicles can release to rapid depletion. The rate of vesicle release exponentially attenuated over time [3]. Neurotransmitter released into the synaptic cleft also complies with a constant internal environment doctrine. Constant internal environment is not static, but constant based on some form of rhythmic activities.

In addition, TME targets are not only limited to the voltage-gated ion channels. Such as AD, external specific electromagnetic field is able to realize electric charge eliminating of nucleus of β-amyloid polypeptide (Aβ), which is the main component of senile plaque, and deacidification of Tau protein, remove Aβ or prevent Aβ polymerization, and protect microtubule assembly and axone transport system.

5. Discussions

The views of this article is both as an deduced assertion based on the existing biochemical results, and as a new view based on the treatment with TME of PD and AD. It is helpful for the understanding of the pathogenesis of PD and AD, thus can drive and explore the safe and effective treatment of PD and AD, provide a theoretical platform.The theory of brain cell activation, which is applicable to encephalopathy but not limited in encephalopathy. This theory can be used as the theoretical basis to create the "physical nosography". All the neurotransmitter-energic neuron degenerative diseases, are closely related to voltage-gated Ca^{2+} channels, which can attempt to be used physical means to resolve. In fact, we also apply TME in epilepsy clinically, also has obtained the astonishing effect, while TME in pediatric cerebral palsy and awaking up persistent coma patients also has a good performance.

Brain activity is extremely complex; the authors clearly know that the new view needs more reliable supporting evidences. Either patch clamp recording or intracellular detection may cause varying degrees of damage in neurons, making it to leave the original real state. At present, we are looking for the directly authentication technology about tracking the living individual neurons with TME stimulation now. TME stimulation is related to the biological properties of membrane ion channels and channel configuration change, which need further confirmed theoretical and experimental validation of molecular biology from the molecular and cell signal transduction levels.

At present, for neuronal degeneration diseases, we seem to be more accustomed to seek a solution for the problem with drug or chemical means, and this may not be a shortcut. Blood-brain barrier (BBB) is the first barrier chemical means to be beyond. The presence of BBB is like defense line builded in the peripherals of central nervous system, which can not only prevent brain damage from external chemical resistance, but also keep a lot of substances being beneficial for brain outside brain [38]; Physical-gated ion channels, are the second barrier chemical means to be beyond. If you want to push the door of gated ion channels occurred physical abnormality through action potentials generated by chemical means, its hardship degree may shake our confidence of coping with the diseases. The frustration on research and development of new drugs for Alzheimer's disease [39] could already prove it.

PD and AD are the world difficult problems. Scientists of all countries attack for a long time with has made some research results in the chemical drug research and development in the recent hundred of years, but is not improved substantially. TME and voltage-gated Ca^{2+} channels all have significant physical properties, and the applications of TME stimulation achieved remarkable results in the clinical treatment of PD and AD, and also suggests the application of physical means or a combination of physical and chemical means may be the

main direction for research on conquering with PD and AD in the future, such as late severe patients with PD, cells of TME targets-dopaminergic neuron death is overmuch, TME and levodopa drugs combined application may be more scientific.

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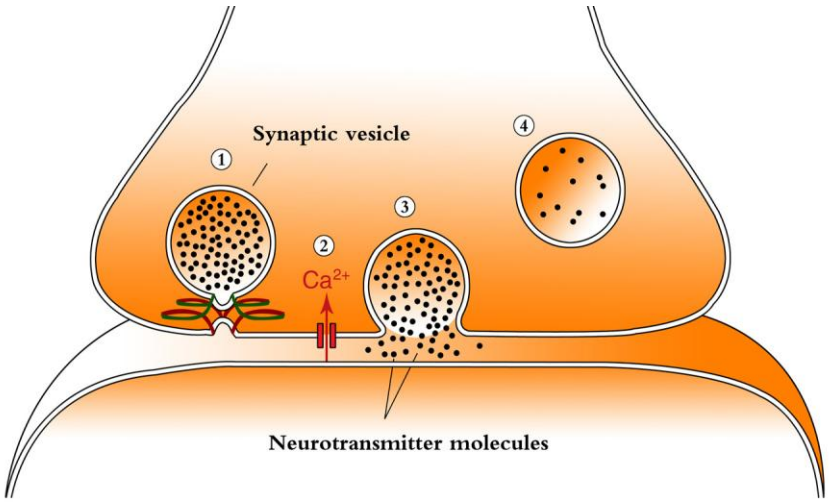
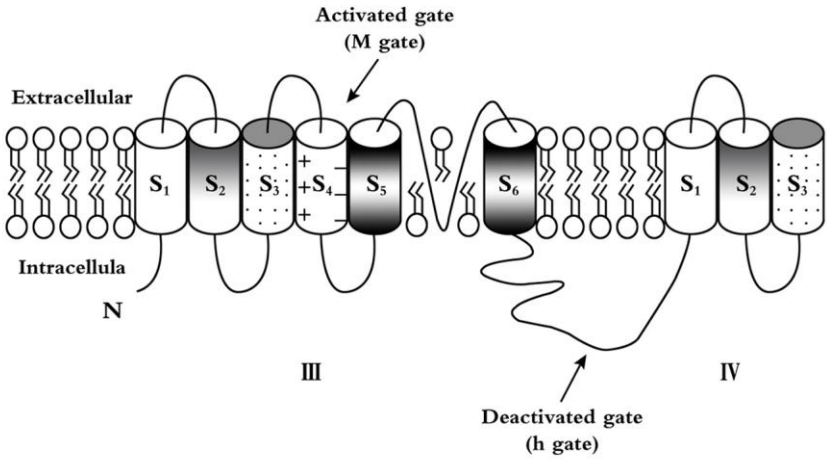
Figure Legends



① Synaptic vesicles containing neurotransmitters;
② Ca^{2+} through voltage-gated channels triggers vesicles reaction;
③ Neurotransmitter will be released into the synaptic cleft through fusion of vesicle membrane and presynaptic membrane;
④ Vesicle will be recycled with endocytosis process finally.

Fig. 1 Neurotransmitters are released by exocytosis [29]



S4 is the voltage sensor, which is the activated gate (M gate). The gate will open when it is activated, and the channel is open. For some calcium channel, the peptide chains connected between Ⅲ and Ⅳ are inactivation gates (h gate), the channel will be inactivated when the gate is closed.

Fig. 2 Molecular Mechanism for calcium gated channels [33]