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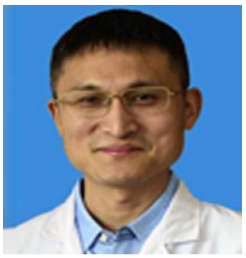
Mechanisms of Acupuncture Effect on Alzheimer's Disease in Animal-Based Researches

Yan Cao[1,2], Li-Wen Zhang[1,2], Jian Wang[2], Si-Qi Du[1], Ling-Yong Xiao[1], Jian-Feng Tu[1] and Cun-Zhi Liu[1,*]

[1]*Acupuncture and Moxibustion Department, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, Beijing, China;* [2]*Shandong University of Traditional Chinese Medicine, Jinan, P.R. China*



Cun-Zhi Liu

Abstract: Alzheimer's disease is the most common type of dementia in the aging population worldwide. The etiology and treatment of Alzheimer's disease are still not very clear. Finding a new treatment is urgent due to the increasing population aging. Acupuncture has been practicing in China for more than 3000 years and reported to be beneficial in treating cognitive impairment of Alzheimer's disease. This paper reviews the recent development on the effect of acupuncture on Alzheimer's disease in animal-based researches. It is suggested that acupuncture improves cognitive function of Alzheimer's disease by regulating glucose metabolism, enhancing neurotransmission as well as reducing oxidative stress, Aβ protein deposition, and neuronal apoptosis. However, it is still difficult to clarify which specific signaling pathway contributes to the acupuncture effect. Better designed studies are recommended to investigate the effects of acupuncture on Alzheimer's disease.

Keywords: Acupuncture, Alzheimer's disease, Cognitive function, Complementary and Alternative medicine, Mechanisms.

INTRODUCTION

Alzheimer's disease (AD) is a neurological disease which is characterized by progressive loss of memory and other cognitive functions [1]. The worldwide number of AD cases is currently estimated at 36 million and will triple by 2050, which impose familial, social and economic burden [2, 3]. Although the findings from researches indicate that the pathological changes of AD are extracellular plaques with amyloid β (Aβ) [4], intracellular neurofibrillary tangles with hyperphosphorylation of Tau [5], and neuronal loss in the brain, the cause and process are still not clear [6]. So far, there are no available treatments to prevent or halt the progression of the disease either [7].

Acupuncture is an ancient form of traditional Chinese medicine that can be traced back for about 3000 years. It is believed to restore the balance of qi which is theorized to influence a person's health. Acupoint is the skin needling points used for acupuncture treatment [8]. Commonly, acupuncture is accomplished by manual manipulation or electrical stimulation via thin, stainless steel needles inserted in corresponding acupoints. Manipulation of manual acupuncture involves lifting, thrusting, twisting, twirling or other complex combinations. It is believed that different manipulations may induce different effects. While electrical acupuncture (EA) is a modified acupuncture technique that utilizes electrical stimulation to enhance the acupuncture effect.

Memory loss accompanied by behavioral abnormalities like anxiety, depression, delusions or psychosis can occur at various stages in age-related cognitive impairment. Though the drug treatment of AD is still a challenging, acupuncture has been reported as an effective treatment improving cognitive function of a wide variety of neurological disorders such as Parkinson's disease [9] and vascular dementia [10]. In fact, acupuncture treatment is a basic therapy for AD in Asians for a long time, but its mechanism is not very clear. Several signaling pathways were demonstrated to be related to the restoration of cognitive function in animal models. In this review, we discuss the recent development of acupuncture effects on AD and the related mechanisms.

ACUPUNCTURE CLEARED AB PROTEIN DEPOSITION

The histopathological features of AD are cerebral plaques with Aβ peptide and neurofibrillary tangles in both neocortical terminal field and medial temporal-lobe structures, which cause neuronal dysfunction [11, 12]. Therefore, the increased aggregation and accumulation of Aβ peptide caused by an imbalance between production and clearance may be an initiating factor in AD progression [13, 14]. Finding a way to decrease the level of Aβ in the brain is a strategy of AD treatment.

EA stimulation at acupoints *Baihui* (GV20), *Dazhui* (GV14), *Taixi* (KI3), *Shenshu* (BL23) and *Zusanli* (ST36),

*Address correspondence to this author at the Acupuncture and Moxibustion Department, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University, 23 Meishuguanhou Street, Dongcheng District, Beijing 100010, P.R. China; Tel: 0086-10-52176043; Fax: 0086-10-52176813; Email: lcz623780@126.com

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once each day, and lasted for 28 days in AD rats which were established by injecting streptozocin into lateral cerebral ventricle, significantly decreased Aβ protein expression in the hippocampus. These effects were shown in AD rats treated with intragastric administration of Memantine as well [15]. Moreover, the expression of Aβ protein and Aβ precursor protein in hippocampus CA1 region and cerebral cortex in amyloid precursor protein (APP) transgenic mice were reduced after EA treatment [16].

The low-density lipoprotein receptor-related protein 1 (LRP1), as an Aβ clearance receptor, is expressed in a wide variety of tissues, articularly in vascular smooth muscle cells. Previous studies have indicated a role of LRP1 in transcytosing Aβ out of the brain [17]. Therefore, LRP1 dysfunction is implicated in the Aβ aggregation in AD brain. Following EA stimulation at acupoints GV20 and KI3, once every other day for 3 months in APP transgenic mice, the expression of LRP1 was significantly elevated and Aβ protein expression was decreased in the hippocampal sulcus microvessels compared with APP mice which received no treatment as control [18].

ACUPUNCTURE PROMOTED NEURAL TRANSMISSION

It has been known that cholinergic dysfunction is involved in AD [19]. Previous studies have showed that reduction of choline acetyltransferase (ChAT) and muscarinic acetylcholine receptor (mAChR) is related to the severity of AD patients [11, 20]. Alteration in the activity of acetylcholinesterase (AChE) was also mentioned in AD [21].

In modern medicine, acupuncture is suggested to activate peripheral afferent nerve fibers and receptors, resulting in sensory interaction at different levels of the central nervous system and release of variety of transmitters and modulators [22]. Acupuncture stimulation of aged rats produced an increase in the cortical cerebral blood flow and increased extracellular acetylcholine release in the cerebral cortex [23]. Levels of ChAT were decreased in Aβ-injected rats and acupuncture stimulation increased the activity of ChAT in the cerebral cortex and hippocampal CA1 region [24, 25]. EA at bilateral *Yingxiang* (LI20) and *Yintang* (EX-NH3) elevated the mAChR density and its maximum binding capacity, and reduced the disassociation content of mAChR in hippocampus compared with Aβ-injected rats receiving no intervention [26].

Age related impairment is related with synaptic failure [27] and some factors might make synapses vulnerable in AD such as high content of the disease-relative protein, high metabolic and oxidative loads [28]. Long-term potentiation (LTP) is a long-lasting enhancement of signal transmission between neurons [29] and LTP in hippocampus represents the synaptic plasticity associated with learning and memory [30, 31]. EA at ST36 and *Sanyinjiao* (SP6) in normal rats could enhance LTP in hippocampus by modulating the function of interneuron [32]. In Aβ-injected rats, the tungsten microelectrodes recording showed the decrease of LTP in hippocampus and EA at KI3, GV14, GV20 and BL23 for 30 minutes, once daily for 7 days, significantly reversed this decrease, suggesting an improvement of the synaptic transmission [33].

ACUPUNCTURE REGULATED GLUCOSE METABOLISM

It was suggested that glucose metabolism in the brain of patients with AD might change [34]. The deficiency or lower activity of triose phosphate isomerase (TPI) might inhibit the process of glycolysis [35]. Therefore, TPI is related to the degeneration of brain functions, such learning and memory [36]. EA at acupoints ST36, *Xuehai* (SP10), *Qihai* (CV6), *Zhongwan* (CV12) and *Danzhong* (CV17) once a day for continuously 21 days in senescence-accelerated mouse prone (SAMP8) mice up-regulated TPI activity in hippocampus. While this up-regulation was not shown in SAMP8 mice which received EA at non-acupoint located on the bilateral hypochondrium, 3 mm above iliac crest [37].

ACUPUNCTURE ATTENUATED NEURON APOPTOSIS

Many dying neurons have been detected in the brain of patients with neurodegenerative diseases such as AD, and this condition is often associated with significant cell loss accompanied by typical morphological features of apoptosis [38]. Acupuncture at CV17, CV12, CV6, SP10 and ST36 in SAMP 8 mice reduced the neuron loss in hippocampal regions CA3 and DG. However, the SAMP 8 mice which received acupuncture at non-acupoint showed far less proliferations and differentiations in the same zones [39]. Similarly, EA at acupoints ST36 and GV20 in normal rats induced cell proliferation and differentiation in subgranular zone of the dentate gyrus (SZDG) [40].

Many neurons undergo apoptosis in AD [41, 42]. The triggers of cell death in AD include Aβ, increased oxidative stress and DNA damage. Once triggered, apoptosis proceeds and induces mitochondrial membrane permeability changes [28]. EA at GV20 and *Yongquan* (KI1), 15 minutes once every other day for about 3 months, could effectively down-regulate the number of apoptosis neurons in the striate cortex in APP transgenic mice that might contribute to improving pathological changes of ultrastructure of neurons [43].

On the other hand, glial cells express many of the genes linked to AD and have been documented in studies of AD animal models and patients. The available data suggested that Aβ play a role in inducing alterations in glial cells [44] and their abnormalities may contribute to synaptic dysfunction and neuronal death [28]. Immunohistochemistry demonstrated that the number of activated glial cells in hippocampus of Aβ-injected rats was significantly decreased after EA at GV20, KI1 and ST36 [45]. Similarly, glial cells were more activated in SAMP8 mice which received acupuncture at ST36, SP10, CV6, CV12 and CV17 as compared to those mice which received acupuncture at non-acupoint located on the bilateral hypochondrium, about 10 to 15 mm above iliac crest [46].

ACUPUNCTURE REDUCED OXIDATIVE STRESS

Many researches suggested that oxidative stress played a role in pathogenesis of cognitive impairment. The level of blood oxidative stress markers correlated with the condition from MCI to AD [47, 48]. Dysfunctional mitochondria release oxidizing free radicals in AD which cause considerable

oxidative stress. EA at GV20 and KI1 in the APP transgenic mice minimized neuronal mitochondrial damage in hippocampal CA1 region [49]. Furthermore, in Aβ-injected rats, there were injuries of mitochondria. EA at GV20 and BL23, once a day for 14 days, protected the function of mitochondria by suppressing overexpression of Aβ-binding alcohol dehydrogenase (ABAD), increasing the activity of cytochrome oxidase IV (coxIV) and level of silent information regulator 1 (SIR1) in hippocampal neuron mitochondria [50, 51]. Furthermore, super oxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were regarded as inhibition of oxidative stress. An increase in SOD and GSH-Px was detected after EA at EX-HN3 and LI20 in Aβ-injected rats [52].

DISCUSSION

It is demonstrated that acupuncture may improve cognitive function of AD through regulating glucose metabolism, enhancing neurotransmission as well as reducing Aβ protein deposition, neuronal apoptosis and oxidative stress (Fig. **1**).

As AD represents a progressive memory loss and cognitive decline, it is essential to improve this impairment of learning and memory in order to treat AD. There are many animal models for exploring pathological mechanisms of AD, such as APP transgenic mice [53, 54], SAMP8 mice [55] and intracerebral Aβ-injected rats [56]. In experimental researches about AD, the Morris water maze task test is the most frequently used method to check the spatial learning and memory abilities of these animals. The spatial memory is the part of memory responsible for recording information about one's environment and its spatial orientation. Studies suggested improvement of learning and memory in AD models after acupuncture. Before acupuncture, the Morris water maze navigation test showed that the escape latencies increased in APP mice [18], SAMP mice [37, 39] and Aβ-injected rats [15, 32, 45, 57]. The Morris water maze spatial probe test showed that the number of platform crossing and time spent in the target quadrants were decreased in these models [15, 45]. Then, manual acupuncture or EA stimulation significantly shortened the escape latencies and increased the target-platform crossing time and percentage of dwell time in target quadrants. This indicated that acupuncture improved learning-memory capacity [15, 18, 32, 37, 39, 45, 57].

In particular, stimulating the following acupoints appears to enhance acupuncture effects on AD: ST36, ST40, KI1, KI3, GV14, GV20, CV6, CV12, CV17, SP10, LI20, BL23 and EX-NH3. Out of 15 studies on acupuncture and AD, 10 studies dealt with GV20, 7 studies with ST36 (Table **1** and Fig. **2**). As the most frequently used, acupoint GV20, meeting point on the Governing vessel with the six yang channels, is anatomically located on the midsagittal line, at the intersection of a line connecting the right and left ear apices [58]. Some researches suggested that acupuncture stimulation at GV20 could ameliorate memory-related performance in many behavioral tests as well as modulate cholinergic neurons and improve cerebral blood flow [59-61].

There are still several issues needed to be discussed. Firstly, because acupoint specificity remains a matter to the efficacy of acupuncture treatment, we should pay attention to the effect of non-acupoint; however, non-acupoint was set as controlled group in only few studies [37, 46]. Therefore we cannot reveal the real effects of acupuncture. The effect of single or combination of acupoints should also be further investigated. In addition, although there are many underlying mechanisms of acupuncture effects on AD, it is difficult to draw a conclusion that which specific signaling pathway contributes to acupuncture effect.

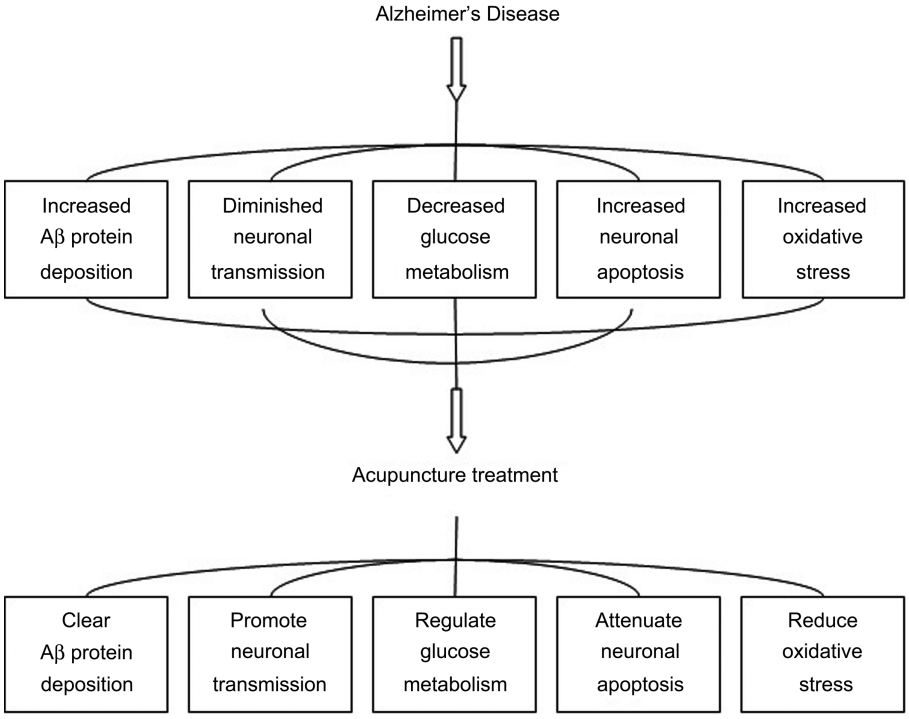

Fig. (1). The proposed mechanisms of AD by acupuncture treatment.

Table 1. The often used combined acupionts in acupuncture treatment of AD.

Combined Acupionts	References	Stimulation
GV20, KI1	Xue, *et al.*,2009 [14]	Electroacupuncture
	Xue, *et al.*,2011 [16]	Electroacupuncture
	Xue, *et al.*,2014 [40]	Electroacupuncture
	Xue, *et al.*,2009 [46]	Electroacupuncture
CV6, CV12, CV17, ST36, SP10	Zhao, *et al.*, 2013 [34]	Electroacupuncture
	Li, *et al.*, 2012 [36]	Manual acupuncture
	Zhang, *et al.*, 2013 [43]	Manual acupuncture
LI20, EX-NH3	Liu, *et al.*,2009 [22]	Electroacupuncture
	Yang, *et al.*,2011 [24]	Electroacupuncture
	Liu, *et al.*,2013 [49]	Electroacupuncture
GV20, BL23	Sun, *et al.*,2014 [47]	Electroacupuncture
	Luo, *et al.*,2014 [48]	Electroacupuncture

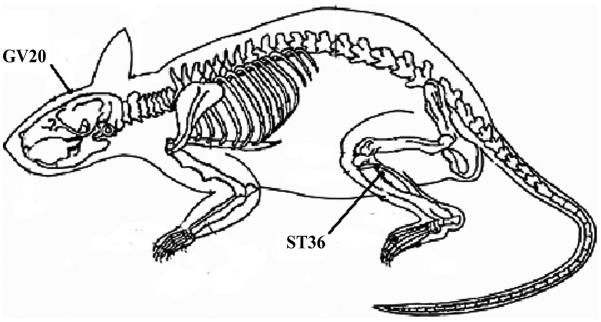

Fig. (2). GV20 and ST36 are the most frequently chosen acupoints in studies for treating AD. GV20 was mentioned 10 times and ST36 was 7 times.

CONCLUSION

This review describes the recent developments of the effect of acupuncture on AD in animal-based researches. Acupuncture treatment can improve cognitive impairment of AD through multiple underlying mechanisms. However, it is difficult to draw a conclusion that which specific signaling pathway contributes to acupuncture effect. Insufficient evidence leads to an unknown outcome between acupuncture group and non-acupoint group, and thus difficult to reveal the real acupuncture effect. Taken together, better designed studies are recommended to investigate further effects of acupuncture treatment on AD although some Chinese traditional drugs have been introduced to clinical study [62].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

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