Effects of acupuncture on Alzheimer’s disease: the mechanistic study

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Introduction

Alzheimer’s disease (AD) is a degenerative disease of the central nervous system characterized by memory loss and cognitive impairment, often accompanied by emotional apathy, agitation, depression, delusions aggression, and other psychological symptoms [1–3]. Psychological symptoms such as apathy, agitation, and depression tend to increase with the duration and severity of AD, seriously affecting the prognosis of patients, and also bringing a heavy burden to society and families [4]. The pathology of AD is characterized by nerve cell dysfunctions and loss of neurons in the central nervous system, ultimately leading to mental changes [5]. However, the etiology of AD is still unclear, among which the recognized mainstream theories include the cholinergic hypothesis, Amyloid β-protein (Aβ) cascade hypothesis, and inflammatory response, etc. Current AD pharmacotherapy relies on cognitive enhancement therapy, and only five AD medications have been approved by the Food and Drug Administration [5], including cholinesterase inhibitors [6] (including tacrine, donepezil, rivastigmine, and galantamine) and Nmethyl-D-aspartate receptor antagonists (memantine) [7]. These drugs have toxic side effects and only temporarily relieve AD symptoms, but can not stop or slow the progression of AD, rather than meeting the clinical need. In addition, the efficacy and safety of drugs targeting Aβ in ameliorating cognitive decline in patients have been greatly questioned. Therefore the search for effective AD treatments remains urgent and challenging. Acupuncture is a non-pharmacologic therapy of traditional Chinese medicine, dating back at least 2,000 years. Its attention and acceptance are growing worldwide, showing promising therapeutic effects and good safety. And we are pleased to see that the number and quality of randomized controlled trials of acupuncture for AD have increased in recent years to scientifically demonstrate the efficacy and safety of acupuncture for AD [8].

Mechanism study of acupuncture in the treatment of AD

Acupuncture improves the cholinergic system

The cholinergic system is the most affected neurocircuit in AD [9], with the most pronounced changes being the degeneration of basal forebrain cholinergic neurons, which is thought to contribute to the deterioration of memory and cognition in AD patients [10]. The cholinergic hypothesis suggests that the increased activity of acetylcholinesterase (AChE) and decreased activity of choline acetyltransferase (ChAT) causes depletion of acetylcholine (ACh) levels, resulting in impaired cholinergic functions in the brain [11]. Zhang et al. [12] used D-galactose intraperitoneally injection to construct aging models and then injected Aβ1-40 into the bilateral hippocampus of rats to establish the AD models. After 4 weeks of acupuncture in DU2 and GB1, AChE activity was weakened, ChAT activity was increased and ACh content was increased, thus improving the learning and memory ability of AD model rats. This is consistent with the cholinergic theory of AD.

The expression of Aβ was decreased

The Aβ cascade hypothesis is currently the most recognized pathogenesis of the many hypotheses for AD [13]. The Aβ cascade hypothesis poses that the pathological process of AD mainly begins with the aggregation of Aβ to form neuritic plaques, and tau abnormally phosphorylated [14]. In the early stage of AD, microglial activation expresses phagocytosis receptors to promote the phagocytosis of Aβ, but as the AD progresses, the hyperactive microglia loses phagocytosis, resulting in accelerated Aβ deposition [15]. Electroacupuncture at GV20 and LI4 combined with donepezil effectively reduces serum Aβ precursor protein (APP) and Amyloid β1-42 (Aβ1-42) levels and improves learning memory in AD patients, and it is superior to the treatment with donepezil alone [16]. Acupuncture plus moxibustion have been shown to reduce Aβ levels within the serum of AD rats, decrease APP expression in the CA1 region of the hippocampus of rats, slow down the pathological process of Alzheimer’s disease, and improve the symptoms of AD rats [17]. Xue et al. [18] performed electroacupuncture on the GV20 and KI1of APP transgenic female mice, and found that the intracellular expression of Aβ1-42 in the mice was weakened after electroacupuncture, suggesting that electroacupuncture may regulate the disorganized self-phagocytosis process of APP transgenic mice, thus reducing the production of Aβ and its neurotoxicity in neurons, and improving the learning and memory ability of the animals.

Suppression of Excessive Inflammation

Deposited Aβ activates microglia and astrocytes [19] around plaques to release inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [20]. TNF-α, IL-1β, and IL-6 are increased in the brains of AD patients [21], which in turn activate microglia and astrocytes to produce APP and Aβ, creating a negative feedback loop [22]. Neuroinflammation can culminate in synaptic degeneration, neuronal death, and exacerbate brain damage [23]. Research has proved that acupuncture on bilateral “LI4” and “LR3” improves the learning and memory ability of AD rats, which may be related to the reduction of IL-1β content in the hippocampus and the improvement of Aβ deposition [24]. Wang et al [25] found that the content of pro-inflammatory factors IL-1β and IL-6 in the frontal region of AD model mice was higher than that of the normal group, and the content of IL-1β and IL-6 in the frontal region of AD model mice in the electroacupuncture group was significantly reduced compared with that of AD model mice, which indicated that acupuncture was able to inhibit the damage of excessive inflammatory response to neural cells and to improve the cognitive ability of mice.

Protection neuron

The brain structures of AD present with reduced synaptic density and reduced thickness of postsynaptic densities [26]. In addition, at the molecular level, the expression of many proteins related to synaptic function is reduced. There is a wealth of research demonstrating acupuncture has a protective effect on hippocampal synaptic plasticity, i.e., increasing the proportion of perforated synapses in their hippocampal tissues, increasing synaptic curvatures and thickness of postsynaptic densities, narrowing the width of synaptic clefts, and downregulating GSK-3 expression, thereby significantly improving the learning memory ability of rats [27-29]. In addition, Zhang et al. [30] found that electroacupuncture not only improved synaptic plasticity, but also significantly increased the expression levels of proteins related to synaptic function (e.g., BDNF, SYN, and NR2B), thus improving learning and memory function in AD rats.
In conclusion, acupuncture improves cholinergic function, enhances AChE and ChAT activity, increases ACh content, reduces Aβ production and its neurotoxic effects in neurons, inhibits excessive inflammatory responses, and protects neurons, thereby playing the therapeutic effect on AD.

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**Author contributions**

An-Lan Zhao performed manuscript writing. Hong-Yue Niu provided guidance and assistance in research activity planning and execution. Xiao-Xu Zhang and Jia-Xin Yuan modified the language and checked the text. All authors contributed to the article and approved the submitted version.

**Competing interests**

The authors declare no conflicts of interest.

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**Abbreviations**

AD, Alzheimer’s disease; Aβ, Amyloid β-protein; AChE, acetylcholinesterase; ChAT, choline acetyltransferase; ACh, acetylcholine; APP, Aβ precursor protein; Aβ1-42, Amyloid β1-42.

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