Acupuncture for Parkinson's Disease: a review of clinical, animal, and functional Magnetic Resonance Imaging studies

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Accepted: February 24, 2015

Abstract

Acupuncture has been commonly used as an adjuvant therapy or monotherapy in the treatment of Parkinson's disease in China and in other countries. Animal studies have consistently show that this treatment is both neuroprotective, protecting dopaminergic neurons from degeneration and also restorative, restoring tyrosine hydroxylase positive dopaminergic terminals in striatum, resulting in improvements in motor performance in animal models of Parkinsonism. Studies show that this protection is mediated through the same common mechanisms as other neuroprotective agents, including anti-oxidative stress, anti-inflammatory and anti-apoptotic pathways at molecular and cellular levels. Restoration of function seems to involve activation of certain compensatory brain regions as a mechanism at the network level to correct the imbalances to the nervous system resulting from loss of dopaminergic neurons in substantia nigra. Clinical studies in China and Korea, in particular, have shown a positive benefit of acupuncture in treating Parkinson’s disease, especially in reducing the doses of dopaminergic medications and the associated side effects. However, large and well-controlled clinical trials are still needed to further demonstrate the efficacy and effectiveness of acupuncture in the treatment of Parkinson’s disease.

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Key words: Parkinson disease; Acupuncture; Neuroprotective agents; Tyrosine 3-monoxygenase; Review

The use of acupuncture for treating different illnesses originated in China about three thousand years ago, as an important part of Traditional Chinese Medicine. The treatment of Parkinson’s tremor with acupuncture and herbal medicine has a long history under the category of "trembling" and "convulsive" disease. Acupuncture treatment not only treats the brain where the dopaminergic neurons have been lost, which is the hallmark of Parkinson’s disease (PD), but also benefits the other organ systems of Traditional Chinese Medicine, and is therefore, also helpful for coping with non-motor related symptoms and overall quality of life in PD patients. This review summarizes the current understanding of how acupuncture works in treating PD, based on information obtained from preclinical and clinical trial studies, and functional network studies in humans.

INTRODUCTION TO ACUPUNCTURE AND ITS USE IN THE TREATMENT OF PD

Acupuncture is the primary therapy of Chinese medicine, as described in Huang Di Nei Jing in the first century BC. Acupuncture is very much respected in China, so much so that its use was approved even during the Chinese culture revolution. Classical acupuncture is based on 14 mapped main channels on the body with about 365 acu-points distributed on the channels...
(meridian system); the flow of Qi (the vital life force or some kind of “energy”) maintains the balance and harmony of Yin and Yang. Any blockage of these channels or abnormal movement of Qi will result in illness, and acupuncture by stimulating these acupoints along the meridian channels with needles helps to restore movement of the Qi and Qi homeostasis (De Qi), thus modulating the autonomic nervous system and relieving the symptoms of various illnesses. Acupuncture is especially known for its effectiveness in reducing pain such as dental and back pain due to triggering release of analgesic neuropeptides. Acupuncture is delivered by manual insertion of a needle or an additional maneuver through twisting of the needles periodically. In addition, the needles can serve as electrodes to deliver a current stimulation with certain frequency (electroacupuncture, EA). For example, in rodents studies, 100 Hz is considered the most effective frequency to achieve a beneficial effect by acupuncture.

The substrate for the meridian channels have been under intense investigation. For example, connective tissues or perivascular space with decreased electrical impedance and increased electrical conductivity have been suggested to constitute the meridian channels with acupoints along the pathway. In addition, the brain regions responsible for acupoint and triggered activity in central nervous system are identified as extending from the dorsomedial prefrontal cortex, medial mesencephalic reticular formation and brainstem network through the medial thalamus and the hypothalamus and lateral habenular nucleus, medulla oblongata and ventrolateral periaqueductal gray. Interestingly, the habenula is suggested to be an anatomical substrate for the control of depression in a PD model, and relief from depression is one of neuropsychiatric benefits resulting from acupuncture treatment of PD. Functional MRI (fMRI) studies suggest additional involvement of posterior medial cortex and temporal cortex in the central effect of acupuncture, named the “limbic-paralimbic-neocortical network”.

For example, acupuncture modulates the fMRI BOLD signal in areas associated with pain (anterior cingulate cortex and periaqueductal gray), emotion (the amygdala), and memory (hippocampal formation and middle temporal gyrus). These areas are thought to be activated in acupuncture which disrupts the pathophysiological neuronal networks and therefore relieves the symptoms by replacing them with “therapeutic” network activation. PD is the second largest neurological disorder next to Alzheimer’s disease. With L-dopa medication treatment, patients often develop involuntary motor movements called L-dopa-induced dyskinesia after 5-10 years of use. When conventional treatment with medication is not satisfactory, patients often resort to complementary alternative medicine such as acupuncture in hope of getting symptomatic improvement without having disruptive side effects of pharmacotherapy.

In practice, complementary alternative medicine (CAM) with acupuncture as the key component is widely used world-wide in treating PD. At least 61% of PD patients in East Asia (Singapore) and 50% of Latin-America (Argentina) and 1/3 in Sweden use at least one type of CAM treating PD symptoms, with acupuncture treating tremor in PD predominantly. A study in America shows that 40% of PD patients use at least one type of CAM for treatment, similar to the United Kingdom; the number of CAM users has been increasing every year. In particular, with the coverage of acupuncture by health insurance, acupuncture users could be expected to further increase.

**CLINICAL STUDIES OF ACUPUNCTURE IN TREATING PD**

Just like the higher use of CAM in Asia, the evaluation of CAM tends to be more positive in Asia and foreign-language journals, for example, China, compared to well-known journals. Acupuncture has been used in Eastern Asia to treat PD under the category of “trembling” and “convulsive disease” long ago, in particular for the control of tremor and pain, along with herbal medicine. In China, clinical studies show that acupuncture can help improve both motor symptoms and non-motor symptoms such as insomnia, depression, constipation and overall life quality for PD patients, and additionally, the dose of medication and its side effect are reduced. Consistently, Korean studies show that acupuncture improves unified PD rating score (UPDRS) and adjuvant therapy combined with medication helps to reduce the doses and side effects. Reviews of Chinese clinical trials, with meta-analysis on selected trials (meeting inclusion criteria) suggest that the effectiveness of scalp acupuncture (a type of acupuncture, in which needles are placed on the head) treatment for PD is promising and a larger well controlled trial is needed to confirm the efficacy of scalp acupuncture.

Acupuncture conducted in western countries has overall promising results, but they are not conclusive in particular for the motor rating score. For example, a practitioner’s notes showed that acupuncture at different locations in the body for a PD patient with 25 treatments for 2-3 months helped to remove or reduced the pain / muscle rigidity, tremor and depression. This treatment works well for the early treatment when PD is first manifested and also for a patient who had PD for 12 years. Pilot studies with PD patients comparing before and after treatment in USA show that acupuncture is safe and well-tolerated, significantly improves sleep and rest in PD patients and the majority of patients reported subjective improvement in handwriting, depression, tremor and slowness. With a quite different acupuncture point placement, another clinical trial in USA showed that there is a trend of im-
NEUROPROTECTIVE ROLE OF ACUPUNCTURE IN ANIMAL MODELS OF PD AND ITS UNDERLYING MECHANISMS

Animals studies using PD models [with 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injection] confirmed that electro-acupuncture at various points or a combination of acupoints [e.g. Duzhui (GV 14) / Baihui (GV 21), Yanglingquan (GB 34) / Xuanzhong (GB 39), Taichong (LR 3), Duzhui (GV 14) / Fengfu (GV 16) / Baihui (GV 20), Zusanli (ST 36), Shanyijiao (SP 6)] improves motor performance (reducing ipsilateral turning, its duration and the initiation time for turning, rod performance) and provides neuroprotection of dopaminergic neurons of the substantia nigra (pars compacta) by significantly increasing the number of TH positive neurons and dopaminergic projection terminals in striatum.9,47-58 Yanglingquan (GB 34) and Zusanli (ST 36) are the most commonly used and effective points, and located at the back of the knee and under the knee joint (lateral to the tibia), respectively. Additionally, striatal dopamine content might increase in the acupuncture group in PD mice compared to PD mouse without acupuncture but does not get back to the original level,56,58 or did not increase significantly, suggesting that the enhancement of motor performance is not necessarily through increase of striatal dopamine content.57,59,60

Pre-and post-synaptic modulation in basal ganglia circuit following acupuncture contributing to enhanced motor performance

In vivo microdialysis shows that acupuncture at Yanglingquan (GB 34) increases dopamine availability (via increasing dopamine turnover ratios) in the striatum and dopamine release in MPTP lesioned mice.61 Single-photon emission computed tomography (SPECT), a measure of cerebral blood flow and western blots show increased dopamine uptake and dopamine transporter (DAT) expression in the striatum and substantia nigra after EA treatment.59 Post-synaptically, acupuncture corrects the post-synaptic changes in PD mice by restoring and reducing up-regulated phosphorylation of DARPP-32,62,63 FosB62 and D. receptor.63 Additionally, in the basal ganglia circuit, dynorphin expressing striatonigral projection represents the direct pathway whereas enkephalin-containing striatopallidal projection represents the indirect pathway.71,72 These two pathways have to be in balance in order to have smooth motor movement. This balance is interrupted in PD and related L-dopa-induced dyskinesia,73 and electroacupuncture can restore the homeostasis of the output of GABAergic neurons. For example, acupuncture can restore down-regulated substance P neuropeptide and up-regulated GAD 67 (GABA synthesizing enzyme) mRNA,57 and reduces GABA content in the midbrain (SNr) and cortex, increases GABA content in the striatum and cerebellum, and ultimately ameliorates motor abnormality in hemiparkinsonian rats (with medial forebrain bundle transection or 6-OHDA lesion).51,65 The above pre- and post-synaptic mechanisms and homeostasis of direct- and indirect-pathways of the basal ganglia circuit may contribute to the therapeutic benefit of electro-acupuncture in PD models and patients.74

Molecular and cellular mechanism underlying the role of acupuncture in neuroprotection in PD models

Lack of neurotrophic factors, apoptosis (programmed cell death), inflammatory process and oxidative stress have been implicated in pathogenesis of PD.45-47,64 Agents that provide the resources of neurotrophic factor (which supports neuronal function), are anti-apoptotic, anti-inflammatory and/or anti-oxidative stress and presumably protect neurons and their circuitry from degeneration as a result of insult.65,66,67 Indeed, neuroprotective processes are thought to underlie the beneficial physiological changes following acupuncture46,48 along with increase of proliferating stem cells in the subventricular zone.69 Peptide finger printing MS identified nine proteins involved in cell death regulation, inflammation or restoration from damage and neuroprotection such as cyclophilin A.66,68 Consistently, microarray analysis of the gene expression profile has shown that pathological changes in genes involving cytokine-mediated apoptosis, inflammation and oxidative stress are corrected by acupuncture in PD models.64 First, with regard to neurotrophic factors, 100 Hz electric acupuncture [at Taoda (Du 13) and Baihui (GV 21), or Baihui (GV 20) - Taiyang (EX-HN5)] increases the expression level of BDNF mRNA and GDNF mRNA at SNc and ventral tegmental area, and GDNF receptor at SN and striatum, and prevents degeneration of dopaminergic neurons in PD rats.35,70,71 Second, apoptosis-triggered cell death is reduced by elec-
tro-acupuncture [at Taichong (LR 3) and Fengfu (GV 16) or Yanglingquan (GB 34)] on day 7 after 6-OH-D
DA lesioning in PD rats.\textsuperscript{53,65} For example, Ubiquitin-conjugating enzyme E2N suggested to be involved in cell death regulation is normalized by electro-acupuncture.\textsuperscript{69} Acupuncture also corrects the down-regulated pathways regulating cytokin-ctyokin receptor interaction and genes (such as deoxyribonuclease 1-like 2) involved in programmed cell death.\textsuperscript{54,65} Third, acupuncture reduces inflammatory processes in PD rodents at acupoint Duzhui (GV 14) / Baihu (GV 21), Yanglingquan (GB 34) and Taichong (LR 3).\textsuperscript{50,60,61,64,74} For example, lesion induced microglia activation, macrophage antigen complex-1 (MAC-1, a marker of microglia activation), cyclooxygenase-1 (COX-2) and inducible nitric oxide synthase (iNOS) and TNF-\textalpha and interleukin (IL)-1\textbeta mRNA are reduced by acupuncture in MFB-transected rats and MPTP lesioned mice.\textsuperscript{50,72} Peptide finger printing MS suggests that inflammatory proteins, for example, CLP-coactosin-like protein, is normalized by daily acupuncture treatment 2 h after MPTP lesion for 7 days.\textsuperscript{64} Gene array analysis confirmed that one of the 5 genes, DUSPs (dual specificity phosphates 4) involved in pathogen-mediated immunity, down-regulated in MPTP mice, were exclusively upregulated by acupuncture at acupoints Yanglingquan (GB 34) and Taichong (LR 3) 2 h after MPTP injection in mice (every 2 days for 14 sessions) in the thalamic region (an area damaged in PD).\textsuperscript{65}

Lastly, on anti-oxidative stress, relatively recent findings show that acupuncture reduces oxidative stress in toxin-lesioned PD rodent models,\textsuperscript{52,64,65,73,74} likely through interactions with intracellular signaling pathways such as PI3K/Akt pathway.\textsuperscript{73} Acupuncture at Yanglingquan (GB 34) / Xuanzhong (GB 39) normalizes proteins that are changed in MPTP mice, including cytosolic malate dehydrogenase, Munc18-1, hydroxyacyl glutathione hydrolase and cytochrome c oxidase involved in cellular mechanism, which restore TH neurons and terminals in SN and striatum possibly through reducing oxidative stress and increasing antioxidant enzyme activity.\textsuperscript{73} Indeed, studies have provided evidence that acupuncture reduces oxidative stress and free radical formation.\textsuperscript{52,66} Antioxidative parameters (including superoxide dismutase, glutathione peroxidase) are decreased and malondialdehyde (MDA)/H\textsubscript{2}O\textsubscript{2} is increased in neurotoxin lesioned rats, and EA at compound acupoints Yanglingquan (GB 34), Taichong (LR 3), and/or Zusanli (ST 36) and Sanyinjiao (SP 6) / Xuehai (10)], applied the same day of 6-OHDA lesioning or the next day following MPTP lesioning, reverses the changes, increases glutathione concentration and improves PD motor function (reducing apomorphine-induced rotation).\textsuperscript{52,66} GeneChip gene array analysis of thalamic genes expression showed that the DUSPs' genes that are involved in regulating the oxidative-stress-activated c-Jun N-terminal kinases (JNKs) (down-regulated in MPTP-lesioned mice) are upregulated by acupuncture stimulation, and the gene uncoupling protein 2 that are involved in oxidative damage by ROS (up-regulated in MPTP mice) is down-regulated by acupuncture at Yanglingquan (GB 34) and Taichong (LR 3).\textsuperscript{69} Similarly, in striatum, genechip microarray analysis and real-time RT-PCR showed that acupuncture stimulation of chronic MPTP mice model (2 h after the first MPTP injection) at acupoints Yanglingquan (GB 34) and Taichong (LR 3) upregulates genes encoding chaperon protein, neuroglybin and neurotrophin, proteins and pathways involved in mitogen-activated protein kinase (MAPK) signaling pathway, suggesting that acupuncture promotes genes and pathways that facilitate neural survival and reduce oxidative stress. On the other hand, acupuncture down-regulates genes such as gap junction protein, tubulin and insulin-like growth factor and pathways involved in cell communication and gap junction, suggesting that acupuncture diminishes genes and pathways that promote neural regeneration.\textsuperscript{64} Additionally, acupuncture, acting as anti-oxidant agent, reduces Fe\textsuperscript{3+} level, the level of which in SN being suggested to contribute to the DA neurons' degeneration.\textsuperscript{69}

Network mechanism underlying acupuncture effect based on imaging studies from the perspective of thalamus connectivity

At the brain circuitry level, Fairgold\textsuperscript{75} hypothesized that EA modulates excitatory and inhibitory networks, and results in network plasticity (mediated by the above discussed neurotropic and other factors). This modified network disrupts the dysfunctional network (consisting of the same conditional multi-receptive neurons in specific brain areas) and reduces the symptoms. This hypothesis might help partially explain how acupuncture mediates effects in PD patients. In PD patients, the substantia nigra, caudate/putamen, thalamus, are parts of the basal ganglia circuit and its functional connectivity is impaired;\textsuperscript{74,75} acupuncture stimulation activates these regions which is evidenced in the increased BOLD signal (index of brain activation) based on fMRI studies and placebo-controlled experiments.\textsuperscript{65,76} This activation of basal ganglia-thalamocortical circuit following acupuncture, correlates with improvement of finger tapping in patients with early stage of PD.\textsuperscript{76} Positron emission tomography (measure of cerebral metabolism) and SPECT studies in patients also support the activation of this modified network by acupuncture (with medication) in the parietal and occipital lobes, frontal lobes, basal ganglia and cerebellum in the affected hemisphere of the patients, compared to medication only group.\textsuperscript{77,78} The most recent fMRI study in a dog model of PD characterized the differential pathway activation of normal, PD versus acupuncture treating PD conditions during a passive movement task.\textsuperscript{79} Neural dopaminergic pathway includ-
ing the basal nuclei, thalamus and limbic system is deactivated in a dog model of PD and experiences similarly reduced fMRI BOLD signal in the limbic and paralimbic regions in telecephalon, diencephalon, brain stem and cerebellum in normal individual. Following acupuncture treatment [at Zusanli (ST 36)], BOLD signals of these areas are enhanced in the non-lesioned motor-sensory areas, bilateral parietal lobes, thalamus, limbic system and the cerebellar vermis. The thalamus, a structure originally thought to be a passive relay of sensory information, along with cerebellum (a structure thought to be involved in motor movement and balance), play an important role in the striato-thalamo-cortical and cerebello-thalamo-cortical pathways. Damage of these pathways may result in akinesia with rigidity and tremor, along with non-motor symptoms. Thalamic nuclei are activated during fMRI following acupuncture in PD, as shown above. The major motor nuclei of the thalamus, the ventral anterior (VA) / ventral lateral (VL) and MD nuclei are robustly connected with the frontal cortex especially the anterior cingulate and dorsolateral prefrontal areas, and basal ganglia structures [SNr and globus pallidus internus (GPi)], and therefore, have a key role for initiation of motor movement, cognition and emotions. Indeed, functional studies show that disruption of these connections is manifested in PD at resting state, which may explain why PD patients have difficulty to initiate motor movement. In addition, the ventral thalamus (intricately connected with the SNr and GPi and cerebellum) have clusters of tremor generation sites in PD, as supported by the evidence that its increased gray matter density (in the posterior thalamic VL nucleus) correlates with resting tremor amplitude in unilateral Parkinsonian tremor. This may help explain why clinical trials show effectiveness of acupuncture in controlling tremor symptoms after modulation of tremor generation sites in the ventral thalamus by acupuncture and how deep brain stimulation of advanced PD at thalamic nuclei are used in controlling tremor and reducing L-dopa induced dyskinesia. Moreover, the thalamic MD nucleus and its connection with the prefrontal cortex are suggested to be involved in non-motor symptoms, including depression and apathy in PD. Thalamic damage, including reduction of gray matter and white matter of frontal cortex and cingulate cortex, are correlated with depression and apathy in PD. Thalamo-cortical projections to the superficial layers of the cortex, represented by calbindin-positive widespread projection system, underlie the sleep-wake cycle and consciousness. This diffuse projection system may be altered by acupuncture and promote sleep and rest (as shown in the clinical trial above). Finally, the anterior thalamic nuclei, which are prominent in primates compared to rodents, play a central role in the Papez’s circuit for emotion and are robustly connected with medial and orbital prefrontal cortex.

This emotional circuitry might influence the expectancy and perception of pain upon acupuncture and underlie the analgesic effect of acupuncture. The function of the individual thalamic nuclei such as the anterior thalamic nuclei underlying acupuncture effect in treating PD needs to be clarified. The above supports clinical evidence of acupuncture to help improve depression, a major neuropsychiatric symptom in PD, and overall life quality through the compensatory activation of thalamic nuclei. The critical role of the thalamus is also appreciated by evidence from microarray studies of molecule candidates isolated from the thalamus, the expression of which are significantly increased or reduced in Parkinsonian models following acupuncture.

**SUMMARY AND FUTURE STUDIES**

Acupuncture has been a popular choice as alternative medicine in USA and Western Medicine for treating difficult cases, pain and cancer patients etc. Studies at the cellular, molecular and circuitry level with animal models of PD and human trials suggest the following mechanisms. First, acupuncture, just like other neuroprotective agents, is anti-inflammatory, anti-oxidative stress, anti-apoptotic and neurotrophic, increases dopamine availability, restores post-synaptic changes due to the dopamine loss through changes in certain gene and protein expression. Second, at the circuitry level in the central nervous system and even organ systems, acupuncture re-activates the dysfunctional brain circuitry for motor and non-motor function and relieves the symptoms. Clinical trials suggest that acupuncture is effective in non-motor symptoms in sleep, rest and depression. A clear benefit is that acupuncture can reduce the therapeutic L-dopa treatment dose and its related side effect, L-dopa-induced dyskinesia. Acupuncture, as potential neuroprotective agent, is supported by preclinical animal studies with consistent efficacy and pilot clinical trials with positive evidence of acupuncture’s benefit in treating PD (and it is safe and well tolerated). A well designed clinical trial to test acupuncture as neuroprotective agent is warranted. For example, acupuncture’s real effect in treating PD, especially in improving Unified Parkinson’s Disease Rating Scale, still waits to be studied in double-blind, randomized, placebo-controlled well-designed trials (considering trial sample size, acupoint selection and treatment protocol etc.). The research or clinical questions should be clear, which will help design well-controlled studies. Perhaps, an early use of acupuncture is the potential to improve PD symptoms. Finally, a future question that needs to be explored is whether acupuncture can slow down the disease progression or facilitate neuronal regeneration.
ACKNOWLEDGMENTS

Thanks to Mr. Marc Breneiser at Dana Farber Institute and Dr. Carl Anderson at McLean Hospital for proof-reading the manuscript. I would also like to thank my mentor Dr. Helen Barbas at Boston University for her continuous encouragement in writing up this manuscript and her help in editing, without her this manuscript would not exist.

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