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Review

Modulation of neurogenesis via neurotrophic factors in acupuncture treatments for neurological diseases

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ABSTRACT

Acupuncture is one of the main healing arts in Oriental medicine. It has long been used in East Asian countries, including Korea and China, and is thought to be an effective alternative treatment for various neurological diseases. The therapeutic effects of acupuncture come from inserting a needle at specific acupoints on the body surface, with subsequent delivery of stimulation via manual rotation or electric pulses (electroacupuncture, EA). In various neurological disease models, peripheral nerve stimulation using acupuncture or EA may have protective effects on neural tissues by increasing expression of neurotrophic factors (NTFs), such as brain-derived neurotrophic factor and glial-derived neurotrophic factor, in the central nervous system, especially the brain. In addition, acupuncture may contribute to recovery from functional impairments following brain damage by encouraging neural stem cell proliferation, which is active at the initial stage of injury, and by further facilitating differentiation. Hence, acupuncture may act as a stimulator activating peripheral nerves at specific acupoints and inducing the expression of various NTFs in the brain. Subsequently, NTFs induced by this treatment trigger autocrine or paracrine signaling, which stimulates adult neurogenesis, thereby exerting therapeutic effects on functional impairments in neurological diseases. Acupuncture may offer an alternative treatment that promotes adult neurogenesis through the expression of NTFs in the brain. It may also have synergistic effects when combined with pharmacological interventions, again facilitating neurogenesis. This review examines recent studies concerning the effects of acupuncture and EA on adult neurogenesis associated with NTF expression in neurological diseases, in particular stroke, Alzheimer's disease, and Parkinson's disease.

Contents

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1. Introduction

Acupuncture, a major medical tool in East Asia with a long history, has been used in the treatment of numerous diseases. Acupuncture is an economical treatment without adverse effects and so has been widely used for the treatment of various neurological diseases, as well as being used in post-illness rehabilitation to aid recovery from functional impairments [1–5]. Traditional explanations for the therapeutic effects of acupuncture are based on the meridian system [6], but such traditional hypotheses are controversial and are difficult to examine empirically. Thus, the mechanisms underlying the effects of acupuncture are not fully understood. Nonetheless, acupuncture is extensively applied in today's aging society as an alternative or complementary treatment for neurological impairments, including sensorimotor dysfunction, cognitive impairments, and depression, without any obvious side effects [1,3–5,7].

It is well known that neurogenesis, the continued growth and development of neurons, can occur throughout life in specific regions of the adult brain, such as the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus [8,9]. Neurological disorders that cause brain damage activate endogenous neural repair systems, such as neurogenesis. Therefore, modulation of this activation and mechanisms underlying such endogenous recovery systems offer attractive therapeutic potential for the treatment of neurological disorders [9–11]. A remarkable insight into adult neurogenesis was the discovery that the persistence and regulation of neurogenesis are readily influenced by extrinsic signals involving neurotrophic factors (NTFs) [9,12]. Moreover, various NTFs have common roles in both embryonic and adult neurogenesis [9]. Functional recovery from impairments caused by neurological diseases requires proliferation, survival, differentiation, and migration of neural progenitor/stem cells (NPCs/NSCs), which temporarily increase following brain damage, as well as eventual functional integration with the central nervous system (CNS) [11,13].

In animal models of neurological diseases such as stroke, Alzheimer's disease (AD), and Parkinson's disease (PD), acupuncture has been shown to have neuroprotective effects and to enhance functional recovery by activating and increasing expression of brain NTFs, including brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) [14–17]. Acupuncture exerts its therapeutic effects by activating and facilitating adult neurogenesis via the stimulation of NSC proliferation and differentiation in the brain [15,18,19]. Therefore, one possible neurophysiological mechanism underlying the therapeutic effects of acupuncture is the regulation of plasticity in the brain (e.g., neurogenesis). NTF levels, which are modulated by the therapeutic effects of acupuncture, are associated with enhancement of survival, proliferation, and differentiation of NSCs [17,18,20].

Better understanding of endogenous neurogenesis could provide opportunities to develop novel strategies in the treatment of neurological diseases. Crucially, acupuncture could also be used in combination with drugs or other therapeutic treatments to stimulate neurogenesis in these diseases. Many previous studies have been conducted to investigate treatment of neurological diseases by promoting neurogenesis, including studies of complementary, alternative, and integrative medicine [4]. The results from these studies have suggested that acupuncture enhances the expression of NTFs in the brain, and that these NTFs may stimulate neurogenesis, thereby exerting a therapeutic effect on functional recovery in neurological diseases [15,18,19]. In this review, we report on recent trends and studies of the therapeutic effects of acupuncture in neurological diseases, especially in stroke, AD, and PD, which share symptoms such as cognitive impairment and depression, focusing on studies of adult neurogenesis and NTF expression in the brain.

2. Properties of acupuncture as peripheral nerve stimulation

According to traditional Oriental medical theory, the meridian system is widely distributed inside and outside the body, including the skin and internal organs. It forms a network, serving an integrative role and creates functional associations within the entire body [21]. Thus, lesions of the internal organs are exposed to the surface of the body through the meridian system, and external stimuli from a treatment are delivered to the internal organs. If the meridian system is described using the concept of a line, the meridian point (acupoint) is described using the concept of a dot distributed as major spots above the meridian system. The acupoint refers to the empty space above the meridian system, which can collect *qi* (vital substances) and *xue* (blood) as a healthy physiological process, or morbid energy as part of pathological processes. Therefore, diseases are diagnosed by examining pain and color changes at these acupoints, and therapeutic effects are obtained by adjusting the condition of the internal organs via stimulation using needles. In other words, the acupoint is not only a diagnostic site but also a therapeutic spot, acting as a door that connects the meridian system to the external space [6,21].

For acupuncture treatment, the proper acupoint is selected according to each different disease, and a needle is inserted [6,22]. To maximize the therapeutic effect, hand manipulation, such as spinning or flicking the needle, is performed to trigger proper stimulation [22]. Although clear evidence of an acupuncture-specific response in the brain and spinal cord remains elusive, stimulation of the acupoint using needles activates the CNS, i.e., the spinal cord and brain, via afferent nerve pathways of the peripheral nervous system and induces various neurophysiological changes [20,23–25]. Furthermore, a model has been proposed in which stimulation from the needles passes through the CNS and acts on the internal organs via brain-gut axis, such as the hypothalamus-pituitary-axis [26]. In summary, a framework in which acupuncture activates the brain and spinal cord is essential, and has been accepted in studies of the therapeutic mechanisms of the treatment [23,24].

In addition to the selection of a specific acupoint, the method of stimulation is also crucial in acupuncture. Today, electric pulses, magnetic fields, ultrasound, and lasers that are used in other physical therapies can also be applied in acupuncture instead of hand manipulation after traditional needle insertion [27,28]. In particular, electroacupuncture (EA), which creates electrical stimulation, allows the modulation of constant pulse width, intensity, and frequency, making it easier to standardize treatment than in traditional manual acupuncture, and aids elucidation of underlying mechanisms [20]. Hence, EA is widely used in the experimental and clinical fields.

Needle insertion at acupoints followed by manual rotation or electric stimulation activates all types of afferent fibers [20,23]. These impulses ascend mainly via the ventrolateral funiculus, and subsequently involve many brain nuclei creating a compli-