Mini Review

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A Mini Review on Research of Fastigial Nucleus Electrical Stimulation

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Abstract

The cerebellar Fastigial Nucleus (FN) is the oldest nucleus in the development of the cerebellar system. It participates in axial, proximal, and eye movements. FN is also involved in the regulation of various non-physical functions, such as eating, cardiovascular and breathing, immune and emotional activities, through morphological connections with non-motor systems, such as the brainstem, hypothalamus, and limbic system. Since the Conditioned Central Neurogenic Neuroprotection (CCNN) was proposed, Fastigial Nucleus Electrical Stimulation (FNS) as a neurogenic protection method has been extensively studied, and it has been proven to protect against cerebral ischemia damage and improve nerves function, cognitive function and the role of depression after stroke.

It has also been reported to have direct neuroprotective effects in other research neighborhoods, such as preclinical models of retina, gastric mucosa, and cardiac ischemia. This article summarizes the research progress of this rehabilitation treatment.

Keywords: Electrical stimulation; Fastigial nucleus

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Introduction

In 1684, Raymond de Vieussens first discovered the cerebellar nucleus [1]. In mammals, the cerebellar nucleus is divided into three parts, from the midline to the outer side: the FN, the intermediate nucleus, and the dentate nucleuses, which are embedded in the dense white matter of the cerebellum and are left and right symmetrical gray matter nuclei. FN is highly conserved throughout the evolution of mammals, while the intermediate nucleus has differentiated into globular nuclei and plug nuclei in humans. This evolutionary feature suggests that FN may play a key role in cerebellar function. FN is located on both sides of the midline of the cerebellar vermis, close to the top of the fourth ventricle and include Glutamatergic, γ-aminobutyric Acid (GABA) and glycinergic neurons [2]. The crawling fibers from the lower olive, the medulla reticulum, the reticular tegmental nucleus and the mossy fibers of the medial vestibular nucleus constitute the most important excitatory glutamatergic afferent fibers. The GABA purkinje cell axons from the cerebellar vermis cortex to FN constitute the most important inhibitory afferent fibers. There are also serotonergic projections from the medulla/pontine network and raphe nucleus, noradrenergic locus coeruleus, and histaminergic and orexinergic projections from the hypothalamus. In addition, the cerebellum has a cholinergic system, and cerebellar cholinergic fibers mainly come from the medial vestibular nucleus and directly innervate the cerebellar cortex and cerebellar nucleus. The fastigial nucleus is a relatively dense area of cholinergic fibers in the cerebellar nucleus, and it has been shown to contain several subtypes of cholinergic receptors [3].

In 1969, Miura et al. [4] found in anesthetized cats that stimulation of FN can trigger a transient increase in arterial pressure and heart rate, which together are referred to as the Fastigial Pressor Response (FPR). In 1983, Nakai first proposed that [5] FNS can cause an increase in local cerebral blood flow, and only FNS has the function of regulating and dilating blood vessels. Electrical stimulation of the cerebellar cortex and dentate nucleus did not cause an increase in blood flow in the brain. Later, some researchers believed that the increase in local brain blood flow had nothing to do with changes in local brain metabolism and was mediated by the release of acetylcholine, because systemic atropine administration would cancel this benefit [6]. However, there is a doubt that the effect of atropine seems to occur mainly in the local vascular layer, rather than the intracerebral pathway. In 1986, Chida et al. [7] injected a small amount of kainic acid into FN, and found that the arterial pressure and heart rate decreased, and called it the Fastigial Depressor Response (FDR). In 1991, Reis et al. [8] observed that FNS resulted in a substantial (40%) reduction in the size of the cerebral ischemic infarction, which led to numerous studies of the FN in the field of neurocerebral inschemia with encouraging results. In 1997, therefore, Reis proposed that when the brain is hypoxic or ischemic, there is a self-protection mechanism in the brain, one of which exists in the FN, which can produce more than 10 days' protective effects against subsequent cerebral ischemia, and called it CCNN [9].

Mechanisms of Cerebral Ischemia Neuroprotection

In 1999, Glickstein et al. [10] used amanin to destroy FN intrinsic neurons, and found that the neuroprotection caused by electrical stimulation and FDR of the fastigial nucleus caused by chemical stimulation were eliminated, but it does not affect the increase in arterial pressure and local cerebral blood flow induced by electrical stimulation. The reasonable explanation is that chemical stimulation only stimulates the intrinsic neurons of FN, while electrical stimulation also stimulates projection or passing fibers. Therefore, the intrinsic neurons and passing fibers in FN may play different autonomic nerve functions. FN intrinsic neurons promote sympathetic inhibition and reduce brain metabolism and local cerebral blood flow. The passing fibers in this area originate from the rostral ventrolateral medulla to

initiate sympathetic excitement and cerebral vasodilation. FN intrinsic neurons play a neuroprotective effect and regulate and protect cerebrallocal ischemia. The neuroprotection cannot be attributed to the relative increase in local cerebral blood flow. According to current research, the mechanisms of cerebral ischemia neuroprotection of FNS may be as follows [11-15]: 1). Inhibition of electrical activity around the lesion. 2). Improvement of tissue edema in ischemic area. 3). Inhibition of neuronal apoptosisin ischemic area of brain. 4). Inhibition of excitotoxic damage on neurons. 5) Inhibition of inflammatory responsein ischemic area of brain. 6) Promotion of nerve tissue regeneration and reconstruction.

Mechanism of Treatment for Vascular Dementia

There is a close relationship between cerebrovascular diseases and cognitive impairments. The cerebellum plays an important role in the pathogenesis of cognitive disorders. Xia D et al. [16] found that FNS could help to recover the lost learning and memory ability in vascular dementia rats. FNS alleviated neuron cell apoptosis and reduced the severity of vascular dementia by suppressing the autophagy process and inhibiting inflammatory responses.

Mechanisms of Mental Disease Treatment

The cerebellum is associated with many non-motor mental disorders [17]. According to recent studies [18], FN plays a key role in the cerebellar cognitive-affective syndrome, a disorder of executive function, spatial cognition and language. Inactivation of FN alters the social behavior of rats [19]. FN involves in modulation of mood and emotion through the direct cerebellar-hypothalamic GABAergic and glutamatergic projections [20]. In Post-Stroke Depression (PSD), the balance between glutamatergic and GABAergic fibers is impaired (GABAergic fibers are more impaired). The GABA and glutamate content in the lateral hypothalamic area were also decreased significantly in the PSD. The improvement of FNS in PSD may be achieved by decreasing the level of inflammatory cytokines in brain tissue via cerebellar-hypothalamic circuit. In addition, Wang M et al. [21] founded that in a rat model, FNS reduced the expression of TNFRSF1A by upregulating miR-29c expression, which suppressed the expression of inflammatory cytokines, resulting in reduced severity of post-stroke depression [21].

Mechanisms of Myocardial Ischemia Neuroprotection

There is an interaction between the brain and heart, and our previous study have shown that FNS improves heart rate variability in Myocardial Infarction (MI), which indicates that it may act on cardiac autonomic nerves [22]. Further research revealed that FNS promoted the regeneration of cardiac autonomic nerves and reduced the incidence of malignant arrhythmias in MI rat model by up-regulating nerve growth factor mRNA expression, decreasing norepinephrine release and increasing acetylcholine release [23]. Microinjection of acetylcholine into FN induced blood depressor response in rats [24]. Therefore, parasympathetic nervous system activation may be an important mechanism of cardiovascular protection of FNS.

Researches in the Field of Respiratory Disease

There is accumulating evidence to show the involvement of the FN in respiratory central control. Bassal and Bianchi first reported an altered respiratory response to electrical stimulation of the FN in cats, elevating ventilation [25]. Li K et al. [26] found an interesting phenomenon in clinical practice that after FNS, asthma patients can gradually reduce or even stop the drug. Therefore, they performed FNS in an experimental rat model of asthma and found that FNS significantly reduced IL-4, IL-13, TNF-α, OVA-IgE and TGF-β1 in serum and BALF, and increased IFN-γ.

Research in the Field of Digestive

FN is involved in the regulation of gastric motility and feeding activity. The FN participates in regulation of Stress Gastric Mucosal Injury (SGMI), and is a specific area in the greater splanchnic nerve for exerting protective effects on the SGMI. Gao L et al. [27] found that microinjection of L-glutamic acid into the FN or FNS markedly attenuated SGMI. Zhu JZ et al. [28] found that Microinjection of the GABA receptor agonist into FN significantly exacerbated the SGMI in a dose-dependent manner, whereas microinjection of GABA receptor antagonist attenuated the damage.

Research in the Field of Immunity

The central nervous system has been shown to regulate the immune system. Previous studies have shown that FN lesions promote the differentiation of thymocytes into mature helper T lymphocyte in the thymus and enhance the function of helper T cells in peripheral immune tissue [29]. Although there is no direct structural link between the cerebellum and the immune system, the hypothalamus is well known for its role in immune regulation and is considered one of the most important centres of immune regulation, regulating immune cell function through sympathetic nervous system and endocrine system. The concrete mechanism, the related research report is inconsistent. On the one hand, several studies have suggested that FN glutamatergic neurons regulate innate and adaptive immune functions and this effect is mediated by the hypothalamus via FN-hypothalamic glutamatergic transmission and sympathetic nerves that innervate lymphoid tissues [30,31]. On the other hand, it has been reported that there is a direct GABAergic projection between FN and Hypothalamus, which participates in modulation of lymphocytes [32]. Therefore, FN glutamatergic/GABAergic neurons-hypothalamus-sympathetic nervous system-lymphocyte pathway may be participated in immunoregulation.

Clinical Application and Prospect

In clinical application, the effective therapeutic current is non-invasively introduced into the FN region through the electrodes attached to the mastoid process of both ears and cerebral circulation function therapeutic apparatus developed by bionic bioelectricity. FNS has been used in the rehabilitation of ischemic cerebrovascular disease, migraine, insomnia, cognitive dysfunction, cerebral developmental backwardness, senile and vascular dementia, post stroke depression, eye ground artery ischemia, Juvenile Myopia, cardiac autonomic dysfunction in stroke patients, and Cerebral Palsy in children.

The biological function of FN is much more complex than we know. Recently, stimulating glutamatergic neurons in the FN may be a promising approach for therapeutic intervention in temporal lobe epilepsy [33]. FNS is a promising therapeutic strategy to promote disease recovery by activating the self-healing mechanism. With the development of research, we have reason to believe that FNS will play a greater role in treatment and benefit more patients.

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