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REVIEW ARTICLE

Cholinergic Vasodilative System in the Cerebral Cortex: Effects of Acupuncture and Aging

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Abstract
This article presents a review of our studies on the cholinergic vasodilative system in the cerebral cortex in relation to the effects of acupuncture and aging. In anesthetized rats, manual acupuncture-like stimulation of the cheek, forepaw, upper arm, and hindpaw increases the cortical cerebral blood flow (CBF). The mechanism for the increased response of CBF due to forepaw stimulation has been found to be a reflex response whose afferents are Groups III and IV somatic afferent fibers and whose efferents are cholinergic fibers that originate in the nucleus basalis of Meynert. Although the cholinergic cortical vasodilation to nucleus basalis of Meynert stimulation at high intensities declines with age, the increased response of CBF induced by natural somatic afferent stimulation, such as an acupuncture-like stimulation of a forepaw, is well maintained even in very old rats (approximately 3 years of age). These findings in anesthetized rats may support the application of acupuncture to elderly people and patients with disturbances in the CBF by activating the intracranial cholinergic vasodilative system.

1. Introduction

Disturbances in the cerebral blood flow (CBF) may impair consciousness and motor and visceral functions. Acupuncture has been used to improve the dysfunctions caused by disturbances in the CBF, such as stroke [1,2], but the mechanisms of this improvement have not yet been clarified.

A cholinergic neural vasodilative response in the cortex, independent of systemic blood pressure and metabolic

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vasodilation, has been reported to occur when cholinergic neurons originating in the magnocellular nucleus of the basal forebrain (the nucleus basalis of Meynert; NBM) and projecting to the cortex are activated [3,4]. This cholinergic vasodilative system, which operates by increasing acetylcholine (ACh) release, relies upon the activation of both muscarinic and nicotinic ACh receptors in the parenchyma of the cortex [3,5]. Cutaneous mechanical sensory stimulation, such as pinching of the skin, has been shown to excite NBM cholinergic neurons [6], release ACh in the cortex [7], and consequently increase the cortical CBF [8]. These results indicate that insufficient cerebral circulation is improved by the stimulation of the skin and underlying muscles through acupuncture.

The cholinergic neurons in the basal forebrain show degeneration in patients with Alzheimer's disease and in healthy aged people [9—11]. It is very important to determine whether the cholinergic vasodilator effect of NBM on the cortical CBF changes with age.

First, this study reviews animal studies that examined the effect of acupuncture-like stimulation on the cortical CBF with regard to the intracranial cholinergic vasodilative system [12]. Second, it reviews studies on aging of the intracranial cholinergic vasodilative system [13—15]. Finally, the effects of acupuncture-like stimulation on the cortical CBF examined in aged rats are presented. The effect of moxibustion-like stimulation on the cortical CBF is also tested and discussed here [16].

2. CBF responses in the parietal cortex to acupuncture-like stimulation to various areas

Acupuncture-like manual stimulation delivered to various segmental areas produced various responses for the cortical CBF in both the parietal cortex and the mean arterial pressure (MAP). Stimulation of the cheek, forepaw, upper arm, and hindpaw produced significant increases in the CBF, but that of the chest, back, lower leg, and perineum did not produce significant responses (Fig. 1A and C). The CBF responses were presented in both sides, ipsilateral and contralateral to the site stimulated. Both ipsilateral and contralateral CBF responses were almost identical, and no significant differences were found (Fig. 1C). Stimulation of the cheek, forepaw, and hindpaw produced an increase in the MAP, whereas that of the back produced a decrease in the MAP. Stimulation of the upper arm, chest, lower leg, and perineum did not produce a significant response in the MAP. Although there were slight discrepancies between the responses of the CBF and the MAP, as stated above, there was a general tendency to produce both these responses in parallel.

3. Neural mechanism of CBF response produced by acupuncture-like stimulation

To prevent an increase in the MAP following an acupuncture-like stimulation of a forepaw, the spinal cord was transected at the first to second thoracic level (T1—2). After the spinal transection, sensory information from the forepaw could ascend via the normal circuitry to the brain through the cervical spinal cord, propagate to the cardiovascular center in the brainstem, and be integrated into the brainstem; however, the information integrated into the brainstem could not descend to the preganglionic sympathetic neurons in the thoracic and lumbar spinal cord because of the transection of the descending pathways at the top of the T1—2 level of the spinal cord.

After spinal transection at T1—2 level, manual acupuncture-like stimulation to the forepaw for 1 minute no longer produced MAP responses, but still produced the increased CBF responses (Fig. 1B and D). This result indicates that the CBF response is independent of MAP. Both ipsilateral and contralateral CBF responses were almost identical; no significant differences were found.

In the spinalized condition, moxibustion-like stimulation, performed by burning an approximately 4 mg moxa cone placed on the forepaw skin, produced a significant increase in the CBF both ipsilateral and contralateral to the site of stimulation [16].

The increased CBF following either acupuncture- or moxibustion-like stimulation to a forepaw was completely abolished after severing the brachial plexus, indicating the inevitable role of somatic afferents in the CBF responses produced by acupuncture- and moxibustion-like stimulation. Acupuncture-like manual stimulation for 1 minute delivered to a forepaw between the second and third digits excited ipsilateral radial, ulnar, and median afferent nerves, innervating the stimulation area. To define the fiber groups, an electrical current was passed through two acupuncture needles inserted into a forepaw. The CBF was increased by repetitive electrical stimulation (electroacupuncture stimulation) only when the stimulus intensity was above the threshold of Group III nerve fibers. Stimulation with supramaximal intensity for all group fibers, including Group IV fibers, produced an even larger increase in the CBF. These results indicate that Groups III and IV afferents are responsible for the CBF response induced by acupuncture-like stimulation.

The CBF response elicited by electroacupuncture stimulation of a forepaw in the spinalized rats did not change significantly by bilaterally cutting either the sympathetic nerves innervating the cerebral blood vessels at the cervical level or the parasympathetic nerves innervating cerebral blood vessels at the palatine ganglia of the facial nerves for parasympathetic nerves. These results indicate that sympathetic and parasympathetic efferents are not essential to the CBF response.

The CBF responses were attenuated after an intravenous (i.v.) injection of atropine, a blood—brain barrier (BBB)-permeable muscarinic ACh receptor antagonist, and were further attenuated by an additional i.v. injection of mecamylamine, a BBB-permeable nicotinic ACh receptor blocker (Fig. 2). By contrast, the CBF responses were not affected significantly by i.v. injections of BBB-impermeable muscarinic and nicotinic ACh receptor antagonists. The CBF response produced by moxibustion-like stimulation of a forepaw was also attenuated by BBB-permeable blockers, atropine, and mecamylamine. These results suggest that activations of both muscarinic and nicotinic ACh receptors in the parenchyma are important to produce CBF response by acupuncture- and moxibustion-like stimulation. Activation of both muscarinic and nicotinic ACh receptors in the