– Somatosensory stimuli including acupuncture modulate blood flow via the autonomic reflexes –

Shinjiro Yamaguchi
Acupuncture & Massage Research Information Center

Introduction

Somatosensory stimuli including acupuncture elicit reflex autonomic responses that affect functions in the cardiovascular system and other organs (Sato et al., 1997). An analysis of the neural mechanisms of somatically induced autonomic reflex responses (somato-autonomic reflex) is essential in developing a scientific understanding of the mechanism underlying the effects of acupuncture therapy.

This article reviews recent studies performed by Japanese researchers regarding vascular reflex responses induced by somatosensory stimuli including acupuncture.

Characteristics of somato-cardiovascular reflex

There has been great progress in research on cardiovascular responses induced by natural somatic stimuli using anesthetized animals in order to eliminate emotional factors. It has been shown that sympathetic rather than parasympathetic nerves play a major role in somato-cardiovascular reflexes. In somato-cardiovascular responses, the brain stem plays an important role as the reflex center. Although spinal segmental stimulation elicits spinal reflex components, such components are usually depressed by descending inhibitory pathways from the brain under a central nervous system (CNS) intact condition. When anesthetized rats are in a CNS-intact condition, somatic afferent stimulation of limbs is particularly effective in producing cardiovascular responses. Limb somatic afferent fibers seem to have specific synaptic connections to the CNS.

Effects of somatosensory stimuli on cerebral blood flow

Background

Recent studies by Sato and colleagues (Sato and Sato, 1992) have shown that cortical cerebral blood flow is regulated by intracranial nerves. Particularly, excitation of the cholinergic nerve fibers originating in the magnocellular nucleus of the basal forebrain (the nucleus basalis of Meynert; NBM) releases extracellular acetylcholine (Ach) in the cortex, resulting in an increase in cortical blood flow, independent of metabolic vasodilation.

Acupuncture-like stimulation

Uchida et al. (2000) demonstrated the effect of acupuncture-like stimulation for 1 min to various skin areas on cortical blood flow measured using a laser Doppler flowmeter in anesthetized rats. The results clearly showed that the increase in cerebral blood flow, independent of systemic blood pressure, elicited by acupuncture stimulation is a reflex response in which the afferent nerve pathway is composed of somatic groups III and IV afferent nerves, and efferent nerve pathway includes intrinsic cholinergic vasodilators originating in the NBM.

As proven by Hotta et al. (2002), ischemia-induced delayed death of rat cortical neurons can be protected by preventing a blood flow decrease in widespread cortices via NBM-originating vasodilative activation. Therefore, it appears that continuous acupuncture stimulation prevents cerebral infarction though its vasodilative effect in the cerebral cortex.

Effects of somatosensory stimuli on peripheral blood flow

Sympathetic reflex

The effect of electro-acupuncture stimulation (EAS) to a hindpaw (0.1-10 mA, 20 Hz, 30 s) on muscle blood flow measured by laser Doppler flowmetry and on mean arterial pressure (MAP) was investigated by Noguchi et al. (1999). EAS to a hindpaw at a strength sufficient to excite group III and IV afferent fibers, can produce a reflex increase and/or decrease in muscle blood flow. They clarified that two types of responses are induced passively by pressor response via a splanchnic sympathetic activity, and/or directly by an activation of muscle sympathetic nerves.

Are small vessels such as arterioles affected by somatic afferent stimulation including EAS? The authors' group (Takagi et al., 2005) investigated the

effects of EAS of the hindpaw and the dorsal Th13-L1 level area on the mesenteric microhemodynamics in anesthetized rats using an intravital microscope system. We observed that the hindpaw EAS evoked intensity-dependent pressor responses and an increase in blood flow velocity, measured by the dual-sensor method developed by the authors, in mesenteric precapillary arterioles, while the dorsal EAS evoked depressor responses and a decrease in blood flow velocity. Occasional but notable reflex vasoconstrictions in the mesenteric terminal arteriole by EAS of both sites were observable on the image under the intravital microscope. These vasoconstrictive responses were not affected by the administration of an alpha-adrenergic blocker. Our study directly demonstrated that hemodynamic changes at the level of precapillary arterioles accompanying EAS either on the hindpaw or the back, mainly depend on the changes of systemic arterial pressure regardless of stimulation current intensities. Moreover, the results in our study suggest some receptors other than alpha-adrenergic receptor might be involved in the mechanism of EAS-induced vasoconstriction in the mesenteric arteriole.

Sato et al. (1996) demonstrated that acupuncture-like simulation induced catecholamine secretion from the adrenal medulla via activation of the adrenal sympathetic nerves in anesthetized rats.

To examine whether such somatically induced catecholamine is effective on microvascular tone, the authors investigated the effects of 10 min (3 mA) of electrical stimulation of the dorsal skin area (Th5-12 level) on the mesenteric arterioles in anesthetized rats using an intravital microscope system (Yamaguchi et al., 2002). Electrical stimulation of the skin for 10 min evoked a decrease in the diameter of arterioles. In the adrenalectomized group, electrical stimulation of the skin for 10 min elicited a slight increase in the diameter (Fig. 1). It is therefore suggested that the constriction of the mesenteric precapillary arterioles induced by the stimulation for 10 min was mediated by humoral adrenaline and noradrenaline released by somato-adrenal medullary reflex.

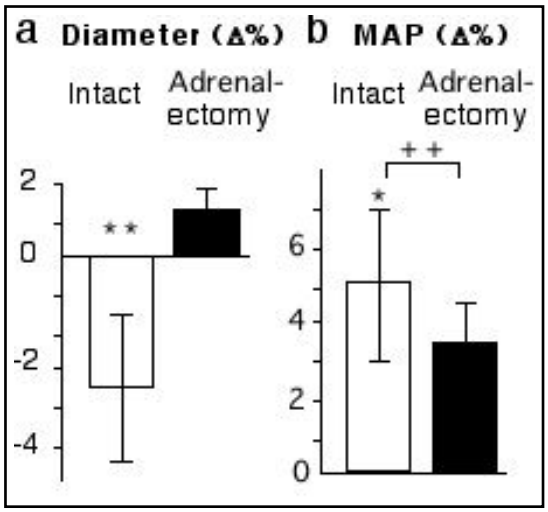

Figure 1: Effects of adrenalectomy on precapillary arteriolar constriction (a) and pressor response (b) induced by electrical stimulation (ES) of the back skin (3 mA, 20 Hz, intermittent, 10 min) in anesthetized rats. The open bar shows the responses to ES in the intact rats. The closed bar shows the responses induced by ES in the bilateral adrenalectomized rats. *p<0.05, **p<0.01; statistical significant is obtained between the pre-stimulus values and the values at 4-5 min (a) and 2-3 min (b) after onset of the stimulus. +p<0.05, ++p<0.01; statistical significance is expressed between responses in two groups. (Modified from Yamaguchi et al. 2002)

Nitric oxide

It is well known that nitric oxide (NO) is a physiologically active substance producing various functions. NO, especially, plays an important role in vasodilation in arterioles.

In the knee joint, blood flow is known to be modulated mainly by sympathetic postganglionic fibers, but recently the release or induction of NO synthesis in response to electrical stimulation has also been suggested. Therefore, direct observation of the microcirculation is needed to further understand the mechanism by which blood flow is regulated by somatic afferent stimulation. The author's group (Loaiza et al., 2002) observed the effects of EAS (5 mA, 0.5 ms, 5 Hz, 30 min) to the vastus medialis muscle on MAP and the knee joint microcirculation using a real-time confocal laser-scanning microscope system.

Significant and persistent increases in arteriolar diameter and MAP, were observed after EAS to the muscle. EAS to the vastus medialis in the presence of N(omega)-nitro-L-arginine methyl ester (L-NAME) produced a strong decrease in diameter of the knee joint arterioles under the baseline with a simultaneous increase in MAP. EAS to the skin did not produce changes in arteriolar diameter while a slight increase in MAP over the baseline occurred after the stimulaitons. EAS to the muscle after neuromuscular blockade did not produce significant changes in diameter, while an increase in MAP was still observed, which suggests that muscle contraction is required to produce vasodilatation (Fig. 2). These responses suggest that a dynamic balance between the autonomic nervous system and the release of NO is the primary mechanism mediating the EAS effects on knee joint microcirculation.

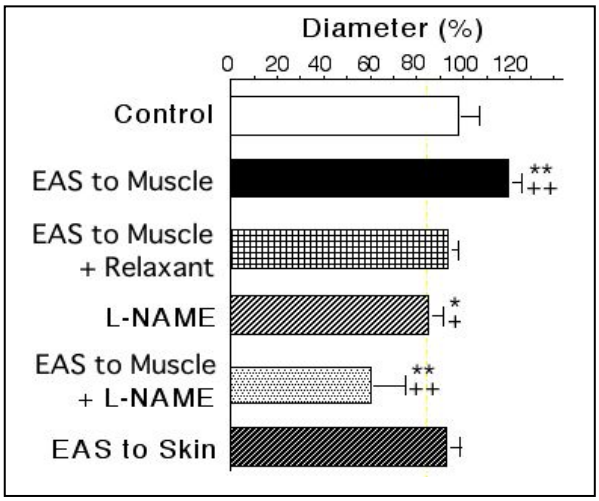

Figure 2: Summarized data on the changes in joint capsule arteriolar diameter in anesthetized rats. The values were registered at 30 min of observation in the control (non-stimulated) and L-NAME group and at the end of the stimulus in the elactro-acupuncture stimulation (EAS) to vastus medialis muscle, EAS to the muscle + L-NAME, EAS to the muscle + relaxant and EAS to skin groups. Statistical significance is indicated as *p<0.05, **p<0.01 when compared to the pre-stimulus values, and +p<0.05, ++p<0.01 when compared to the control group. (Modified from Loaiza et al. 2002)

Axon reflex

When an axon reflex is induced by cutaneous stimulation, the excited afferent terminal releases vasodilative substances, such as calcitonin gene-related peptide (CGRP).

The contribution of CGRP to antidromic vasodilation of skeletal muscle blood flow following electrical stimulation of muscle afferent was investigated by Sato and colleagues using anesthetized rats. They concluded that antidromic vasodilation in skeletal muscles following stimulation of unmyelinated C afferents in dorsal roots is independent of systemic blood pressure and is mediated essentially by CGRP. They described that this CGRP-related antidromic vasodilation is probably important in the clinical improvement of skeletal muscle blood flow caused by physical therapy such as acupuncture.

The authors assessed by measurement of two different hemodynamic parameters: muscle blood flow using a laser Doppler flowmeter; and the changes in diameter of the muscle arterioles observed directly using an intravital microscope system in order to examine the effects of electrical stimulation (5 V, 20 Hz, 30 s) to the saphenous nerve on microcirculation of the gracilis muscle in anesthetized rats (Loaiza et al., 2002). We found that ipsilateral nerve ES produced vasodilative responses in the muscle accompanied by increases in muscle blood flow independently of the sympathetic nerve activity. Furthermore, CGRP was found to be directly involved in the reflex neural regulation of the muscle microcirculation, which suggests the participation of an axon reflex mechanism (Fig.3).

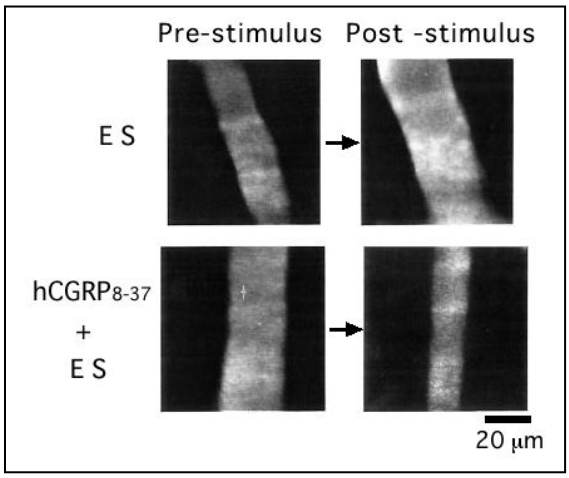

Figure 3: Effect of ipsilateral electrical stimulation (ES) of the saphenous nerve on gracillis muscle arteriolar diameter in the absence and presence of

topical CGRP8-37. Representative photographs of two different arterioles, observed pre- and post-stimulus are illustrated. (Modified from Loaiza et al. 2002)

Conclusions

1. The cerebral blood flow response induced by acupuncture-like stimulation of a forepaw in rats, independent of MAP, is a reflex response whose afferents are group III and IV somatic afferent fibers, and whose efferents are cholinergic fibers originating in the NBM.
2. The somatically induced peripheral circulatory regulation system consists of three types of mechanisms as follows.
   (1) Hemodynamics in the region of interest is affected by systemic circulatory changes induced by the somatic afferent stimulation.
   (2) The observed blood vessels are directly affected by activating the autonomic efferent nerve fibers including nonadrenergic, noncholinergic fiber that can release NO.
   (3) Vasodilative response induced by the CGRP through activating the primary afferent fibers (axon reflex).

These physiological findings may support the effectiveness of acupuncture therapy on patients with circulatory disturbances.

References

1. Sato A, Sato Y, Schmidt RF: The impact of somatosensory input on autonomic functions. Rev Physiol Biochem Pharmacol 130: 1-328, 1997
2. Sato A, Sato Y: Regulation of regional cerebral blood flow by cholinergic fibers originating in the basal forebrain. Neurosci Res 14: 242-274, 1992
3. Uchida S, Kagitani F, Suzuki A, Aikawa Y: Effect of acupuncture-like stimulation on cortical cerebral blood flow in anesthetized rats., Jpn J Physiol 50: 495-507, 2000
4. Hotta H, Uchida S, Kagitani F: Effects of stimulating the nucleus basalis of Meynert on blood flow and delayed neuronal death following transient ischemia in the rat cerebral cortex. Jpn J Physiol 52: 383-393, 2002
5. Noguchi E, Ohsawa H, Kobayashi S, Shimura M, Uchida S, Sato Y: The effect of electro-acupuncture stimulation on the muscle blood flow of the hindlimb in anesthetized rats, J Auton Nerv Syst 75: 78-86, 1999
6. Takagi K, Yamaguchi S, Ito M, Ohshima N: Effects of electroacupuncture stimulation applied to limb and back on mesenteric microvascular hemodynamics. Jpn J Physiol 55: 191-203, 2005. Epub 2005 Sep 7
7. Yamaguchi S, Ito M, Ohshima N: Effects of electrical stimulation of the dorsal skin on systemic and mesenteric microvascular hemodynamics in anesthetized rats. Jpn J Physiol 52: 257-65, 2002
8. Loaiza LA, Yamaguchi S, Ito M, Ohshima N: Electro-acupuncture stimulation to muscle afferents in anesthetized rats modulates the blood flow to the knee joint through autonomic reflexes and nitric oxide. Auton Neurosci. 97: 103-9, 2002
9. Sato A, Sato Y, Shimura M, Uchida S: Calcitonin gene-related peptide produces skeletal muscle vasodilation following antidromic stimulation of unmyelinated afferents in the dorsal root in rats. Neurosci Lett 283: 137-140, 2000.
10. Loaiza LA, Yamaguchi S, Ito M, Ohshima N: Vasodilatation of muscle microvessels induced by somatic afferent stimulation is mediated by calcitonin gene-related peptide release in the rat. Neurosci Lett 333: 136-40, 2002