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REVIEW ARTICLE

Adult Neurogenesis and Acupuncture Stimulation at ST36

Min-Ho Nam [1,3], Chang Shik Yin [2], Kwang-Sup Soh [3], Seung-hoon Choi [1,*]

[1] *Department of Pathology, College of Oriental Medicine, Kyung Hee University, Seoul, Republic of Korea*
[2] *Acupuncture and Meridian Science Research Center, College of Oriental Medicine, Kyung Hee University, Seoul, Republic of Korea*
[3] *Nano Primo Research Center, Advanced Institute of Convergence Technology, Seoul National University, Suwon-si, Gyeonggi-do, Republic of Korea*

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Abstract
Although it was believed that the brain was incapable of regeneration after embryonic development, neurogenesis is now known to occur into adulthood. Adult neurogenesis has been demonstrated in the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampus. Acupuncture has long been used to treat neurologic conditions, and recent reports suggest that neurogenesis may account for its beneficial effects. ST36 was the most often used acupoint in previous reports and was shown to enhance cell proliferation and neuronal differentiation. This acupoint may be linked to the brain through the primo vascular system, an anatomic structure thought to correspond to acupuncture meridians. This primitive vascular-like system appears to be involved in physiologic and pathologic processes by circulating substances throughout the body. The role of the primo vascular system as the link between the skin and brain underlying the beneficial effects of acupuncture requires further investigation.

1. Introduction

Neurogenesis was traditionally thought to occur primarily during embryonic development, and neuron loss in adulthood due to injury, disease, and aging was considered permanent. Although neurogenesis is now known to continue into the postnatal period [1], a decline in neurogenesis and regenerative capacity of the nervous system contributes to age-related impairment [2]. Since the first study demonstrating neurogenesis in the adult mammalian brain was published in 1965 [3], research has focused on the involvement of neural stem cells [4] and neurogenesis-regulating factors [5] in this process. There is evidence to suggest that neurogenesis is altered in individuals experiencing cognitive decline and neurodegenerative disorders [6]. Although acupuncture has been widely used for neurologic disorders in the East, its effectiveness for treating stroke [7] and Alzheimer's disease [8,9] remains unclear. A recent study demonstrated that acupuncture induces cell differentiation and neuroblast differentiation

* Corresponding author: Seung-hoon Choi, Department of Pathology, College of Oriental Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul, 130-701, Republic of Korea.
E-mail: choish@khu.ac.kr (S.-h. Choi).

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in the rat hippocampus [10], providing evidence for its utility as a neurogenesis-stimulating therapy. In this review, we provide an overview of neurogenesis and acupuncture, and discuss this topic in relation to the primo vascular system (PVS), a proposed anatomic structure corresponding to acupuncture meridians [11,12].

2. Adult Neurogenesis in Mammals

Adult neural stem cells can self-renew and differentiate into all the major types of neural cells of the adult nervous system, including neurons, astrocytes, and oligodendrocytes (Fig. 1) [13]. Because the stem cell properties of adult neural stem cells were shown *in vitro*, but were not demonstrated convincingly *in vivo* until recently, the term "neural progenitors" is used to describe all dividing cells with some capacity for differentiation [14].

The first study on adult neurogenesis, published in 1965, used 3H-thymidine autoradiography to detect neuronal proliferation in young adult rats [3]. These new cells exhibited morphologic characteristics of granule neurons and were detected in the olfactory bulb and dentate gyrus (DG). Newer methods include the use of bromodeoxyuridine (BrdU), which is incorporated along with 3H-thymidine into cells during the S phase of the cell cycle to label proliferating cells and their progeny [15]. BrdU can be combined with other immunohistochemical stains to identify specific types of proliferating cells, such as neuronal nuclei, neuron-specific enolase, and N-methyl-D-aspartate receptor subunit NR1 [15].

Adult neurogenesis occurs in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the DG in the hippocampus (Fig. 2) [14]. The SVZ is a paired brain structure that lies adjacent to the lateral walls of the lateral ventricles [16]. Neural stem cells of the SVZ migrate to the olfactory bulb via the rostral migratory stream, where they differentiate into interneurons [13]. Because neurogenesis in the adult central nervous system appears to be restricted to the DG and SVZ, studies have

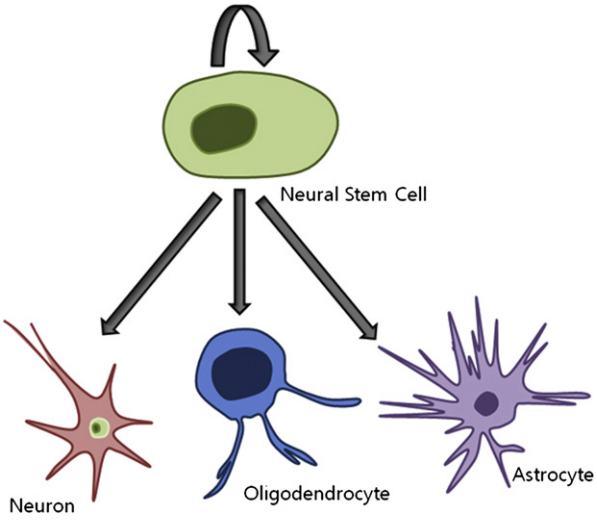

Figure 1 Adult neural stem cells can self-renew and differentiate into all major types of neural cells, including neurons, astrocytes, and oligodendrocytes.

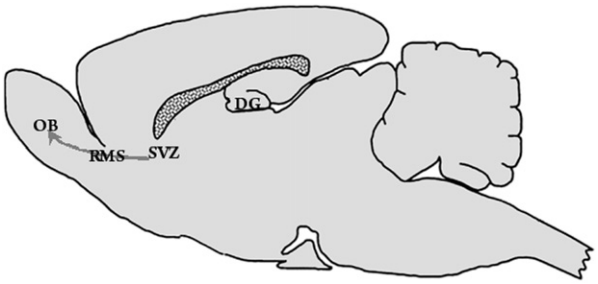

Figure 2 Adult neurogenesis occurs in two locations of the brain: the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus in the hippocampus. Neural stem cells of the subventricular zone migrate to the olfactory bulb via the rostral migratory stream, where they differentiate into interneurons. Therefore, the dentate gyrus and olfactory bulb are considered two neurogenic areas of the adult central nervous system.

focused on these two areas as targets for neurogenesis-stimulating treatment [9,17].

The hippocampus, which plays a central role in learning and memory, demonstrates a high degree of structural plasticity [18,19]. Among the hippocampal formations, only the DG continues to develop through adulthood. Progenitor cells in the germinal zone of the DG continuously generate granule cells, which integrate into the existing neuronal circuits [15]. Thus, DG cell proliferation, differentiation, and survival influence adult hippocampal neurogenesis [20].

Impaired hippocampal neuron replacement in adulthood is associated with a number of neurologic conditions, including epilepsy [21], stroke [22], Alzheimer's disease [23], Parkinson's disease [24], and inflammation of the brain [25]. The reduced proliferative activity of brain cells associated with aging appears to be specific to granule cells in the DG [26]. Neurogenesis increases in the hippocampus and SVZ in the wake of epileptic seizures and ischemic stroke, but it is not clear whether the new cells survive and integrate to compensate for the brain injury [14]. Changes in the local environment, such as a reduction in peptide growth factors, may also play a role in age-related impairments. Thus stimulating neurogenesis may be a key factor in recovering from these conditions.

3. Acupuncture and Neurogenesis

Acupuncture stimulation has been used for more than 2000 years in East Asian countries as an integral part of the medical armamentarium [27]. Traditional indications cover a wide range of conditions, and a recent report from a Consensus Panel on Acupuncture indicated that acupuncture may be an effective adjunctive therapy for addiction, stroke rehabilitation, headaches, menstrual cramps, epicondylitis, fibromyalgia, lower back pain, carpal tunnel syndrome, and asthma [28].

Regarding neurologic conditions, acupuncture has been reported to be an effective therapy for brain disorders such as sequelae of stroke [7], Parkinson's disease [29], dementia [30], and epilepsy [31]; however, its effectiveness for these conditions remains controversial [32,33]. Studies conducted

in Korea and China suggest that acupuncture may have the potential to be developed as an adjunct for managing brain disorders [34,35]. Acupuncture has been investigated using functional magnetic resonance imaging of the brain [36,37], electroencephalography [38], and physiological measurements [39,40], but the precise mechanism underlying its beneficial effects have not yet been elucidated.

Recent studies using rodent models have suggested that acupuncture stimulates neurogenesis. In particular, stimulating the following acupoints by acupuncture or electroacupuncture appears to induce neuronal proliferation: ST36 [41—43], GV20 [44], PC6 [45], HT7 [46], CV17, CV12, CV6, SP10 [9], GV16, GV8 [47], LI11, SJ5, and GB30 [48]. Neurogenesis is regulated by a number of signaling pathways. In rats, the cAMP response element-binding protein, a downstream target of cAMP signaling, is activated by electroacupuncture at ST36 and GV20. This transcription factor is important in the proliferation, differentiation, and survival of neuronal precursor cells, and directly regulates the expression of brain-derived neurotrophic factor, which supports the growth, differentiation, and survival of neurons [49].

4. Neurogenesis effect of acupuncture stimulation on ST36

ST36, an acupoint located on the anterior tibia muscle (Fig. 3), is one of the most important acupoints in clinical acupuncture. Simulation of ST36 is carried out for a wide range of conditions affecting digestive system, cardiovascular system, and immune system, and nervous system. Furthermore, ST36 is one of the seven acupoints used for stroke treatment [50], and has been widely used for brain disorders [30,51—53].

Recent studies have reported that acupuncture stimulation may enhance adult neurogenesis at the SVZ and DG in the brain (Table 1). In 2001, Kim et al provided the first evidence for the increased generation of DG progenitor cells after acupuncture treatment in ischemic gerbils (aged 11—13 weeks). Manual acupuncture at ST36 significantly increased the number of BrdU-positive cells after ischemic injury [42]. Subsequently, acupuncture stimulation at ST36 was reported to enhance cell proliferation in the DG a rat model of diabetes [41]. In SAMP8 mice, which serve as a model for Alzheimer's disease, simulation of ST36, as well as CV17, CV12, CV6, and SP10, induced cell proliferation in different brain regions [9]. In healthy rats, acupuncture and electroacupuncture stimulation at ST36 and GV20 significantly increased cell proliferation in the SGZ of the DG [49], and electroacupuncture stimulation at ST36, LI11, SJ5, and GB30 produced a sustained effect on progenitor cell proliferation and promoted cell differentiation in young rats [48]. However, one study reported a beneficial effect on neurogenesis with acupuncture stimulation at HT7, but no effect at ST36 [46].

Several proteins found in the brain appear to be increased by acupuncture therapy. Furthermore, stimulation at ST36 upregulated the expression of neuropeptide Y, which promotes the proliferation of neuronal precursor cells [42,54]. In addition, modulation of brain-derived neurotrophic factor expression appeared to mediate the effects of electroacupuncture stimulation at ST36, which attenuated the neuropathologic effects of stress in rats

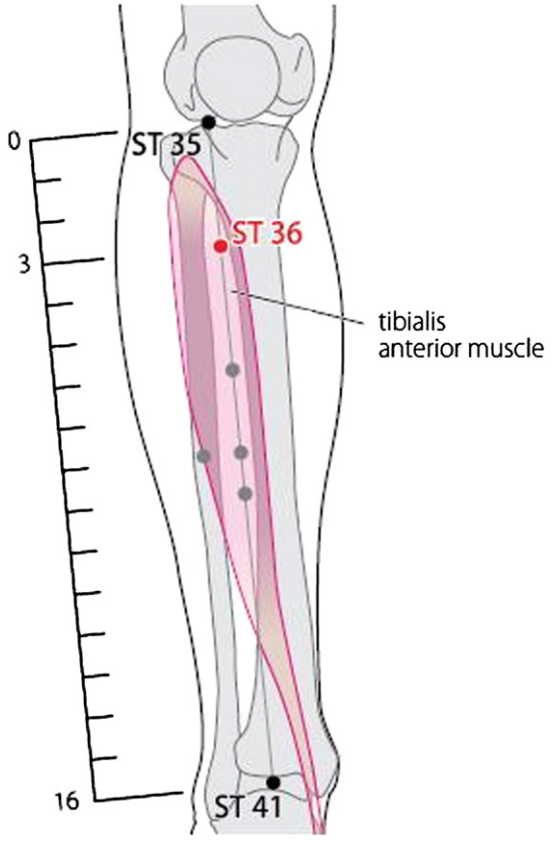

Figure 3 ST36, one of the most important and most frequently stimulated acupoints, is located on the tibialis anterior muscle. This figure originated from World Health Organization Standard Acupuncture Point Locations.

[43]. Upregulation of brain-derived neurotrophic factor and activation of the cAMP response element-binding protein in the DG were also demonstrated in rats that exhibited increased neuroblast plasticity after electroacupuncture at ST36 and GV20 [49]. In this study, neurogenesis was detected by immunostaining against Ki67, a marker of cell proliferation, and doublecortin, which is specifically expressed in neuronal precursors in the developing and adult central nervous system [10,49].

5. Discussion: Neurogenesis Effect of ST36 and the Primo Vascular System

Three reports have been published showing that acupuncture stimulation at ST36 enhances cell proliferation in the DG of the hippocampus [41—43]. Four additional studies claimed that simultaneous stimulation at several acupoints (including ST36) increased cell proliferation in the SGZ of the DG [9,10,48,49]. Although one study [46] did not find a beneficial effect with ST36, further investigation into the mechanism behind the effects of acupuncture at ST36 on adult neurogenesis is warranted.

An important first step in understanding the role of ST36 in neurogenesis is investigating the anatomy and physiology of acupoints, in particular, identifying and characterizing the anatomic structure connecting the acupoint ST36 and the brain. Recently, the PVS was proposed as the anatomic

Table 1 Summary of Papers on Adult Neurogenesis by Acupuncture at ST36

Study	Year	Animal model	Acupoints	Stimulation	Results
Kim et al [42]	2001	Mongolian gerbils (11—13 weeks) with transient global ischemia	ST36	Acupuncture; 20 min, 2 times/day for 9 days	Acupuncture increased cell proliferation in the dentate gyrus of ischemic gerbils.
Kim et al [41]	2002	Sprague Dawley rats (6 weeks) with streptozotocin-induced diabetes	ST36	Acupuncture; 20 min, 2 times/day for 7 days	Acupuncture at ST36 enhanced proliferation of neuronal precursor cells in the dentate gyrus.
Yun et al [43]	2002	Male Sprague Dawley rats (6 weeks)	ST36	Electroacupuncture; 2 Hz, 1—2 mA, 0.3 ms pulse width	Electroacupuncture restored brain-derived neurotrophic factor expression attenuated by immobilization stress.
Park et al [46]	2002	Sprague Dawley rats (14 days)	ST36, HT7	Acupuncture; once per day for 1 week, 3—mm depth, both sides, twisting the needle 2 times/s for 30 s, and removing immediately	Acupuncture at HT7 stimulated cell proliferation in the dentate gyrus. Acupuncture at ST36 did not produce a significant effect.*
Gao et al [48]	2011	Sprague Dawley rats (14 days)	ST36, LI11, SJ5, GB30	Electroacupuncture (2 Hz, 0.7 mV); 30 min, once per day for 1 week	Electroacupuncture produced a sustained effect on progenitor cell proliferation and promoted differentiation into neurons.
Hwang et al [10]	2010	Male Wistar rats (13 weeks)	ST36, GV20	Acupuncture; 20 min, once per day for 3 weeks at 5-mm depth Electroacupuncture (dense-dispersed waves of 5/20 Hz, 2—4 mA); 20 min, once per day for 3 weeks at 5-mm depth	Both acupuncture and electroacupuncture enhanced cell proliferation, but the effect of electroacupuncture on neuroblast differentiation in the dentate gyrus was greater than that of acupuncture.
Hwang et al [49]	2010	Male Wistar rats (13 weeks)	ST36, GV20	Electroacupuncture (dense-dispersed waves of 5/20 Hz, 2—4 mA) 20 min, once per day for 3 weeks at 5-mm depth	Electroacupuncture enhanced cell proliferation and neuroblast differentiation in the dentate gyrus.
Cheng et al [9]	2008	Male SAMP8 mice (4 months)	ST36, CV17, CV12, CV6, SP10	Acupuncture; once per day for 15 days with a rest on day 8	Acupuncture treatment stimulated cell proliferation in the dentate gyrus of this autogenic senile strain.

* Maternal separation is known to increase the risk of emotional problems later in life; HT7 is used to treat neuropsychiatric disorders in Oriental medicine.

structure of acupuncture meridians [55]. This idea was originally put forth by Bong-Han Kim in the early 1960s [56], but was ignored until recently because the Japanese anatomist Fujiwara was the only researcher able to confirm this discovery [57].

The PVS forms a network throughout the body in which so-called primo fluid flows. This circulatory system has several subsystems, one of which is the superficial PVS in the skin, thought to correspond to acupuncture meridians and acupoints [56]. The growth of the PVS around tumor tissues has been characterized [58,59], as well as its possible role as an additional pathway of cancer metastasis [60]. The PVS has also been observed in the brain ventricles, the central canal of the spinal cord [61], the subarachnoid space of the brain [62], and along the epineurium of the sciatic nerve [12]. These observations are consistent with Bong-Han Kim's claim that a primo vessel from the primo node at ST36 has a course along the sciatic nerve [56]. Primo vessels in the spinal nerves are thought link the complex PVS network to the spinal cord and brain, [63]. If ST36 is connected to the brain via the PVS, the neurogenesis effect may be mediated by the circulating fluid, which contains primo microcells [64,65] that function like the very small embryonic-like stem cells discovered by Ratajczak [66]. Bong-Han Kim claimed that primo microcells may be involved in tissue regeneration, similar to the role of pluripotent stem cells [63]. Thus, appropriate stimulation at ST36 may promote adult neurogenesis by improving the flow of primo microcells to the brain. This hypothesis can be tested by investigating the putative PVS path from the ST36 to the brain, followed by characterizing the substances flowing along this path and their therapeutic effects.

6. Conclusion

Adult neurogenesis, which may be a key process in recovering from brain disorders, occurs in two distinct regions of the brain: the SVZ of the lateral ventricles and the SGZ of the DG. Numerous studies have reported that acupuncture stimulation at ST36 appears to enhance adult neurogenesis. Circulation through the PVS may be the underlying mechanism of this beneficial effect of acupuncture stimulation.

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