Review Article

A Review of Acupuncture Combined with Pharmacology in the Treatment of Neurodegenerative Diseases: A Comprehensive Analysis

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This study is a comprehensive analysis that aims to explore the pharmacological targeting and neuroprotective effects of acupuncture combined with pharmacology for the treatment of neurodegenerative diseases. The paper reviews the clinical research progress, pharmacological targeting mechanism and neuroprotective mechanism of acupuncture combined with pharmacology for different types of neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, etc.). The paper shows that acupuncture combined with pharmacology can effectively clear or inhibit the aggregation and deposition of neurodegenerative proteins (such as beta-amyloid, etc.), improve the structure and function of neurons, regulate oxidative stress, inflammatory response, neuronal apoptosis and other signaling pathways, protect neurons from damage, improve the neurological function and quality of life of patients, and reduce the adverse reactions of drugs. The paper provides theoretical basis and guidance for the application of acupuncture combined with pharmacology in the treatment of neurodegenerative diseases.

Key words: Acupuncture, pharmacology, neurodegenerative diseases, randomized controlled trial, efficacy and safety

Neurodegenerative diseases are a group of chronic diseases characterized by gradual loss and dysfunction of neurons, mainly affecting the central nervous system or peripheral nervous system. According to the different affected brain regions and protein aggregation types, neurodegenerative diseases can be divided into various subtypes, such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic Lateral Sclerosis (ALS), etc. These subtypes have their own clinical manifestations and development processes, but they also share some common features, such as oxidative stress, mitochondrial dysfunction, inflammatory response, autophagy disorder, neuronal apoptosis, etc. The pathogenesis of neurodegenerative diseases is not clear, and may be related to various factors such as genetics, environment, metabolism, immunity, etc.

Neurodegenerative diseases are serious diseases that impair human health and quality of life, and their incidence and mortality are on the rise, bringing heavy burden to patients, their families and society. At present, the clinical treatment of neurodegenerative diseases mainly relies on symptomatic drugs, such as dopamine precursors, cholinergic drugs, monoamine oxidase inhibitors, etc., but these drugs can only temporarily relieve some symptoms, and cannot stop or delay the degenerative changes of neurons, and also have adverse reactions and drug resistance problems.

Therefore, finding effective treatment methods and strategies to improve the prognosis and quality of life of neurodegenerative diseases is an important topic in the current medical field.

Acupuncture is a traditional Chinese medicine treatment method, which stimulates acupoint at specific parts of the human body, regulates the circulation of qi and blood, and achieves the purpose of preventing and treating diseases. Acupuncture has

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various effects such as regulating nervous system function, improving cognitive and motor disorders, reducing oxidative stress and inflammatory response. Acupuncture has become a popular and promising treatment option for neurodegenerative diseases in recent years, and its therapeutic effect on these diseases has been verified by many animal studies and clinical trials.

Pharmacology is a basic and applied science that deals with drugs, involving their chemistry, biology, pharmacology, formulation, clinical aspects, etc. The goal of pharmacology is to develop safe and effective drugs, and to explore their mechanisms and methods of action and application in the prevention and treatment of various diseases. Pharmacology also plays an important role in the treatment of neurodegenerative diseases, and there are many drugs that are used in clinical practice or under development, such as antioxidants, neurotrophic factors, cytokines, gene therapy, etc.

Acupuncture combined with pharmacology refers to the combination of acupuncture and drugs, using the specific stimulation effect of acupuncture and the targeting effect of drugs, to achieve comprehensive intervention for neurodegenerative diseases. Acupuncture combined with pharmacology cannot only exert the advantages of acupuncture and drugs, but also synergize or antagonize each other, enhancing or weakening their effects.

The purpose of this paper is to explore the pharmacological targeting and neuroprotective effects of acupuncture combined with pharmacology for the treatment of neurodegenerative diseases. This paper analyzes from three aspects; the clinical research progress of acupuncture combined with pharmacology for the treatment of neurodegenerative diseases, summarizing the treatment protocols, evaluation indicators and effects of acupuncture combined with pharmacology for different types of neurodegenerative diseases (such as AD, PD, HD, etc.); the pharmacological targeting mechanism of acupuncture combined with pharmacology for the treatment of neurodegenerative diseases, explaining how acupuncture combined with pharmacology can clear or inhibit the aggregation and deposition of neurodegenerative proteins (such as Amyloid Beta (Aβ), etc.), thereby improving the structure and function of neurons; the neuroprotective mechanism of acupuncture combined with pharmacology for the treatment of neurodegenerative diseases, illustrating how acupuncture combined with pharmacology can regulate oxidative stress, mitochondrial function, inflammatory response, autophagy disorder, neuronal apoptosis and other signaling pathways, thereby protecting neurons from damage.

CLINICAL RESEARCH PROGRESS OF ACUPUNCTURE COMBINED WITH MEDICINE IN THE TREATMENT OF NEURODEGENERATIVE DISEASES

Yijun Zhan recruited a total of 44 patients diagnosed with mild to moderate AD and 22 healthy subjects as controls[1]. The AD patients were randomly assigned into either the treatment group or the control group. The control group received donepezil treatment alone while the treatment group received combined therapy of donepezil and acupuncture targeting specific acupoints including DU24, EX-HN3, DU20, EX-HN1, GB12, HT7, KI6 and GB39. After duration of 12 w intervention period, the results demonstrated that the AD Assessment Scale-cognitive component (ADAS-cog) score in the treatment group was significantly lower than that in the control group. Furthermore, functional Magnetic Resonance Imaging (fMRI) scans revealed decreased fractional Amplitude of Low-Frequency Fluctuations (fALFF) values primarily located in regions such as right inferior temporal gyrus, middle and inferior frontal gyrus, middle occipital gyrus, left precuneus, and bilateral superior temporal gyrus when comparing AD patients with healthy subjects."

Compared to the control group, the treatment group exhibited the largest change in fALFF value in the right precuneus following intervention. Furthermore, there was a positive correlation between the difference in ADAS-cog scores after intervention and the difference in fALFF values within the left temporal lobe. Functional Connectivity (FC) analysis based on the right precuneus revealed that, compared to the control group, altered FC patterns were predominantly observed within bilateral middle temporal gyrus regions in the treatment group. These findings demonstrate that acupuncture combined with donepezil significantly enhances cognitive function in patients with AD, surpassing the effects of donepezil alone. The pivotal role of precuneus in mediating this therapeutic effect and its relationship with middle temporal gyrus provide promising targets for potential AD treatments.

Ren Xiaoming conducted a study in which 50 patients with PD were treated with acupuncture combined with Madopar in the treatment group, while 30 patients in the control group received only Madopar[2]. In the treatment group, plum-blossom needle was gently tapped on Shaoyang meridian, foot Yangming meridian, foot Taiyang meridian, and foot-Taiyang meridian. Acupuncture points TE 4, LI 5, LI 11, LU 5, TE 14, LI 15, LR 4, KI3, SP9, BL40, GB30 and BL36 were used. The results demonstrated that the overall effective rate in the treatment group was significantly higher at 92 %, leading to significant relief of movement disorders compared to the control group ($p<0.05$). Furthermore, the dosage of Madopar required by patients in the treatment group was significantly lower than that of the control group after treatment ($p<0.05$). These findings indicate that acupuncture can enhance the therapeutic effect of Madopar and reduce its minimum dosage requirement for patients.

The patient, a 55 y old woman, was diagnosed with ALS. She presented with weakness in her right arm and legs for duration of 4 mo. Additionally, she experienced muscle spasms and limb clumsiness that rapidly worsened 4 mo prior to the onset of symptoms. Physical examination revealed grade 2 inability to dorsiflex both feet and weakness in grip strength of the right hand. Significant atrophy was observed in the muscles of both feet and ankles, along with fasciculation's in both legs and the right arm. Bilateral extensor reflexes were noted upon testing the plantar reflex. While she could ambulate within her home using her feet, climbing stairs proved challenging for her. Her Karnofsky status was measured at 70. The patient's treatment plan included oral administration of riluzole at a daily dose of 50 mg alongside acupuncture therapy. Riluzole acts by reducing presynaptic glutamate release and has been shown to extend the lifespan of ALS patients by approximately 2-3 mo; it is particularly beneficial for bulbar-onset cases. Acupuncture point selection encompassed LI15, LI11, LI5, LI4, LI10, SI9, LU5, GB30, GB31, GB34, ST31, ST32, ST36, SP6, GB39, ST41, BL32, BL40, BL57, GB40, GB41 etc.

Acupuncture treatment was administered for two courses, each lasting 8 w. The results demonstrated that patients exhibited improved stair-climbing ability following the first course of treatment (8 w). Hamstring muscle strength reached level 4, and Karnofsky performance status improved to 100. A 3 y follow-up revealed significant symptom amelioration approaching normal levels. Electromyography indicated disease progression cessation compared to 3 y prior. These findings highlight the efficacy of acupuncture in combination with riluzole as a therapeutic approach for progressive freezing disease, offering symptom relief and enhancing quality of life[3].

Chen Xiuhua conducted a randomized allocation of 60 patients into two groups; the abdominal acupuncture group (30 cases) and the control group (30 cases)[4]. The control group received only Madopar medication, while the abdominal acupuncture group underwent abdominal acupuncture in addition to taking Madopar medication. Specific acupoints such as cv 12, cv 10, cv 6, and cv 4 were selected for treatment purposes. After three courses of treatment, the overall effective rate was found to be 90 % in the abdominal acupuncture group and 83.3 % in the control group respectively. This difference between both groups was statistically significant ($p<0.05$). Gastrointestinal symptoms, hypotension, switching phenomenon, movement disorders and mental symptoms were observed as side effects among PD patients from both groups after treatment completion. However, it was noted that these side effects were significantly lower in the abdominal acupuncture group compared to those in the control group ($p<0.05$). These findings demonstrate that combining abdominal acupuncture with western medicine can enhance clinical efficacy and reduce side effects associated with primary PD when compared to western medicine alone.

A total of 98 PD patients were randomly assigned to either the acupuncture group (n=49) or the western medicine group (n=49)[5]. The western medicine group received oral levodopa and benserazide tablets as standard treatment while the acupuncture group underwent Jiaji Panlong acupuncture at C2-L5 points in addition to western medication. Evaluation of both groups included pre-treatment assessment as well as post-treatment and 1 mo follow-up assessments using Unified PD Rating Scale (UPDRS-III, UPDRS-IV), TCM syndrome scores, and Parkinson's Quality of Life Questionnaire (PDQ-39). Safety comparison was also conducted between the two groups. Following

treatment and during follow-up period, both groups exhibited lower scores for UPDRS-III, UPDRS-IV, TCM syndrome scores and PDQ-39 compared to baseline values ($p<0.05$), with significantly lower scores observed in the acupuncture combined with medication group compared to the western medication group ($p<0.05$). The incidence rate of adverse reactions in the acupuncture group was 10.4 % (5/48), which was significantly lower than that in the western medicine group at 29.2 % (14/48) ($p<0.05$).

The results demonstrate that the combination of Jiaji Panlong needling with levodopa and benserazide hydrochloride tablets is more effective in treating PD patients than using levodopa and benserazide hydrochloride tablets alone, significantly improving motor dysfunction, clinical symptoms, and quality of life while maintaining a high level of safety.

THE PHARMACOLOGICAL TARGETING MECHANISM OF ACUPUNCTURE COMBINED WITH PHARMACOLOGY FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

Jing Jiang administered donepezil at a dosage of 0.65 μg/g/d to male SAMP8 mice, an established animal model for AD, and combined it with acupuncture at GV20, GV26, and Yintang acupoints respectively[6]. Spatial learning and memory ability were assessed using the Morris water maze test. The results revealed that the number of cross-platforms was significantly higher in the group receiving acupuncture plus donepezil compared to the group receiving only donepezil ($p=0.036$). Additionally, the swimming distance ratio was higher in the acupuncture plus donepezil group than in the donepezil-only group ($p=0.001$). Furthermore, compared to the donepezil-only group, there was a significant reduction in Integral Optical Density (IOD) of cortical β-amyloid protein in the acupuncture plus donepezil group ($p<0.001$). These findings demonstrate that combining hand acupuncture with donepezil can enhance spatial learning and memory abilities while reducing IOD levels of cortical β-amyloid protein.

Yang Shuquan randomly allocated 60 patients with AD into an observation group (30 cases) and a control group (30 cases)[7]. The control group received oral administration of donepezil hydrochloride tablets (5 mg/day), while the observation group underwent abdominal acupuncture embedding therapy in addition to the treatment given to the control group. Acupoints selected for treatment included cv12, cv10, st24, st26, sp15 etc., with a frequency of once every 10 d. Both groups were treated for duration of 2 mo. The Mini-Mental State Examination (MMSE) scores, ADAS-Cog scores, Activity of Daily Living Scale (ADL) scores, Neuropsychiatric Inventory (NPI) scores as well as serum levels of APP and Aβ1-42 were assessed before and after treatment in both groups.

After treatment completion, the MMSE score was significantly higher in the observation group compared to the control group ($p<0.05$). Additionally, ADAS-Cog scores, ADL scores, NPI scores were significantly lower in the observation group compared to the control group ($p<0.05$). Levels of β-Amyloid Precursor Protein (APP) and Aβ1-42 decreased significantly post-treatment within both groups ($p<0.05$), with greater reduction observed in the observation group compared to the control group ($p<0.05$).

The combination of abdominal acupuncture embedding therapy and donepezil hydrochloride tablets, based on Biaom's theory of brain-gut communication, exhibits potential to enhance cognitive function, daily living ability, and mental behavior in patients with mild to moderate AD, while also reducing serum levels of APP and Aβ1-42. Notably, the clinical efficacy surpasses that of donepezil hydrochloride tablets alone.

Sixty adult SD rats were randomly allocated into the following groups; normal group, sham operation group, model group, electro acupuncture group, gastrodin group, and acupuncture combined with medicine group each consisting of 10 rats.

After 2 w of modeling, the rats in the electro acupuncture group and the acupuncture combined with medicine group received treatment with electro acupuncture at gv20, gv14, and bilateral st36. The gastrodin group and the acupuncture-drug combination group were treated with intraperitoneal injection of gastrodin injection. The rats in the normal group, model group, and sham operation group did not receive any intervention. Immunohistochemistry was used to detect expressions of B-Cell Lymphoma-2 (Bcl-2) and B-Cell Lymphoma-Associated X Protein

(BAX) in hippocampal CA1 region of rats from each experimental condition.

The expression of Bcl-2 and BAX proteins in the hippocampus of rats from each group was assessed using Western blot analysis. Abnormal deposition of Aβ in the brain is a crucial factor in the pathogenesis of AD, primarily damaging neurons through aberrant apoptosis pathways. Currently, endogenous apoptosis mainly involves Bcl-2 family proteins, with Bcl-2 acting as an anti-apoptotic protein within this family, while BAX functions as a mitochondrial membrane protein that promotes apoptosis. By forming a heterodimer with BAX, Bcl-2 inhibits its pro-apoptotic effects and extends cell survival cycles. Immunohistochemistry and Western blot results demonstrated that compared to the electro acupuncture or gastrodin groups, the acupuncture combined with gastrodin group exhibited increased expression of Bcl-2 and decreased expression of BAX (all $p<0.05$). These findings indicate that electro acupuncture and gastrodin significantly inhibit the expression of BAX while upregulating the expression of Bcl-2. Notably, acupuncture combined with gastrodin exerted the most pronounced effect, suggesting a synergistic action against hippocampal neuron apoptosis in AD rats. This may represent one mechanism underlying the therapeutic potential of acupuncture combined with gastrodin for treating AD lesions.

THE NEUROPROTECTIVE MECHANISM OF ACUPUNCTURE COMBINED WITH PHARMACOLOGY FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

Studies have demonstrated that the pathogenesis of AD primarily involves the deposition of Amyloid β (Aβ) and the entanglement of nerve fibers[8]. Aβ deposition leads to extracellular free radical formation, resulting in significant oxidative damage to cell membrane lipids, alterations in cell membrane permeability, and neuronal apoptosis. Additionally, AD patients exhibit elevated levels of Malondialdehyde (MDA) and other end products within areas where cerebral nerve fibers are entangled, confirming a strong association between pathological changes in AD and heightened oxidative damage caused by free radicals. Research has revealed that MDA can directly impact transmission, transcription, and replication processes through protein-nucleic acid cross-linking mechanisms which subsequently manifest as declines in memory and cognitive abilities. Superoxide Dismutase (SOD) and Glutathione Peroxidase (GSH-Px), crucial antioxidant metal enzymes responsible for scavenging free radicals within the body to prevent excessive oxidative damage.

The Morris maze test demonstrated that the acupuncture combined with eugenol group exhibited significantly shorter escape latency and average swimming distance compared to the eugenol group. Moreover, the acupuncture combined with eugenol group showed a significant decrease in MDA content ($p<0.05$), along with significantly increased activities of SOD and GSH-Px ($p<0.05$). Conversely, no such alterations were observed following olfactory nerve transection. These findings indicate that the combination of acupuncture and eugenol can enhance learning and memory abilities in AD rats, reduce MDA levels, and increase SOD and GSH-Px activity within the hippocampus, with its efficacy dependent on the olfactory pathway.

Levodopa has demonstrated significant potential in the treatment of patients with PD. However, its administration is associated with notable side effects. Consequently, researchers have been actively seeking alternative treatments that can mitigate these adverse reactions while maximizing the therapeutic benefits of levodopa. In this study, we discovered that combining acupuncture with levodopa enhances its efficacy and reduces the occurrence of adverse reactions[9]. To mimic semi-Parkinsonism in C57Bl/6 mice, Seung-Nam Kim unilaterally injected 6-OHDA into their striatum. Different doses of levodopa were administered alongside acupuncture at GB34 for treatment purposes. Motor function and abnormalities were assessed using cylinder tests and Abnormal Involuntary Movement (AIM) evaluations respectively. Our findings revealed that, reducing the dosage to 50 % (7.5 mg/kg) combined with acupuncture yielded motor function improvement comparable to mice treated with standard dosages of levodopa (15 mg/kg), and when equivalent dosages of levodopa were used, the combined treatment approach (levodopa+acupuncture) significantly outperformed the control group in terms of AIM score reduction. In this study, we discovered that combining acupuncture with levodopa enhances

its therapeutic effects and reduces its detrimental responses.

Twenty nine female 5XFAD mice were randomly allocated into three groups; control group (Tg), selegiline group (Tg+SEL), and combined treatment group (Tg+SEL+EA)[10]. The selegiline group received oral administration of 10 mg/kg SEL daily, while the combined treatment group received electro acupuncture at KI3 (1 mA, 2 Hz) in addition to selegiline.

The 5XFAD mice were subjected to 1 w of SEL treatment followed by 2 w of EA treatment. Subsequently, cognitive function was assessed using novel object recognition and Y-maze tests. To elucidate the molecular mechanisms underlying the combination therapy, Western blots, Aβ1-42 Enzyme-Linked Immunosorbent Assay (ELISA), and micro-positron emission tomography were employed to evaluate pathological markers and processes.

RESULTS

Selegiline combined with electro acupuncture enhances cognitive function in 5XFAD mice. The exploration time of 5XFAD mice towards familiar objects was significantly prolonged by 1.8 times compared to non-transgenic mice. Treatment with selegiline (Tg+SEL) and the combination therapy (Tg+SEL+EA) resulted in a significant reduction of exploration time by 1.6 times and 1.4 times, respectively, compared to the transgenic group.

Selegiline combined with electro acupuncture treatment attenuates neuroinflammation in 5XFAD mice. Compared to the control group, treatment with selegiline combined with electro acupuncture reduced the expression levels of CD11B and GFAP in the prefrontal cortex of 5XFAD mice. Additionally, this combination therapy decreased COX2 expression in the prefrontal cortex of 5XFAD mice by approximately 1.7 times.

Selegiline combined with electroacupuncture reduces oxidative stress-related protein expression in 5XFAD mice. The expression level of HO1 in the hippocampus of combination-treated 5XFAD mice decreased by approximately 1.6 times. Furthermore, HSP70 expression was also reduced in the combination treatment group, while transferrin levels were significantly lower than those observed in the control group by approximately 2.8 times within the prefrontal cortex region. BAX expression was also decreased following combination therapy administration. The combined treatment did not directly regulate Aβ production but exhibited regulatory effects on glucose metabolism.

Compared to the control group, treatment with SEL combined with EA significantly reduced the levels of APP and APOE in 5XFAD mice by 2.8-fold and 1.8-fold, respectively. Micro PET was employed to assess the impact of combined therapy on glucose metabolism, as APOE is implicated in neuroinflammation and glucose metabolism during AD pathogenesis. In comparison to Tg mice, SEL combined with EA treatment led to a 1.2-fold increase in average glucose metabolism within the frontal cortex associated with working memory function. These findings demonstrate that compared to the control group, mice receiving combined treatment exhibited enhanced cognitive function and reduced neuroinflammation, indicating stronger anti-neuroinflammatory and anti-oxidative effects of the combination therapy. Furthermore, SEL combined with EA treatment improved cognitive function by activating the frontal cortex and increasing glucose metabolism. Additionally, mice treated with SEL and EA demonstrated greater levels of glucose metabolism. Our results highlight that compared to the control group, SEL combined with EA treatment resulted in superior cognitive function due to inhibition of neuroinflammation and increased glucose metabolism.

A total of 60 patients diagnosed with PD complicated by depression were randomly assigned to either the acupuncture group or the western medicine group, with 30 cases in each group[11]. Both groups received conventional treatment including oral Madopar and fluoxetine. In addition to this standard treatment protocol, the acupuncture group underwent electro acupuncture at specific acupoints such as du20, du29, ex-hn1, lr3, sp6 etc. The levels of Brain-Derived Neurotrophic Factor (BDNF) in serum and Hamilton Depression Scale (HAMD) scores were compared between the two groups before and after a 3 mo treatment period to evaluate their efficacy.

Oxygen free radicals play a crucial role in the pathogenesis of PD. Oxygen stress refers to the tissue and organ stress response caused by either weakened mechanisms inhibiting free radical

production or increased free radical production due to environmental factors or nutritional conditions. Free radicals generated through peroxidation reactions are referred to as oxygen free radicals, which can induce lipid peroxidation of unsaturated fatty acids, leading to oxidative damage of proteins and Deoxyribonucleic Acid (DNA), ultimately resulting in cellular degeneration and death. Wang Shun conducted a clinical study where 76 PD patients were randomly divided into two groups; treatment group (head electro acupuncture+Madopar) consisting of 37 cases, and control group (Madopar alone) consisting of 39 cases. Effects of head point-through-point electro acupuncture on SOD and Lipid Peroxide (LPO) levels in patients with PD. The control group received oral Madopar treatment only while the treatment group underwent electro acupuncture targeting specific acupoints on the head in addition to Madopar administration. The selected acupoints were ex-hn1, du21, du17, bl9, gb19, gb20. Levels of SOD and LPO were measured before and after treatment. Results showed that the effective rate was significantly higher in the treatment group (97.3 %) compared to the control group (61.5 %). Furthermore, significant improvements were observed in SOD and LPO levels within the treatment group when compared with the control group ($p<0.01$).

CONCLUSION

Head point-through-point electro acupuncture therapy can effectively enhance SOD and LPO levels within the body while providing therapeutic benefits for PD.

Author's contributions:

Shun Wang and Ning An have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

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