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Review

The Possible Role of Stem Cells in Acupuncture Treatment for Neurodegenerative Diseases: A Literature Review of Basic Studies

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This review reports on recent findings concerning the effects of acupuncture and electroacupuncture (EA) on stem cell mobilization and differentiation, in particular with regard to neurogenesis. Traditional Chinese acupuncture has a history of over 2,500 years and is becoming more popular worldwide. Evidence has demonstrated that acupuncture may be of benefit in stroke rehabilitation, parkinsonism, dementia, and depression. This article reviews recent studies concerning the effects of acupuncture/EA on stem cell mobilization and on progenitor cell proliferation in the CNS. The reviewed evidence indicates that acupuncture/EA has beneficial effects in several neurodegenerative diseases, and it may prove to be a nondrug method for mobilizing stem cells in the CNS.

Key words: Neurodegenerative diseases; Neurogenesis; Acupuncture; Electroacupuncture (EA)

NEURODEGENERATIVE DISEASES

Neurodegenerative diseases involve the death of neurons in the brain or spinal cord and the gradual loss of structure or function. Acute neurodegeneration, such as stroke or trauma, may result in partial or complete loss of neurons in the injury area. Chronic neurodegenerative diseases occur over a long period of time and result in loss of either systemic or a specific subtype of neuronal populations. For example, Alzheimer's disease (AD) is due to extensive neuronal damage throughout the brain, while Parkinson's disease (PD) primarily involves specific and localized damage in substantia nigra dopaminergic (DA) neurons. The mechanisms underlying these neuronal losses are complicated, and the treatments for these neurodegenerative diseases have not yet been met by clinical means.

NEUROGENESIS

Neurogenesis constitutes the process by which new neurons are generated from neural stem cells and progenitor

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cells. Neurogenesis is responsible for populating the growing brain with neurons. It has long been thought that the adult mammalian CNS does not generate new neurons. However, recent experiments conducted in mammals and humans demonstrate that they can produce new neurons, which can functionally integrate into neural circuitry of specific regions as mature neurons (16,24).

Adult neurogenesis occurs within the subventricular zone bordering the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus of mammals (32,55). Neural progenitors in the subgranule zone become immature neurons, which migrate into the inner granule cell layer and then differentiate into granule neurons. In the subventricular zone, the newly generated neurons migrate through the rostral migratory stream (RMS) to the olfactory bulb to become interneurons (21,81). Adult neurogenesis is subjected to modulation by physiological and pathological conditions including the environment, aging, stress, epilepsy, stroke, and depression; however, the molecular regulation mechanism is not entirely clear.

ACUPUNCTURE AND ELECTROACUPUNCTURE (EA)

Traditional Chinese acupuncture has a history of over 2,500 years and is becoming more popular worldwide. Notably, the World Health Organization (WHO) has published a guidance on the efficacy of acupuncture in the cure or relief of 64 different clinical conditions, such as chronic pain of the locomotor system, headache, hemiplegia and other sequelae of brain diseases, depression, nausea and vomiting, among others (78). Acupuncture therapy uses two different strategies: manual acupuncture (MA) and electroacupuncture (EA). EA is a modified form of the traditional MA. Nowadays, most studies use EA, since it is possible to standardize this method by frequency, voltage, wave form, length, etc. (39).

ACUPUNCTURE/EA THERAPY FOR TREATMENT OF NEURODEGENERATIVE DISEASES

Acupuncture is used widely throughout Asia for stroke rehabilitation (51), although the evidence is conflicting as to the effectiveness of acupuncture for this condition. While recent systematic reviews (49,56) and a 1997 National Institutes of Health consensus statement (50) suggest that acupuncture may be a useful adjunct to stroke rehabilitation, a meta-analysis (71) of randomized controlled trials (RCTs) that evaluated the benefits of acupuncture administered during the acute stage of recovery from stroke concluded that acupuncture has no effect on motor recovery but may improve disability. In chronic stroke, acupuncture leads to improvements in dysphagia (64), balance (42), and cognition (8). In regard to quality of life or spasticity, the majority of the reviewed studies indicated positive effects (19,43,63,87).

For PD treatment, acupuncture is a treatment of choice (12,15,61,65,73). Following acupuncture treatment, 70–80% of patients reported improvements in subjective symptoms and several motor scores as well as significant amelioration of their sleep and mood (76). For dementia treatment, a research group led by Professor Jingxian Han has developed *Yiqitiaoxue and Fubenpeiyuan* acupuncture (14,86), which has been shown to improve cognitive abilities in dementia and aging models as well (9,85).

THE MECHANISM OF ACUPUNCTURE/EA

Extensive research has investigated the effects of acupuncture and the mechanism of acupuncture analgesia. Endogenous opiates are considered to play important roles in acupuncture analgesia. However, in 2010, Goldman et al. (25) demonstrated the role of adenosine in acupuncture analgesia in a mouse study. They found that adenosine was released locally when acupuncture was performed, and A_1 receptor activation was required for acupuncture analgesia. Furthermore, long-term EA reduces the activities of T- and B-cells in the lymph nodes of collagen-induced arthritic mice (84). In another study, the activity of splenic natural killer (NK) cells in mice was enhanced after long-term EA. EA is capable of modulating the imbalance between the innate and acquired immune systems and adjusting the pattern of leukocytes (granulocytes and lymphocytes) in human subjects (48). Several lines of evidence indicate that this effect is associated with the hypothalamus–pituitary–adrenal (HPA) axis (7,36,37,66,70). Acupuncture also has direct effects on the autonomic nervous system (ANS) (31). Acupuncture has been shown to influence some known indicators of autonomic activities, such as blood pressure (68,72,79), pupil size (53), skin conductance, thermographic skin temperature measurements (17,29), microneurographic evaluation of muscle sympathetic nerve activities (35,68), heart rate and/or pulse rate (29,52), and heart rate variability (28,30,38,40).

How can acupuncture provide beneficial effects in neurodegenerative diseases? One hypothesis is that acupuncture is able to mobilize regenerative stem cells. This article reviews recent studies concerning the effects of acupuncture/EA on stem cell mobilization and on progenitor cell proliferation in CNS as shown in Table 1.

EA MOBILIZED STEM CELLS IN A HUMAN STUDY

Scant research has been conducted in human subjects investigating the effects of acupuncture upon stem cell mobilization. In 2010, Moldenhauer et al. (47) recruited 14 healthy subjects and performed acupuncture on the acupoints for spinal cord injury. Cluster of differentiation 133-positive CD34-negative ($CD133^+CD34^-$) cells were used as a marker because the CD133 antigen is present in hematopoietic, endothelial, and fetal neurogenic stem cells (3), as well as

Table 1. Recent Studies Investigating the Effects of Acupuncture/EA on Stem Cell Mobilization and Progenitor Cell Proliferation

Human/Animal Model	Acupoints	Major Findings	Experimental Groups	Reference
Healthy volunteers	Total 11 points were manually stimulated: GV4 (Mingmen), GV14 (Dazhui), GV20 (Baihui), LI4 (Hegu), SI3 (Houxi), BL23 (Shenshu), BL62 (Shenmai), HT7 (Shenmen), SP6 (Sanyinjiao), KI6 (Zhaohai) and Extra point 1 (Yin Tang)	• $CD133+CD34^-$ cells in peripheral blood: doubled 48 h after acupuncture • Serum concentrations BDNF and MMP-9 levels: decreased after acupuncture	14 Healthy volunteers were included in the study	(47)
Spinal cord transected in rats	GV9 (Zhiyang), GV6 (Jizhong), GV2 (Yaoshu) and GV1 (Changqiang)	• Neurotrophin-3 (NT-3) levels in spinal tissue (ELISA): increased in EA and EA+MSCs group • Differentiation of MSCs into neuronal-like cells and oligodendrocyte-like cells and number of 5-HT positive nerve fibers: enhanced in the EA+MSCs group compared to EA and MSC groups • Behavioral evaluation of paralyzed hind limbs: enhanced in the EA+MSCs group compared to EA and MSC groups	Control group, EA group, MSC, EA+MSCs group	(83)
Postnatal day 14 rats	LI11 (Quchi), TE5 (Waiguan), GB30 (Huantiao), and ST36 (Zusanli)	In the dentate gyrus: • Number of proliferated and survival cells, as indicated by BrdU labeling: levels were significantly increased by EA treatment • Number of newly differentiated neurons, as indicated by BrdU/NeuN double labeling: levels were significantly increased by EA treatment	Control group, ketamine anesthesia group, nonacupoint group, acupoint EA group	(23)
Right middle cerebral artery occlusion in the rat	LI4 (Hegu)	• Neurobehavioral evaluation scored on a five-point scale: EA treatment improved behavioral recovery • Expression of stem cell factor (SCF), receptor c-kit and MMP-9 protein and mRNA in the cortical ischemic region: EA treatment upregulated positive cells and mRNA expression of SCF, c-kit, and MMP-9 after cerebral ischemia/reperfusion	Sham group, model group, and EA group	(44)
Rat model of depression induced by chronic unpredictable stress	GV20 (Baihui) and Anmian	• Open field test and forced swimming test: EA treatment significantly reversed the behavioral deficit induced by depression • Hippocampal progenitor cell proliferation in the dentate gyrus (as indicated by BrdU) labeling: EA treatment significantly blocked the decrease induced by depression	Control, EA+control, stress, sham EA+stress, EA+stress	(41)
Senescence-accelerated mouse prone 8 (SAMP8): an autogenic senile strain characterized by early cognitive impairment and age-related deterioration of learning and memory	*"Yiqitiaoxue and Fubenpeiyuan"* at CV17 (Danzhong), CV12 (Zhongwan), CV6 (Qihai), SP10 (Xuehai), and ST36 (Zusanli)	• Morris water maze test: acupuncture significantly improved cognitive impairments • Proliferated cells as indicated by BrdU-specific immunodetection: the decreased cell proliferation in the dentate gyrus was greatly enhanced by the therapeutic acupuncture	SAMP8 acupuncture group, SAMP8 nonacupoint control group, SAMP8 control group, and SAMR1 normal control group	(6)
Isolated bone marrow mesenchymal stem cells (BMSCs) from Sprague–Dawley (SD) rat bone marrow in vitro	Electrostimulation was applied in vitro	• Third-generation SD rat BMSCs (P3 BMSCs) were harvested and characterized by flow cytometry with FITC staining. • Electrostimulation-induced morphological changes (displaying typical morphology of early chondrocytes) and increased expression of glycosaminoglycan and expression of chondrocyte-specific matrix protein type II collagen	Blank control and electrostimulation group	(80)

EA, electroacupuncture; CD133, cluster of differentiation 133; BDNF, brain-derived neurotrophic factor; MMP-9, matrix metalloproteinase 9; BrdU, 5-bromo-2′-deoxyuridine; MSC, mesenchymal stem cell; 5-HT, 5-hydroxytryptamine; NeuN, neuronal nuclei; SAMR1, senescence-accelerated resistant mouse 1 (control group); FITC, fluorescein isothiocyanate.

on ependymal cells of the adult brain (58). In contrast to hematopoietic and endothelial progenitors, $CD133^+$ neurogenic stem cells do not express CD34 (10). Moldenhauer et al. (47) indicated that $CD133^+CD34^-$ cell counts in peripheral blood were increased twofold by 48 h following acupuncture performed at acupoints, which are for the treatment of spinal cord injury. Brain-derived neurotrophic factor (BDNF) and matrix metalloproteinase-9 (MMP-9) levels were also reduced. However, subjects who received acupuncture at acupoints for the treatment of sleeping disorders (i.e., control counterpoints) showed no changes in $CD133^+$ cell numbers, which suggests that acupuncture performed at the right location can mobilize human $CD133^+CD34^-$ cells. It also mentioned that "whether $CD133^+34^-$ cells are also mobilized in patients with spinal cord lesions treated by acupuncture and whether the mobilized cells have neurogenic potential should be clarified in future studies" (47, p. 1649).

EA MOBILIZED STEM CELLS IN ANIMAL STUDIES

Several animal models have been used to test the effect of acupuncture/EA on neuerogenesis and their relationship to stem cells.

AD Model

In 2008, Cheng et al. (6) tested whether acupuncture improves cognitive deficits and regulates brain cell proliferation in a genetic AD animal model. They used the senescence-accelerated mouse prone 8 (SAMP8), which is an autogenic senile murine model characterized by significant age-related impairments of learning, memory, and behavioral changes (5,46). The authors tested the effects of acupuncture on learning and memory, as well as on brain cell proliferation in the dentate gyrus and ventricular/subventricular zone (2,20). They found that *Yiqitiaoxue and Fubenpeiyuan* acupuncture improved cognitive deficits in this animal model and attenuated the decrease in cell proliferation in the dentate gyrus, as indicated by 5-bromo-2′-deoxyuridine (BrdU)-specific immunodetection.

Depression Model

Depression is a severe illness with a lifetime prevalence of between 10% and 20% (57). Recent studies have indicated that hippocampal neurogenesis can be affected by stress (34). Adult neurogenesis in animals is decreased by many different types of stressors, including predator odor (22), social stress (13,26), acute and chronic restraint stress (59,62,74), footshock stress (45,74), and chronic mild stress (1).

In 2007, Liu et al. (41) tested whether EA attenuates the decrease of hippocampal progenitor cell proliferation in adult rats exposed to chronic unpredictable stress. In open field and forced swimming tests, chronic unpredictable stress decreased behavioral activity, while EA treatment significantly reversed this behavioral deficit. Moreover, EA treatment effectively attenuated the decrease in hippocampal progenitor cell proliferation, as indicated by BrdU-specific immunodetection. This study suggested that EA treatment has a potential antidepressant-like capacity, as well as upregulation of hippocampal progenitor cell proliferation.

Focal Cerebral Ischemia/Reperfusion Model

Stroke leads to both high morbidity and mortality. Acupuncture/EA, as a traditional nonmedicine therapy, plays a definitive role in improving cerebral ischemia recovery. Endothelial progenitor cells (EPCs) can promote neurogenesis and angiogenesis after cerebral ischemia (18,54). The multifunctional cytokine stem cell factor (SCF) is activated by MMP-9. By binding to the c-kit receptor, SCF leads to the mobilization and migration of EPCs (33,69).

In 2013, Lu et al. (44) studied whether EA improves behavioral recovery and increases SCF/c-kit expression in rats subjected to filament occlusion of the right middle cerebral artery as an animal model of stroke. EA treatment was shown to improve a five-point scale neurobehavioral evaluation in conjunction with increasing the protein and mRNA expression of SCF, c-kit, and MMP-9.

Young Rat Model

As mentioned above, acupuncture may improve neurogenic cell proliferation in pathological conditions. In 2011, Gao et al. (23) investigated whether EA altered cell proliferation and differentiation in the dentate gyrus of postnatal rats. EA was performed bilaterally for 7 successive days and cell activity studied 4 weeks later. BrdU labeling showed that the number of proliferating and surviving cells was significantly increased by the EA treatment. BrdU/neuronal nuclei (NeuN) double labeling also demonstrated a significant increase in the number of newly differentiated neurons. The results suggest acupuncture may be a promising clinical application for pediatric cerebral injury rehabilitation.

Spinal Cord Injury Model

The treatment of spinal cord injury remains an unmet clinical need. Mesenchymal stem cells (MSCs) have been a major focal point because they are easily isolated and can be used for autotransplantation. Notably, MSCs have the potential to differentiate into neuronal lineage cells (4,67).

In 2011, the combined effects of MSC transplantation and EA treatment upon the differentiation of MSCs and the regeneration of nerve fibers following spinal cord transection in rats were explored by Yan et al. (83). The animals were assigned to a control group, EA group, MSC transplantation group, or EA plus MSC transplantation

group. Neurotrophin-3 (NT-3) levels in spinal tissue were found to be increased in the EA and EA plus MSC group, while the differentiation of MSCs into neuronal-like cells and oligodendrocyte-like cells as well as the number of 5-hydroxytryptamine (5-HT)-positive nerve fibers were enhanced in the EA plus MSC group compared to the EA or MSC groups. In addition, the EA plus MSC group showed enhanced behavioral evaluation of paralyzed hind limbs compared to the EA or MSC groups. These results suggested that the combination of EA and MSC transplantation can facilitate the differentiation of MSC and nerve fiber regeneration in injured spinal cord and improve hind limb paralysis.

In Vitro Model

The effects of acupuncture on stem cell mobilization have been evaluated in vitro. Bone marrow mesenchymal stem cells (BMSCs) are multipotent stem cells that can differentiate into osteoblasts, chondrocytes, adipocytes, myoblasts, and neural cells (11,27,60). The cell surface markers of BMSCs have been characterized and include the antigens $CD90^+$, CD105 ($SH2^+$), CD73 ($SH3^+$), and $CD124^+$, etc., but not hematopoietic markers such as CD45, CD1lb, CD14, CD34, and CD31 (77). Research proposes that microarray analysis may be a more reproducible and reliable method for defining MSCs (75). In 2011, BMSCs were isolated from Sprague–Dawley (SD) rat bone marrow by Wu et al. (82). Optical and transmission electron microscopy were applied to address the potential effect of acupuncture. The results showed that morphological changes that were representative of early chondrocytes were induced in BMSCs by EA treatment. Toluidine blue staining of cytoplasm and extracellular matrices suggested enhanced expression of glycosaminoglycan after EA treatment. The expression of chondrocyte-specific matrix protein type II collagen was significantly induced in a dose-dependent manner that coincided with potentially causative increasing levels of the transcription factor sex-determining region Y box 9 (Sox9) mRNA expression. These results suggested that the non-drug-inducing differentiation of BMSCs into chondrocytes could be performed by EA.

CONCLUSION

This review of the evidence has shown that acupuncture/EA results in beneficial effects in animal models of AD, depression, spinal cord injury, and stroke and that these effects may, at least in part, be associated with progenitor cell proliferation or stem cell mobilization in the central nervous system (CNS). EA also results in proliferation and neuronal differentiation of proliferated surviving cells in the dentate gyrus in neonatal rats. It is postulated that acupuncture/EA may have the potential to cause stem cell mobilization in humans.

The studies reviewed in this article indicate that acupuncture/EA has beneficial effects in neurodegenerative disease and may be a nondrug method for mobilizing stem cells in the CNS. However, it remains unclear as to how acupuncture/EA exerts these effects. Moreover, the parameters of EA have not been systemically studied, that is, the optimal acupoints and optimal treatment schedule, such as treatment frequency and duration. These issues need to be clarified.

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