PERSPECTIVES

Acupuncture: a potent therapeutic tool for inducing adult neurogenesis

Acupuncture has been broadly used as a major therapeutic tool for at least 2,100 years in East Asia. Acupuncture is used for improving the pathological condition of remote organs, such as stomach, liver, brain, *etc.* by stimulating skin and muscle with fine metal needles through meridians which have been regarded as pathways of *Qi* within the body (Ernst, 2006). Physicians in East Asia have tried to treat many kinds of diseases by acupuncture and it was considerably successful. Various diseases for which acupuncture is known to be effective, are neurological diseases, including sequelae of stroke, Alzheimer's disease (AD), Parkinson's disease (PD), and so on (Nam et al., 2013).

These diseases have a common pathological factor, which is the massive death of neurons. Sequelae of stroke are caused by necrosis of neurons which is triggered by ischemia of the brain tissue. The symptoms of AD and PD are also known to be caused by gradual death of neurons of hippocampus and nigrostriatal region, respectively. From the long history of clinical experience, physicians noticed that acupuncture increases recovery from the sequelae of stroke, dementia and dyskinesia (Lee et al., 2007). Many researchers studied the mechanisms of this acupuncture effect, and one of the most plausible theories is that acupuncture induces neurogenesis in the adult brain (Nam et al., 2013). As the results of those studies, acupuncture was proved to be effective for improving the birth of new neural stem cells and neural/glial differentiation (Nam et al., 2011, 2013).

In this study, we briefly reviewed the efficacy of acupuncture for neurogenesis and, also, its therapeutic benefits for some neurological diseases. Based on these previous studies, we suggest that acupuncture can be considered as a potent tool for inducing adult neurogenesis and an effective therapeutic tool for neurodegenerative diseases.

Adult neurogenesis: It has long been believed that neurogenesis cannot occur in adulthood, however, now it is broadly accepted that new neural stem cells (NSCs) are generated and mature into functional neurons and glia throughout life (Abrous et al., 2005). There are two limited brain regions where adult neurogenesis occurs, called neurogenic niche: the subgranular zone in the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles.

Even though adult neurogenesis is localized in limited areas, it affects the whole brain. In the hippocampus, only dentate gyrus is responsible for cell proliferation and differentiation, however NSCs in the subgranular zone in the dentate gyrus migrate into other regions of hippocampus. On the other hand, NSCs originated from subventricular zone of the lateral ventricles migrate into the olfactory bulb *via* rostral migratory stream. Throughout the neurogenesis in the adult brain, new functional neurons are continuously generated for replacing degenerated neurons (Abrous et al., 2005). Although the functional relevance of adult neurogenesis is uncertain, however it is reported to be important for learning and memory by several investigators (Neves et al., 2008).

Therapeutic use of neurogenesis for brain diseases: Adult neurogenesis is dynamically regulated by some pathological conditions, such as neurodegenerative diseases, stroke and depression. In terms of AD, some studies have reported that altered neurogenesis is observed in the brains of patients with AD, PD and stroke, contributing to the main symptoms of the diseases (Abdipranoto et al., 2008). The major therapeutic agent for PD, L-Dopa is known to be effective on increasing the number of proliferating NSCs in the subventricular zone (Abdipranoto et al., 2008). It is expected that adult neurogenesis can be useful for the recovery from AD, PD and sequelae of stroke by replacing degenerated neurons (Abdipranoto et al., 2008).

This dynamic change of neurogenesis in the diseases renders a possibility that neurogenesis can be a target of the therapies. Even though the number of newly generated neurons by adult neurogenesis is much lower than the vast number of degenerating neurons in many brain regions, however, strategies to enhance adult neurogenesis may still have a therapeutic potential (Nam et al., 2013).

On this basis, several therapies have been attempted to treat the brain diseases by enhancing neurogenesis. For example, stem cell therapy for AD, PD and stroke is vigorously being researched. In terms of PD, some clinical trials with intrastriatal transplantation of human embryonic mesencephalic tissue suggested that neuronal replacement can work in PD patients (Lindvall and Kokaia, 2010). Moreover, some therapies are being developed such as intraventricular infusion of basic fibroblast growth factor (bFGF), epidermal growth factor, brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor, which aim to provide more optimum environment for neurogenesis (Nam et al., 2013).

Even though stem cell-based therapies seem to be very promising, however, these therapies are not well verified because the development for neurodegenerative diseases is still at an early stage. There can be undesired growth and genetic alterations of embryonic stem cells. Managing NSCs to obtain a more complete repertoire of various types of cells for replacement should be guaranteed. New NSCs should be regulated to be in harmony with existing neural networks. In addition, there are some well-known side effects of stem cell therapy, such as infection, graft-versus-host disease, graft rejection, *etc.*

Acupuncture effect on adult neurogenesis: As a mechanism of acupuncture effect on neurodegenerative diseases, several studies have reported the phenomena of raising enhanced adult neurogenesis by acupuncture treatment (Nam et al., 2011, 2013). In particular, stimulating the following acupoints by manual acupuncture or electroacupuncture appears to promote neuronal proliferation (Nam et al., 2013): ST36, GV20, PC6, HT7, GV26, CV17, CV12, CV6, SP10, LI11, TE5, GB30, GV16, GV8, CV4, CV6, CV24. Among those acupoints, ST36 and GV20 were most researched for

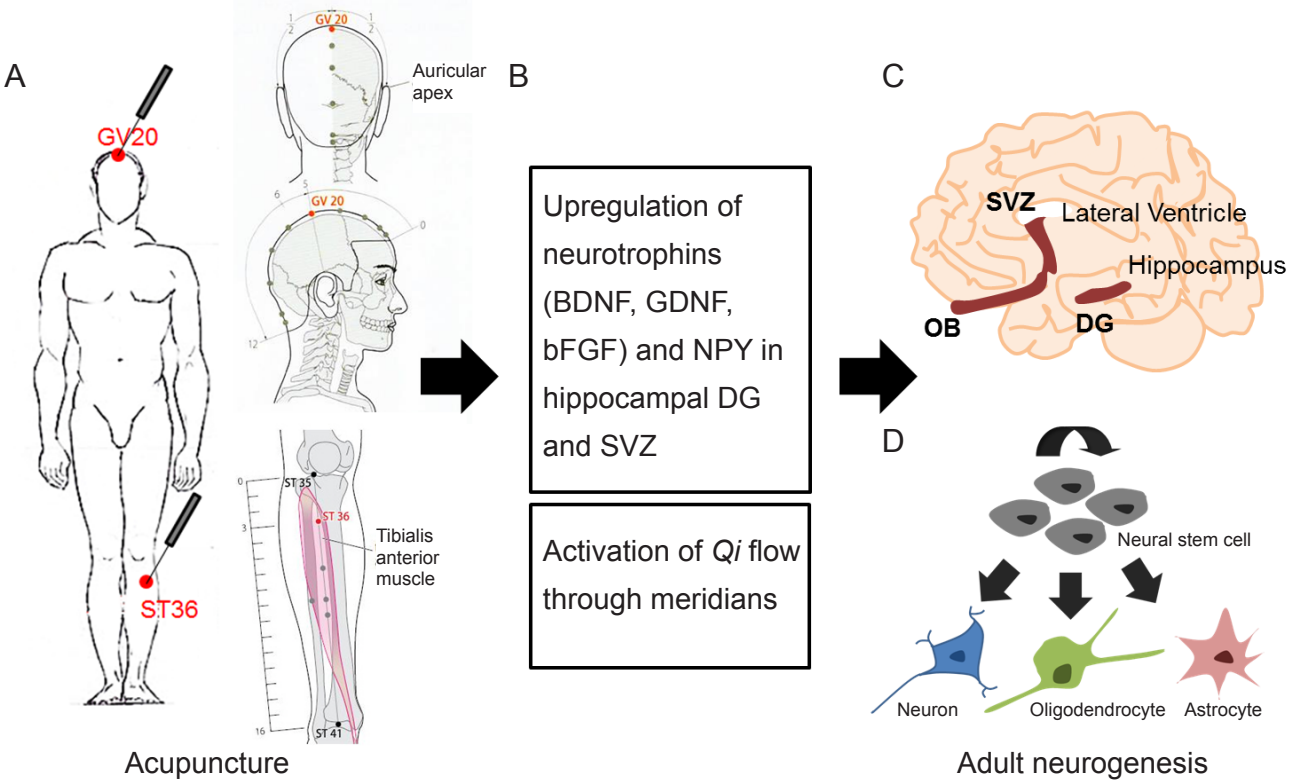

Figure 1 Acupuncture stimulation at GV20 and ST36 is effective for inducing adult neurogenesis through upregulating the levels of BDNF, GDNF, bFGF and NPY.
(A) Anatomical location of GV20 and ST36. This figure is originated from WHO Standard Acupuncture Point Locations. (B) The brief mechanisms of acupuncture effect on neurogenesis. (C) Neurogenic niches in the adult brain. (D) Neural stem cells can proliferate and differentiate into neurons, oligodendrocytes and astrocytes. The proliferation and differentiation can be enhanced by acupuncture treatment. BDNF: Brain-derived neurotrophic factor; GDNF: glial cell line-derived neurotrophic factor; bFGF: basic fibroblast growth factor; NPY: neuropeptide Y; SVZ: subventricular zone; OB: olfactory bulb; DG: dentate gyrus.

its beneficial effect on adult neurogenesis (Nam et al., 2011, 2013). ST36 is located on the anterior tibia muscle and GV20 is located on the scalp (**Figure 1**). These two are the most widely used acupoints for neurological diseases such as AD, PD, stroke, and so on (Nam et al., 2013).

Acupuncture stimulation at ST36 and GV20 is revealed to induce adult neurogenesis in the subventricular zone and dentate gyrus in the brain of animals with stroke, diabetes, stress and high tendency to AD (Nam et al., 2013). Based on a review summarized previous studies about acupuncture and adult neurogenesis, the method of acupuncture stimulation can be found to have a notable trend (Nam et al., 2013). In terms of acupuncture at ST36, manual acupuncture was given for 7, 8, 15 or 21 days and all of them were effective for inducing neurogenesis. Electroacupuncture was given for 7 or 21 days in a consistent manner, low-frequency (2 Hz) and low pulse-width (0.3, 0.5 ms), low amplitude (1–2 mA, 2–4 mA), and this electric stimulation was beneficial. Some of the studies figured out that disperse-dense waves (1 and 20 Hz, 5 and 20 Hz) are also effective. In terms of acupuncture at GV20, only one study used manual acupuncture for 21 days. Electroacupuncture at GV20 was also given in the same manner as ST36, a low-frequency (4 Hz) and low amplitude (2 mA, 2–4 mA) wave. The electroacupuncture at GV20 was effective when it was treated not only for 21 days but also for 3 days. Both EA and MA were shown to be effective for increasing cell proliferation (Nam et al., 2013). EA at ST36 was effective not only for neuronal differentiation but also for astrocytic differentiation (Tao et al., 2010). This effect lasted until 4 weeks after the last stimulation, meaning that EA treatment can be considered beyond a transient remedy (Cheng et al., 2009; Gao et al., 2011).

For investigating the neurogenic effect of acupuncture, most of the studies applied BrdU incorporation method (Nam et al., 2013). In some cases, Ki67 staining was used instead of BrdU incorporation in order to confirm cell proliferation (Nam et al., 2011). In many cases, additional immunostainings, such as NeuN, Nestin, neuron-specific enolase, doublecortin and glial fibrillary acidic protein, were performed together with BrdU or Ki67 staining (Nam et al., 2013). NeuN and neuron-specific enolase were used for detecting mature neurons; doublecortin for immature neurons; Nestin for neural progenitor cells; glial fibrillary acidic protein for astrocytes.

Mechanism of the neurogenic effect: Traditionally, acupuncture was understood on the basis of meridian system, which is the system of several lines connecting acupoints. Meridian was believed to be a mediator which makes it possible that acupuncture stimulation treats a distant part through activating *Qi* flow through the meridian. Out of 12 main meridians and 8 extra meridians, Governor Vessel (GV) and Conception Vessel (CV) are thought to be directly

connected to the brain. For this reason, acupoints from GV and CV were chosen to be studied further for neurogenesis. Although ST36 does not belong to those two vessels, this acupoint is indirectly connected with the brain *via* other meridians, and its therapeutic effect on various brain diseases is broadly accepted (Nam et al., 2013).

Besides these traditional explanations, some researchers tried to figure out the mechanism of the neurogenic effect of acupuncture (**Figure 1**). First, acupuncture treatment upregulates some neurotrophins such as BDNF, glial cell line-derived neurotrophic factor, and bFGF (Nam et al., 2013). Neurotrophic factors are well-known to be responsible for the growth and survival of developing neurons, and necessary for adult neurogenesis. bFGF is also known to be helpful for neurogenesis (Nam et al., 2013). Additionally acupuncture stimulation at ST36 and GV20 upregulated cyclic adenosine monophosphate response element-binding protein which can regulate the transcription of BDNF (Nam et al., 2013). Secondly, acupuncture therapy also increases the expression of neuropeptide Y in the central nervous system, resulting in promoting the proliferation of neuronal precursor cells (Nam et al., 2011, 2013).

Acupuncture for brain diseases: As mentioned, modulating neurogenesis can be a potent method to treat neurodegenerative diseases, for example, AD, PD and stroke. However, transplanting stem cells to improve neurogenesis or injecting neural growth factor still have some limitations. Fortunately, several papers revealed that acupuncture is effective for inducing adult neurogenesis without any adverse effects.

Acupuncture has long been used for treating various neurodegenerative diseases, and several scientific reports prove that acupuncture therapy is beneficial for improving AD, PD and stroke. In order to improve symptoms of AD, PD and stroke, acupoints ST36 and GV20 are widely used in clinical and animal studies. These acupoints are coincidently the most used ones for enhancing neurogenesis in the adult brain. This raises the possibility that the effectiveness of acupuncture for those diseases can be attributed to improved neurogenesis. On the other hand, acupuncture is a therapeutic technique which is puncturing skin and stimulating muscle. It is much safer than injection of some tissues or materials into the brain. In this context, acupuncture can be considered as a potent and safe tool for modulating neurogenesis for treating neurodegenerative diseases.

Future perspectives: Although many studies have tried to analyze the potential neurogenic effects of acupuncture, however the mechanisms are not fully elucidated yet. Now we can only affirm that some neurotrophins such as BDNF and GDNF are involved in this effect. However, it eludes explanation how the stimulation of skin and muscle by acupuncture can affect the neurogenic niche in the brain. And it is not clearly understood that how BDNF and GDNF release is increased upon acupuncture treatment. Moreover, on the basis that not only neurons but also astrocytes are deeply and crucially participating in the neurogenesis, acupuncture effect on astrocytes should also be deciphered.

Now it is established that acupuncture improves neurogenesis in several pathological conditions of the adult brain. Therefore acupuncture can be effective for treating the diseases the pathology of which is related to neurogenesis, not only confined to AD, PD and stroke, but also amyotrophic lateral sclerosis, depression, *etc.* It should be profoundly studied that how modulating the process of neurogenesis is required for acupuncture effect on those diseases. Additionally, acupuncture can also be used for inducing neurogenesis with other therapeutic methods such as administration of nerve growth factor (Nam et al., 2013).

Here we briefly reviewed the prior studies about acupuncture effect on adult neurogenesis. Since the pathology of neurodegenerative diseases is related to decreased neurogenesis (in some cases, increased by self-recovery mechanism); enhancing neurogenesis can be a proper therapeutic target. In this context, acupuncture treatment which effectively induces neurogenesis can be a potent therapy for various neurodegenerative diseases including AD, PD and stroke.

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