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Review

Somatosensory regulation of resting muscle blood flow and physical therapy

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ABSTRACT

Somatosensory stimulation can affect skeletal muscle blood flow (MBF) at rest in anesthetized animals via pressor reflex response or antidromic and local vasodilation. Increase in MBF due to reflex pressor response occurs generally in the skeletal muscles of the entire body, while antidromic and local vasodilation are limited to the peripheral stimulation site. Since increased MBF improves several disorders (muscle stiffness, pain, etc.), it is reasonable to further explore the effective use of somatic stimulation in physical therapies, such as massage, acupuncture, anma, and shiatsu or acupressure, in treating skeletal muscle disorders.

1. Introduction

The skeletal muscles account for about half of a healthy person's total body mass. At rest, approximately 20% of cardiac output is directed to maintaining blood flow to the skeletal muscle (Fig. 1). The low skeletal muscle blood flow (MBF), at rest, is partly due to the tonic activity of sympathetic vasoconstrictors innervating the muscle blood vessels. During heavy exercise, 80% of the total blood flow will be channeled to the skeletal muscle to supply sufficient oxygen and nutrients. Metabolic and neural regulation coordinate the large MBF during exercise. There have been many studies on the muscle vasodilation mechanism during exercise.

On the other hand, the significance of vasodilation in skeletal muscle at rest is yet to be fully elucidated. Recent studies show that somatosensory stimulated vasodilation in resting skeletal muscle (Sato et al., 2000; Sandberg et al., 2003) could be clinically significant; for instance, it may improve painful disorders by physical procedure. Therefore in this article, we review studies of resting MBF investigated mostly in anesthetized animals. In the latter part, in light of these basic studies, we discuss how somatosensory-induced vasodilation can be clinically applied.

2. Neural control of skeletal MBF

At first, we review the neural control of MBF, mediated by sympathetic vasoconstrictors and vasodilators, as well as parasympathetic vasodilators.

2.1. Sympathetic vasoconstrictor

Sympathetic nerve activities innervating blood vessels of the mammalian skeletal muscle at rest can be measured indirectly by recording blood flow in anesthetized cats (Löfving, 1961; Johansson, 1962), and directly by recording electrical discharge in humans (Hagbarth and Vallbo, 1968) and anesthetized cats (Koizumi and Sato, 1972). Single unit recording has shown spontaneous discharge rates of 1.8 ± 1.2 impulses/s (mean ± SD) with some rhythmicity (Koizumi and Sato, 1972) (Fig. 1).

Integrative reflexes of sympathetic fibers in skeletal muscles, such as reflexes by baroreceptor, chemoreceptor, metaboreceptor and somatosensory receptor, involve brain stem pathways and supramedullary networks (Shoemaker et al., 2016).

Sympathetic vasoconstrictor fibers on the ends of blood vessels within the skeletal muscle continuously release noradrenaline (NA) from the nerve endings. Besides NA, adenosine triphosphate (ATP) and neuropeptide Y (NPY) can be co-released (Shoemaker et al., 2016). There are alpha- and beta-adrenergic receptors in muscle blood vessels. Under normal physiological conditions, NA activates the alpha-adrenergic receptor, and vasoconstriction is dominant in adrenergic transmission (Johnson, 1989; Shoemaker et al., 2016). Since the tonus of sympathetic adrenergic fibers is relatively high, the resting muscle blood vessels remain constricted; thus, the whole skeletal MBF of the body remains low in the resting state.

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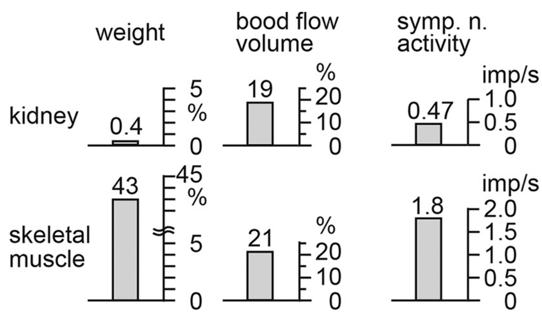

Fig. 1. Comparison in weight, blood flow volume, and sympathetic nerve activity of kidney and skeletal muscles at rest.
Weight and blood flow volume: human data based on Wade and Bishop (1962). Sympathetic nerve activity (single-unit): kidney (rat, Rogenes, 1982), skeletal muscle (cat, Koizumi and Sato, 1972).

2.2. Sympathetic vasodilator

Skeletal muscle vasodilation following neural stimulation in the frog was first reported by Gaskell in 1877. Subsequently, Bülbring and Burn (1935) found that vasodilation in a dog's hind limb skeletal muscles occurs after the sympathetic chain is stimulated. This result was confirmed by Folkow and Uvnäs (1948), who studied cats' hind limb muscles. Sympathetic vasodilators are cholinergic fibers, which activities are generated in the motor cortex and act on muscarinic receptors of the skeletal muscle blood vessel (Uvnäs, 1966). They do not have tonic activity, but are activated in emergency situations or emotional states, such as rage or fear, and anticipatory to muscular effort (Blair et al., 1959; Uvnäs, 1966; Bolme et al., 1970; Shepherd, 1983; Johnson, 1989; Ishii et al., 2017). However, several studies disagree with the existence of sympathetic cholinergic vasodilators in human muscle (see Joyner and Dietz, 2003; Shoemaker et al., 2016, for review).

2.3. Parasympathetic vasodilator

Ishii et al. reported evidence for parasympathetic cholinergic and noncholinergic vasodilator fibers in rat masseter skeletal muscle (Ishii et al., 2005).

3. Muscle vasodilation by somatosensory stimulation

Muscle vasodilation by sensory stimulation has been examined for over 100 years. For example, Bayliss (1901) reported that stimulation of sensory afferent fibers causes vasodilation in dogs' hind limb muscles. Stimulation of a somatic afferent nerve can increase blood flow of several tissues, such as the skin and muscle in anesthetized animals (Johansson, 1962; Webb-Peploe et al., 1972; Clement et al., 1973).

Somatosensory stimulation, such as pressure, heat, or painful stimulus to the skin, excites the afferent fibers in skin as well as the underlying muscles, joints, connective tissue, and blood vessels. All these modalities are together called somatovisceral sensibility, which consists of mechanoreception, chemoreception, thermoreception, and nociception, and the information is transmitted to the central nervous system (CNS) by afferent fibers. The population of unmyelinated afferent fibers which carry somatosensory information comprises nearly 50% of all cutaneous and muscle afferent fibers (Handwerker in Schmidt, 1995; Sato et al., 1997).

Acupuncture treatments are known to improve muscle stiffness of the neck and frozen shoulder (Mann, 1987; Lundeberg et al., 1988). In these muscles, accumulated metabolites excite unmyelinated muscle afferents, which may cause a reflex muscle vasoconstriction via a reflex increase in muscle sympathetic activity. Electro-acupuncture stimulation (EAS) to hind limbs or fore limbs has been known to excite various somatic afferent fibers in anesthetized rats (Toda, 1978; Kawakita and Funakoshi, 1982; Noguchi et al., 1999) and produce a variety of cardiovascular responses. Noguchi et al. (1999) showed that EAS to a hind paw excites Aδ (group III) and C (group IV) fibers in anesthetized rats, resulting in increased skeletal MBF in hind limbs, accompanied by an increase in systemic mean arterial pressure (MAP) (Fig. 2A). Following severance of splanchnic nerves, EAS induced only a slight increase in MAP and a decrease in MBF (Fig. 2B). The decrease in MBF was abolished by further severance of lumber sympathetic trunks which include sympathetic vasoconstrictors to the muscle biceps femoris (Fig. 2C). From these results, they concluded that EAS to a hind paw, with sufficient stimulus strength to activate the Aδ and C afferent fibers, can

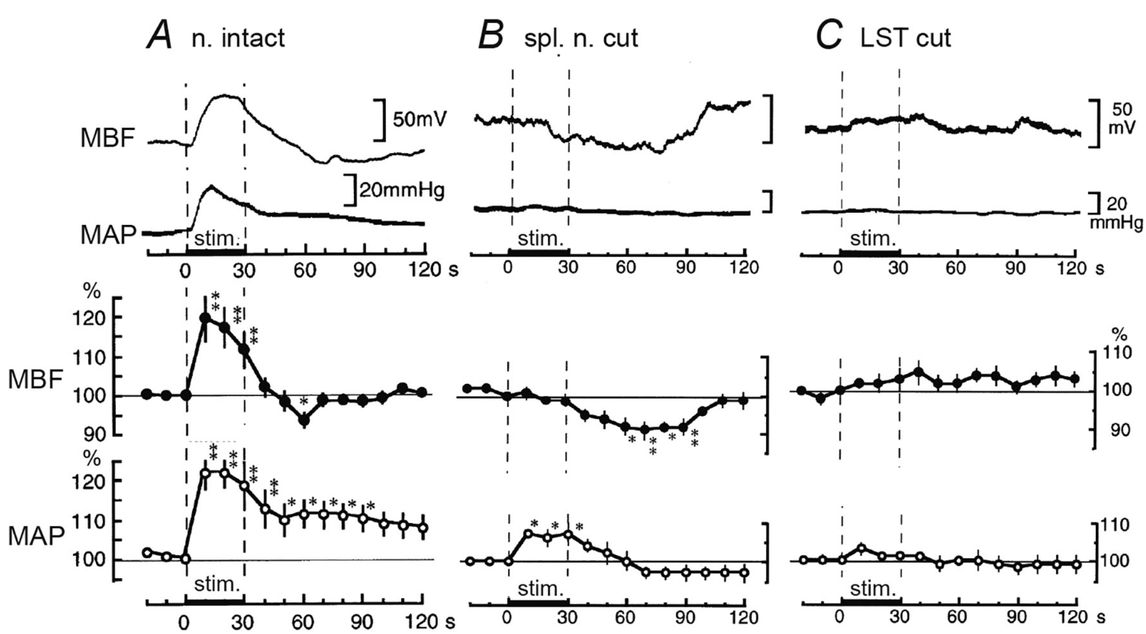

Fig. 2. Responses of the muscle blood flow (MBF) in the muscle biceps femoris and mean arterial pressure (MAP) to electroacupuncture stimulation of the hind paw at 10 mA, 20 Hz for 30 s in anesthetized rats. A: intact nerves. B: splanchnic nerves (which include sympathetic vasoconstrictors to the visceral organs) were sectioned bilaterally. C: splanchnic nerves and lumbar sympathetic trunks (LST) at the L2-L3 levels (including sympathetic vasoconstrictors to the muscle biceps femoris) were sectioned bilaterally. * $P < 0.05$, ** $P < 0.01$; significantly different from the pre-stimulus control values. (modified from Noguchi et al., 1999).

produce a reflex decrease in MBF via a reflex activation of the muscle sympathetic nerves. The decrease in MBF is overridden by an increase in MBF, which is caused passively by the reflex MAP pressor response after an increase in splanchnic sympathetic activity.

Depending on the stimulus modalities, tissues, and the area of the body, somatosensory stimulation produces pressor and depressor response (Sato et al., 1997; Mitchell and Schmidt, 1983). Massage-like stroking of the abdomen (Kurosawa et al., 1995) or manual acupuncture stimulation of a hind limb muscle (Ohsawa et al., 1995), produces a depressor response in anesthetized rats. Koizumi and Sato (1972) found that repetitive electrical stimulation of the Aβ (group II) and Aδ fibers of somatic afferent nerves in the hind limbs produces a long depression in the spontaneous activity of sympathetic fibers to skeletal muscle in anesthetized cats (Koizumi and Sato, 1972).

4. Antidromic muscle vasodilation

As mentioned, Bayliss (1901) reported vasodilation in dogs' hind limb muscles by sensory stimulation. This muscle vasodilation was triggered by antidromic excitation of the 7th lumber dorsal root without changes in MAP (Bayliss, 1901). Krogh (1920) and Krogh et al. (1922) observed vasodilation in the muscles of frogs' tongues and hind limbs by stimulating sensory afferent fibers occurring in an antidromic pathway. Hilton and Marshall (1980) confirmed these early studies in cat gastrocnemius muscle and found that antidromic stimulation of thin myelinated and unmyelinated somatic afferent fibers increases MBF, which may be partly mediated by prostaglandins; however, the possibility of prostaglandins in MBF has been disproved (Küçükhüseyin and Kayaalp, 1996; Shinbara et al., 2015).

Calcitonin gene-related peptide (CGRP) was discovered in 1982 by Amara et al., and this neuropeptide was soon found to be a potent vasodilator (Brain et al., 1985; Kawasaki et al., 1988). CGRP is now recognized as a vasodilator approximately 10-fold more potent than prostaglandins and 10–100 times more potent than other vasodilators, such as acetylcholine (ACh) and substance P (SP) (Russell et al., 2014). CGRP exists alone or coexists with other peptides, such as SP, in sensory nerves (Lundberg et al., 1985). Prolonged antidromic vasodilation in rat skin is caused by CGRP (Delay-Goyet et al., 1992). CGRP's release into skeletal muscle was reported by Sakaguchi et al. (1991), following repetitive antidromic electrical stimulation of the afferent fibers in the dorsal roots of anesthetized rats. The major source of CGRP was found to be the high-threshold sensory afferent terminals. Further, Pórszász and Szolcsányi (1994) demonstrated antidromic vasodilation in muscles in response to stimulation of dorsal roots and suggested a mediating role for capsaicin sensitive afferents in anesthetized rats. Yamada et al. (1997) observed muscle vasodilation following electrical stimulation of the sciatic nerve and proposed that CGRP released from nerve endings partly mediates vasodilation in anesthetized rats.

Sato et al. (2000) investigated CGRP's contribution to antidromic vasodilation of skeletal MBF by measuring the biceps femoris MBF in anesthetized rats. Repetitive, antidromic electrical stimulation of unmyelinated C fibers in ipsilateral dorsal roots at the 3rd–5th lumbar segments for 30 s caused an increase in MBF for 3–15 min without significant change in systemic arterial blood pressure (Fig. 3A, C). The MBF response was totally abolished by topical application of hCGRP (8-37), a CGRP receptor antagonist (Fig. 3B, C). From these data, Sato et al. 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. Consequently, they suggested that improvement of skeletal MBF following clinical physical stimulation to skeletal muscles, e.g. acupuncture stimulation, mechanical manipulative stimulation, and heat stimulation, may involve the antidromic CGRP-related vasodilation mechanism. In a subsequent experiment, Noguchi et al. (2009) showed CGRP-related local increase in MBF following heat stimulation in rat model. Shinbara et al. (2008, 2013) showed partial participation of CGRP in the local increase in MBF in rat model following acupuncture stimulation. In addition to CGRP, Shinbara et al. nominated other vasodilators, such as nitric oxide, adenosine, adenosine diphosphate (ADP), and ATP in somatosensory-induced muscle vasodilation (Shinbara et al., 2015, 2017; Nagaoka et al., 2016). Sandberg et al. (2003) showed an increase of MBF and skin blood flow following needle stimulation in healthy human subjects. In human cases, CGRP seems to be a potent mediator of increased blood flow via local vasodilation in the skeletal muscle or tissues by sensory stimulation (Sandberg et al., 2003; Neal and Longbottom, 2012; Lundeberg, 2013).

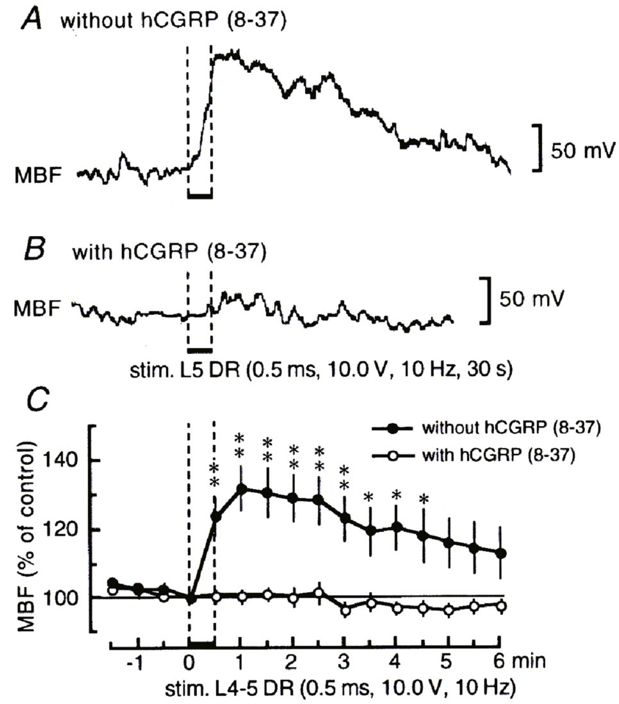

Fig. 3. CGRP's contribution to antidromic vasodilation of skeletal MBF by measuring biceps femoris MBF. A, B: Sample recording of MBF responses to antidromic electrical stimulation of the L5 dorsal root (DR) before (A) and 25 min after (B) topical application of hCGRP (8-37) (10^{-4} M). C: Summary of MBF responses to antidromic electrical stimulation of the L4–5 DR before (closed circles) and after (open circles) topical application of hCGRP (8-37). $^*P < 0.05$, $^{**}P < 0.01$; significantly different from the prestimulus control values. (from Sato et al., 2000).

5. Local muscle vasodilation

Besides neural control, we summarize the dilative property of skeletal muscle blood vessels, which have a considerable relation to neural control of MBF (Fig. 4A).

First of all, many smooth muscles can contract and dilate without neuronal activation. This property is of muscular origin and is known as myogenic tone.

Second, the influence of endothelial cells is important. The artery, which provides blood to skeletal muscles, consists of three different layers, i.e., outermost layer (connective tissue), middle layer (smooth muscle cells and elastic fibers), and innermost layer (endothelial cells). Among these cells, the endothelial cells have significant influence on smooth muscle dilation (Fig. 4B).

Substances such as ACh, ATP, SP, and CGRP, act on endothelial cells which release nitric oxide (NO) (Furchgott and Zawadzki, 1980; Ignarro et al., 1987; Palmer et al., 1987). Since NO is a strong vasodilator, these substances are called vasodilation substances. Vascular endothelial cells also release NO following mechanical stimulation of blood flow (Baratchi et al., 2017). Namely, shear stress generated by blood flow

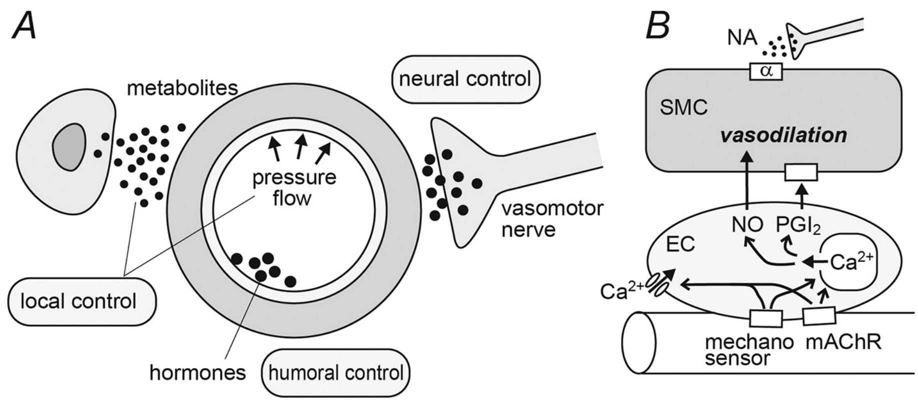

Fig. 4. Schematic diagram showing the main vasodilators controlling arteriolar diameter in skeletal muscle.
A: Neural control, by neurotransmitters released from vasomotor nerves (NA, ACh, CGRP, etc.); Hormonal control by hormones in the bloodstream (adrenaline, atrial natriuretic peptide, etc.); Local control by metabolites (CO_2, H^+, K^+, lactate, ATP, adenocine, etc.), myogenic response to distension, and endothelium-dependent regulation (NO, PGI_2, etc.).
B: Role of endothelial cells in regulating vascular tone. Activation of mechanosensors and mAChRs on the endothelial cell membrane triggers release of several vasodilators from endothelial cells. EC: endothelial cell, SMC: smooth muscle cell, NA: noradrenaline, NO: nitric oxide, PGI_2: prostacyclin, mAChR: muscarinic acetylcholine receptor.

triggers Ca^{2+} release inside endothelial cells and activates NO synthase, leading to smooth muscle vasodilation (Yamamoto et al., 2018). Besides NO, prostaglandin I_2 (PGI_2, prostacyclin) is also significant.

Third, local metabolic substances are also important. Decrease of O_2 or increase of CO_2 in the tissue or blood can dilate the vascular smooth muscle (Korthuis, 2011).

6. Hormonal control of skeletal MBF

Circulating hormones, such as adrenaline and atrial natriuretic hormone, dilate the vascular smooth muscle (Fig. 4A; Laragh and Atlas, 1988; Korthuis, 2011). Somatic stimulation such as EAS to a hind paw produces an increase in the adrenaline secretion rate from the adrenal gland in anesthetized rats (Sato et al., 1997; Mori et al., 2000). The increased circulating adrenaline by somatic stimulation may influence skeletal MBF in the body.

7. Clinical application of somatosensory induced muscle vasodilation

Physical therapy, such as active or passive movement of the muscle, massage, acupuncture, heat therapy, or other kinds of cutaneous/muscle stimulation, can increase tissue blood flow and bring positive effects to the body. Clinical reports and animal studies show that physical stimulation increases blood flow in the cerebral cortex, skin, peripheral nerves or skeletal muscles (Sato et al., 1997). Increased MBF by physical therapy may contribute to improved muscle stiffness (as well as frozen muscle pain relief). We reviewed the detailed mechanisms of increased MBF at rest by somatosensory stimulation.

Increase in MBF due to increased arterial blood pressure is thought to occur generally in the skeletal muscles, and improves muscle stiffness in the entire body. Of note, this vasodilation cannot be applied to patients suffering from cardiovascular diseases, e.g., severe hypertension, unstable angina, arrhythmia. On the other hand, antidromic or local vasodilation, occurring only locally, can be used for patients who have muscle stiffness, muscle pain and are suffering from cardiovascular diseases. It is quite difficult to regulate MBF by our own minds, but somatic stimulation or, in other words, physical therapies, e.g., massage, acupuncture, anma, shiatsu or acupressure, can affect MBF via antidromic or local vasodilation. There are two points to be emphasized: antidromic vasodilation occurs with little exercise, namely in the resting state, and occurs independently of arterial pressure. Therefore, physical stimulation to the local part of the body can be applied in patients who have been confined to their beds for a long time or suffer from cardiovascular diseases.

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