

Research advances in neurobiological mechanism of acupuncture for amblyopia

针刺干预弱视的神经生物学机制研究进展

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Abstract

Amblyopia greatly affects the physical and mental development of children. Acupuncture is effective for amblyopia, though its mechanism remains unclear. This article summarized the mechanism of acupuncture treatment of amblyopia from the perspectives of morphology of neurons in visual cortex, visual electrophysiology, and molecular biology, etc. It was found that acupuncture may treat amblyopia through repairing the morphological and ultrastructural damages of neurons in visual cortex, promoting the electrical activities in visual pathway and visual cortical neurons, and modulating the synthesis and expression levels of factors involved in visual system. Nevertheless, further studies are required to unveil the mechanism of acupuncture treatment of amblyopia.

Keywords: Acupuncture Therapy; Child; Amblyopia; Vision, Ocular; Neurobiology; Review

【摘要】 弱视严重影响患儿生理及心理发育。针刺疗法是治疗弱视的有效方法之一，但对其机制尚未完全明确。从视皮层神经元形态学、视觉电生理、分子生物学等方面总结针刺干预弱视的机制，发现针刺通过修复视皮层神经元形态及超微结构损害，促进视觉通路及视皮层神经元电活动，调控视觉系统相关分子合成和表达水平达到干预弱视的目的。对于针刺干预弱视机制仍需进一步研究。

【关键词】 针刺疗法；儿童；弱视；视觉；神经生物学；综述

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Amblyopia is an eye condition that results in decreased vision in one or both eyes. Various factors that occur during visual development can lead to this condition, including monocular strabismus, uncorrected anisometropia, severe refractive error and visual form deprivation. It can also be defined when vision of the affected eye is two rows weaker than that of the other eye on an eye chart^[1]. In China, amblyopia affects 1.0%-2.0% of the kids, while the prevalence is 1%-5% based on the whole population^[2]. Domestic epidemiological survey has revealed a higher detection rate compared with that at a global scale^[1,3]. Not correctable to the normal vision level, and accompanied by 3-D visual defect and poor binocular coordination and orientation, amblyopia may greatly affect kids' learning and living abilities^[4]. Acupuncture has been proved effective in improving vision or visual function, and it is easy to operate and usually takes a short treatment course while producing minor side effects. Besides, since it is also well accepted by kids, it has been widely applied in ophthalmology department^[5-6]. By focusing on the repair of the ultrastructural damages of

visual cortical neurons, promotion of the electrical activities in visual pathway and visual cortex, and regulation of the synthesis and expression levels of the relevant factors in visual system, the mechanism of acupuncture treatment of amblyopia is summarized as follows.

1 Acupuncture Repairing the Morphological and Ultrastructural Damages of Visual Cortical Neurons

Ultrastructural damage of neurons in visual cortex is the morphological basis of form deprived amblyopia and strabismic amblyopia^[7-8]. Rat models have demonstrated that monocular form deprivation can lead to morphological changes in visual cortical neurons^[9-10]. Light microscope shows that visual cortical neurons shrink in rats with visual form deprived amblyopia. Under electron microscope, early-stage para-apoptosis can be seen in visual cortical neurons in form deprived amblyopia rats^[11]. Mild cytoplasmic swelling, merging or disappearance of mitochondrial crista and membrane, disordered arrangement, rough endoplasmic reticulum degranulation, and nuclear membrane shrinkage can be detected in the neurons in

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region 17 layer IV of the contralateral visual cortex^[12]. Transmission electron microscope detects decreased amount of synapses, enlarged synaptic cleft, shortened active zone, reduced curvature of synaptic interspace and thickened postsynaptic density in the contralateral visual cortical neurons^[13-14]. However, some studies find that the postsynaptic density becomes thinner in form deprived amblyopia^[15]. In a cat model of form deprivation, the amount and shape of neurons show the most significant change at 1 month after the deprivation^[16]. In the rat model of form deprivation, the ultrastructural damages present most significantly at the age of 35 d and 49 d^[14], or at 11 week and 13 week in adult rats^[17] in region 17 of visual cortex. The ultrastructure of ganglion cells, lateral geniculate body and visual cortical neurons and their synapse in central retina of form deprived eyes degenerates and shrivels to different levels. Generally speaking, amblyopia has its subcellular pathological basis, and early-stage visual disturbance may cause histopathological damage to visual system^[18].

Acupuncture can repair the pathological damages in region 17 of visual cortex in form deprived rats, improving synaptic structure, synaptic cleft, medullary sheath structure and myelin-like changes, and extending the synaptic active zone. The improvement is most significant in the early stage. As for the abnormal changes in electrophysiology and synaptic ultrastructure in visual cortex region 17 of monocular form deprived rats, acupuncture can obviously regulate the plasticity of visual cortex, encourage the formation of neurite, enhance the synaptic connection, and restore the active zone and transmission efficiency. Its therapeutic efficacy is closely related to the intervention time^[19].

2 Acupuncture Promoting the Electrical Activities in Visual Pathway and Visual Cortex

Currently, the commonly used electrophysiological detection techniques for amblyopia include in-vitro multi-microelectrode array neural signal collection technique and visual evoked potential (VEP), and the latter can be further divided into pattern visual evoked potential (P-VEP) and flash visual evoked potential (F-VEP).

P-VEP can reflect the visual pathway, visual transmission ability and the function of visual cortex^[20]. P100 is a major waveform of P-VEP and has become a key indicator in clinical examination and visual function evaluation because of its good stability and repeatability. The amplitude of P100 mainly indicates the function of optic nerve axons and the latent period suggests the function of optic nerve sheath^[21]. Under amblyopia, the visual cortex neurons that are responsible for graphic motion and boundary contrast may go wrong^[22], which can cause a longer P-VEP latent period and decreased

amplitude in every type of amblyopia^[23]. In the sensitive stage, acupuncture can up-regulate the P100 amplitude and shorten the latent period^[24]. In general, acupuncture can repair the damaged visual system in amblyopia by effectively strengthening the bioelectrical activity in visual pathways.

The damage caused by form deprivation to visual system is mainly manifested by longer latent period and decreased amplitude of waveforms N1, P1 and N2 in F-VEP. After acupuncture at certain acupoints, F-VEP shows improvements to different extents^[25-26]. Other evidence also tells that F-VEP has great instability and there is no significant difference between the lazy eye and the normal eye comparing the F-VEP, and thus disagrees to consider this index in diagnosing and rechecking amblyopia^[27]. It is also showed that acupuncture can enhance optic nerve conduction and improve VEP via regulating M and P pathways^[28].

The microelectrode array neural signal collection technique adopts extracellular record to monitor the synchronized electrical activity of neurons and is able to capture the electrical information of a large amount of neurons at the same time. In rat models of monocular form deprivation, declined neuron discharge frequency and abnormal neural coding mode are detected in region 17 of the visual cortex; in the same area, the amplitude of action potential decreases, the interspike interval extends, disordered spatio-temporal coding mode occurs and the power spectral density region enlarges. Finally, there occurs poor synchronization in neural electrical activity and abnormal information integration duration. It is found that acupuncture can produce significant effect in regulating and improving the neural coding and information integration time, and its therapeutic efficacy is associated with the time of intervention. Early intervention is essential in achieving satisfactory efficacy due to the developmental plasticity of visual cortical neurons in the sensitive stage^[29-30].

3 Regulating the Synthesis and Expression Levels of Visual System-related Factors

3.1 Regulation of the expression levels of synaptic spasticity protein in visual system

The expression levels of neuronal nitric oxide synthase (nNOS), c-fos^[31-32], cyclic-AMP response binding protein (CREB)^[33], growth associated protein (GAP-43)^[34], protein kinases C (PKC)^[35] and postsynaptic density-95 protein (PSD-95)^[36] are found related to the development of amblyopia^[37], and these proteins all play a role in modulating the plasticity of visual cortex in the crucial period of visual development.

Among these proteins, nNOS affects the formation, integration and transmission of visual information during the visual development. Rats with nNOS gene knockout present obvious delay in visual system

development and visual disturbance^[38]. After form deprivation, the expressions of nNOS protein and positive neurons in the visual cortex region 17/lateral geniculate body and retina of the rats are significantly decreased. Form deprivation results in insufficient photostimulation to the amblyopic eye and damage to the visual nervous system. Acupuncture can regulate and enhance the expression of nNOS protein, promote the development of visual system and improve visual function^[39-40].

The expression level of c-fos determines the degree of plasticity of visual cortex neurons, and is an indicator of plasticity of visual cortex^[41-42]. With light stimulation to induce the production of c-fos, visual cortex of adult rats at the end of the key visual development stage still displays a certain degree of plasticity^[43]. Acupuncture can improve visual function and visual system plasticity by regulating the expression level of c-fos protein^[44].

GAP-43 is closely related to the development of the nervous system, reconstruction of synaptic connection, and neural plasticity and regeneration. It affects the growth of axons by guiding axon growth and regulating the formation of new connections, which makes it an intrinsic determinant in the development and regeneration of axons. Acupuncture intervened during the critical period of visual development can regulate the expression of retinal GAP-43 in monocular form deprivation rats and improve the visual function^[45].

3.2 Regulation of the expressions of neurotrophic factors in the visual cortex

Neurotrophic factors may play an important role in the development of the visual system and in maintaining the normal visual function and binocular balance in the binocular competition mechanism^[46]. Introduction of exogenous neurotrophic factors into the visual cortex can significantly improve visual acuity and sensitivity^[47], and effectively antagonize the damage of visual deprivation to visual cortex in the critical visual development stage^[48]. Giving brain derived neurotrophic factor (BDNF) to adult monocular deprivation rats can re-initiate the visual plasticity even after the sensitive period of visual development^[49]. Neurotrophic factors participate in the regulation of visual plasticity in the critical period, and its abnormal expression may be one of the important factors in causing amblyopia.

Studies have shown that the change in BDNF expression in the visual cortex is consistent with visual development stages and participates in synaptic shaping during the critical development stage of vision^[50]. The expression of BDNF in the layer IV region 17 of the cat's visual cortex reaches the highest at the 6th week, then decreases gradually, and form deprivation inhibits its expression^[51]. After acupuncture treatment, the expression of BDNF in increases significantly in the retina, lateral geniculate body and different layers of

visual cortex. It is through promoting the synthesis and secretion of neurotrophic factors and their receptors that acupuncture exerts the effect of protecting and nourishing visual neurons, effectively antagonizing the deprivation effect in the critical period of vision development, thereby improving synaptic development and correcting visual disorders. Acupuncture can reverse the deprivation-caused degeneration of neurons, promote the recovery of neuronal conduction and the reconstruction of synaptic transmission, and regulate the plasticity of visual function^[52-53].

3.3 Regulation of visual cortex-related gene expressions

Studies have shown that N-methyl-D-aspartic acid (NMDA) receptor NR1 (NMDAR1) directly affects the plasticity of ocular dominance. The activity and number of NMDAR1 in region 17 of visual cortex both decline during and at the end of the sensitive period in visual deprivation. The monocular visual deprivation may significantly inhibit the expression of NMDAR1 mRNA in region 17 of the visual cortex in rats. It is demonstrated that the expression increases after acupuncture, and acupuncture can regulate the expression of the relevant factors, the release of neurotransmitter and synaptic connection, so as to reduce the influence of visual deprivation on visual cortex^[54].

4 Summary

The pathogenesis of form-deprivation amblyopia has subcellular pathological basis, i.e., the morphological and ultrastructural damage of visual cortical neurons, which leads to the dysfunction of visual cortex neurons and visual environment disorder, manifested as visual electrical information transmission and integration failures, and abnormal synthesis and expression levels of the relevant proteins, neurotrophic factors and genes in visual system.

During visual development, visual system can adapt to changes in the external visual environment, stimulating and adjusting the original connection among neurons and the synaptic structure. The time when these changes and adjustments happen is considered the critical period of visual development plasticity^[1]. Intervening, regulating and working against the visual cortical damage during the critical period of visual plasticity can effectively treat amblyopia. Acupuncture during the critical period can effectively repair the morphological and ultrastructural damage of visual cortical neurons and adjust the plasticity of the neurons, which is significant for the reconstruction of visual cortical function. From the perspective of spatiotemporal pattern of neuron clusters, acupuncture can encourage the electrical activity of visual pathway and visual cortical neurons, improve the neural information transmission in visual system and the

information processing in visual cortex. Via modulating the expression levels of synaptic plasticity protein, neurotrophic factors and genes, acupuncture can regulate the plasticity changes during the critical period of visual development, and antagonize the visual cortex damage brought by deprivation, to finally achieve the purpose of treating amblyopia. Because of the age-dependent feature of visual development, early intervention during the sensitive period of visual development should be the key to achieving efficacy.

Amblyopia has a complex pathogenesis and the research mainly focuses on morphology, molecular biology and neural mechanism. The mechanism research of acupuncture treatment of amblyopia is rather limited. For example, the studies of Golgi apparatus, mitochondria and other ultrastructural indicators of visual cortex neurons are not quantified, lacking of gene expression and identification, observation of synaptic plasticity protein pathway, and comparative studies. The current mechanism studies of acupuncture intervention for amblyopia mainly target the regulation of primary visual cortex, while the collaboration between visual cortex and other brain regions is missed. Moreover, there still requires a standardized acupuncture treatment protocol to better study its mechanism in treating amblyopia, since the acupuncture treatments adopted in the studies are various in details. Different acupoint selection, needling angle, manipulation, stimulation intensity, and needle retaining time may all lead to a different result. Regarding the visual development stages, current research mainly adopts acupuncture in the critical period of visual development, but rarely after the stage.

In summary, the mechanism research of acupuncture intervention for amblyopia should adopt a standardized treatment protocol, further explore the related genes and signal pathways, apply comparative approach, and pay attention to the collaboration between visual cortex and other brain regions. At the same time, the mechanism of acupuncture intervention for amblyopia after the critical period of visual development also needs studying, so as to comprehensively and deeply understand how acupuncture works for amblyopia.

Conflict of Interest

The authors declared that there was no conflict of interest.

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