HIGHLIGHTED TOPIC | Skeletal and Cardiac Muscle Blood Flow

Neural control of muscle blood flow during exercise

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Thomas, Gail D., and Steven S. Segal. Neural control of muscle blood flow during exercise. J Appl Physiol 97: 731–738, 2004; 10.1152/japplphysiol.00076.2004.—Activation of skeletal muscle fibers by somatic nerves results in vasodilation and functional hyperemia. Sympathetic nerve activity is integral to vasoconstriction and the maintenance of arterial blood pressure. Thus the interaction between somatic and sympathetic neuroeffector pathways underlies blood flow control to skeletal muscle during exercise. Muscle blood flow increases in proportion to the intensity of activity despite concomitant increases in sympathetic neural discharge to the active muscles, indicating a reduced responsiveness to sympathetic activation. However, increased sympathetic nerve activity can restrict blood flow to active muscles to maintain arterial blood pressure. In this brief review, we highlight recent advances in our understanding of the neural control of the circulation in exercising muscle by focusing on two main topics: 1) the role of motor unit recruitment and muscle fiber activation in generating vasodilator signals and 2) the nature of interaction between sympathetic vasoconstriction and functional vasodilation that occurs throughout the resistance network. Understanding how these control systems interact to govern muscle blood flow during exercise leads to a clear set of specific aims for future research.

THE STRONG POSITIVE RELATIONSHIPS among exercise intensity, oxygen consumption, and blood flow illustrate that the vascular supply of oxygen to active skeletal muscle is related intimately to the somatic neural recruitment of motor units (Fig. 1). The manifestation of coupling between blood flow and energy expenditure in isolated muscles as well as in limbs of animals and humans indicates that the mechanisms governing this coupling are intrinsic to skeletal muscle and its vascular supply. In essence, the contraction of skeletal muscle fibers relaxes vascular smooth muscle cells to increase capillary perfusion and vascular conductance. At the same time, activity of the sympathetic division of the autonomic nervous system exerts extrinsic control over the skeletal muscle vasculature, primarily through the release of norepinephrine to cause smooth muscle contraction. This brief review considers the vasodilator responses effected through the activation of muscle fibers in light of the vasoconstrictor signals generated by sympathetic nerve activity (SNA). Our goals are to define how and where these respective control systems interact to govern muscle blood flow during exercise, to help resolve contradictory findings in the literature, and to identify specific aims for future research.

VASCULAR RESISTANCE OF SKELETAL MUSCLE

A large fraction of the total vascular resistance across skeletal muscle resides in the small muscular arteries that are located external to the tissue. These “feed” arteries arise from larger conduit vessels (e.g., femoral and brachial arteries) that conduct the blood to peripheral tissues with minimal energy loss. Feed arteries are positioned anatomically to control the total amount of blood entering the muscle and can present as much as half of the total resistance to blood flow for resting muscle (14). Furthermore, because feed arteries are external to the muscle, they are not directly exposed to vasoactive stimuli arising from skeletal muscle fibers. On entering a muscle, feed arteries give rise to arteriolar networks, which govern the distribution and magnitude of blood flow within the muscle. Terminal arterioles are the final branches of the microvascular resistance network and control the perfusion of capillaries with red blood cells (17, 84).

In the absence of sympathetic nerve activity, vasomotor tone in the resistance network of skeletal muscle at rest represents the interaction between myogenic constriction of smooth muscle cells in response to blood pressure (16) and the modulating influence of the endothelium, e.g., through release of NO in response to luminal shear stress exerted by the flowing blood (15). Under these conditions, the resting tone of resistance vessels is typically 50–70% of their maximal diameter (40, 94). The initial vascular response to motor unit activation is...
A rich adventitial plexus of sympathetic nerve fibers surrounds feed arteries and extends throughout the arteriolar network, including its terminal branches. Nevertheless, norepinephrine released onto nearby arterioles can diffuse to and constrict venular smooth muscle cells. Sympathetic nerves also innervate large and small veins, with constriction of postcapillary vessels serving to promote the return of venous blood to the heart.

A limitation to studying the role of sympathetic innervation in whole muscles of animals and intact limbs of humans is that the precise location and extent of vasoconstriction within the resistance network can be difficult to ascertain. Thus complementary studies in rodents and cats have used intravital microscopy to determine specific segmental vasomotor responses to SNA. In resting muscles, sympathetic nerve stimulation constricts all resistance vessels. Increasing the stimulus frequency of SNA from 0.5 Hz through 16 Hz produces a full range of vasoconstriction mediated primarily through the release of norepinephrine (5, 21, 50, 60, 95). However, there is a rank order of responsiveness to SNA that varies with location in the resistance network. For example, in the rat cremaster muscle, small arterioles readily constrict at all frequencies of SNA, with maximal responses obtained at 4 Hz, whereas large arterioles constrict progressively over the entire frequency range through 16 Hz (60). In the hamster retractor muscle, the absolute decreases in vessel diameter during SNA are largest in feed arteries and progressively smaller in first- through third-order arterioles. However, when these responses to SNA are normalized to the respective resting diameters, the magnitude of vasoconstriction is largest in the distal branches and smallest in the proximal branches (50, 95).

SYMPATHETIC INNERVATION OF SKELETAL MUSCLE VASCULATURE

The autonomic regulation of skeletal muscle blood flow is dominated by the activity of the sympathetic nervous system. A rich adventitial plexus of sympathetic nerve fibers surrounds feed arteries and extends throughout the arteriolar network, including its terminal branches (26, 31, 50). However, neither capillaries nor venules in skeletal muscle are directly innervated (26). Nevertheless, norepinephrine released onto nearby arterioles can diffuse to and constrict venular smooth muscle cells (49). Sympathetic nerves also innervate large and small veins, with constriction of postcapillary vessels serving to promote the return of venous blood to the heart.

Dilation of the terminal arterioles (17, 84), which promotes the extraction of available oxygen (2) by increasing the surface area for diffusion through capillary recruitment (44). However, as metabolic demand increases, greater total delivery of oxygen is required to support the aerobic production of ATP. This increase in total blood flow is achieved by the progressive dilation of successively larger and more proximal branches of the resistance network (27, 30). Indeed, direct observations have confirmed that as motor unit recruitment and work intensity increase, vasodilation “ascends” progressively from distal arterioles, through intermediate branches, and into proximal arterioles and feed arteries (94, 98). The initiation of ascending vasodilation has been linked to muscle fiber recruitment (94, 98) and is mediated by cell-to-cell conduction of a vasodilator signal along the vessel wall (37, 78).

SYMPATHETIC ESCAPE IN RESTING MUSCLE AND THE DISTRIBUTION OF ADRENORECEPTOR SUBTYPES

When SNA is sustained (2–3 min) in resting muscle, distal arterioles have a tendency to “escape” from sympathetic vasoconstriction and exhibit a secondary relaxation (5, 27, 60). In contrast, vasoconstriction is sustained in proximal arterioles and feed arteries (50, 95). Such regional differences in the ability to escape from sympathetic vasoconstriction are even more dramatic during exercise and are discussed later in this review. One variable contributing to these regionally heterogeneous responses to SNA may be the differential distribution of postjunctional α1- and α2-adrenoreceptors on smooth muscle cells within the resistance network. In the rat cremaster muscle, constriction of smaller, distal branches of the arteriolar network is controlled mainly by α2-adrenoreceptors, which appear to be relatively more susceptible to metabolic inhibition (3, 24). In contrast, constriction of larger proximal arterioles and feed arteries are controlled by both α1- and α2-adrenoreceptors (24). Whether the microcirculation of other muscles in animals or in humans is characterized by similar spatial distributions and functional roles of the α-adrenoreceptor subtypes is not known and requires further study. However, findings from a recent study in which α-adrenoreceptor antagonists were infused into the forearm of conscious human subjects indicate that both α1- and α2-adrenoreceptors contribute to the component of basal vasomotor tone that is caused by tonic SNA (19).

There are three recognized subtypes of α1-adrenoreceptors (α1A, α1B, α1D) and of α2-adrenoreceptors (α2A/D, α2B, α2C) (32). However, the relative contributions of each receptor subtype to sympathetic vasomotor responses in skeletal muscle have yet to be defined, as do the signaling pathways through which they exert their respective effects in the microcirculation of skeletal muscle. Many vessels express more than one α-adrenoreceptor subtype, and there may be redundancy in respective signaling events, making it difficult to dissect func-
tional roles for individual receptor subtypes by use of the pharmacological tools presently available. Nevertheless, selective receptor agonists and antagonists have linked constrictor responses of large arterioles in the rat cremaster muscle to α₁B- and α₂A/2B-adrenoreceptors (85). An alternative approach to define the role of respective vascular adrenoreceptors is to study mice that have been genetically engineered to selectively eliminate one or more of these receptor subtypes (67). In turn, findings from transgenic animals can provide valuable new insight for defining and investigating vasoactive signaling pathways in humans (73, 88).

ACTIVATION OF MUSCLE SYMPATHETIC NERVES DURING EXERCISE

Physical exercise presents a potent stimulus to the autonomic nervous system, decreasing parasympathetic nerve activity while enhancing SNA, which increases with the intensity of contractile activity and with the mass of active muscle (1, 48, 77, 96). The effect of exercise to increase SNA is mediated in part by the parallel activation of central somatotomotor and sympathetic pathways (central command) and by reflexes that arise from stimulation of mechanically and metabolically sensitive afferent nerve endings in the exercising muscles (exercise pressor reflex) (55). Both of these mechanisms also are implicated in the resetting of the arterial baroreflex to operate around a higher arterial pressure during exercise, which may further contribute to the sympathoexcitatory response (51, 63). This resetting occurs without a change in sensitivity so that the baroreflex continues to modulate SNA in response to changes in blood pressure during exercise (25, 63, 76). These respective signaling pathways evoke specific changes in regional autonomic outflows during exercise, such that central command increases sympathetic discharge to skin and the heart (96, 97), whereas stimulation of the muscle metaboreceptors increases sympathetic discharge to both resting and exercising skeletal muscle (36, 48, 75, 96). Taken together, these findings raise an important question: what is the functional consequence of increased sympathetic nerve activity in exercising muscle?

CONSTITUTIVE SYMPATHETIC VASOCONSTRICTION IN EXERCISING MUSCLES

A dramatic illustration of the importance of sympathetic vasoconstriction in the integrated hemodynamic response to exercise in humans is the classical observation that patients with autonomic failure cannot maintain arterial pressure during exercise, even when performing light activity while supine (79). The lack of sympathetic vasoconstriction in visceral organs and resting skeletal muscle likely contributes to this idiopathic hypotensive response to exercise, yet the inability to constrict the vasculature in active muscle may also play an important role. Blood flow to exercising muscle increases on interruption of sympathetic outflow or antagonism of α-adrenoceptors, demonstrating ongoing sympathetic restraint of blood flow to the active muscles (6, 8, 41, 58, 61). Furthermore, activation of postjunctional α-adrenoceptors by SNA or with α-agonist infusion reduces blood flow in exercising muscles, demonstrating the potential for sympathetic control of muscle blood flow during muscular activity (20, 41, 42, 59, 68, 69, 71, 72, 80, 83, 86, 90, 91, 93, 95). During dynamic exercise of the knee extensors in humans, peak blood flow in the active muscle can increase up to 100-fold above resting values (2). Thus, during intense whole body exercise, restriction of blood flow by increasing SNA to active muscles (in addition to other vascular beds) may be integral to prevent this large capacity for vasodilation from surpassing the ability of cardiac output to maintain systemic arterial blood pressure (70). However, blood flow in exercising muscles generally increases despite concomitant sympathoexcitation. This raises another key question: is the responsiveness of the resistance vasculature to SNA altered in exercising muscle?

IS SYMPATHETIC VASOCONSTRICTION MODULATED IN EXERCISING MUSCLE?

The interaction between functional vasodilation and sympathetic vasoconstriction in exercising muscle has long been a subject of investigation (10). As early as 1930, Rein (64) reported that reflex activation of sympathetic nerves decreased blood flow to a greater extent in resting vs. exercising dog hindlimb. In 1962, Remensnyder et al. (65) coined the term “functional sympatholysis” to describe the markedly reduced vasoconstrictor responses that they observed in exercising muscle in response to activation of sympathetic nerves or local intra-arterial infusion of norepinephrine. However, perusal of the literature indicates that functional sympatholysis has not been a consistent finding. Overall, a continuum of changes in vascular responsiveness to SNA in exercising muscle has been reported, ranging from well-preserved vasoconstriction to complete inhibition of vasoconstriction (20, 35, 41, 42, 59, 66, 68, 71, 72, 80, 83, 86, 87, 90, 91, 93, 95). In retrospect, these inconsistent findings are not surprising because the measured vascular responses are influenced by the experimental preparation, the nature and intensity of the vasoconstrictor stimulus, as well as the mode, intensity, and duration of the exercise stimulus. These factors, alone and in combination, have varied considerably among studies. Thus the literature contains disparate conclusions regarding the ability of SNA to produce vasoconstriction in active muscle.

A key factor affecting the interpretation of some of these studies is the use of resistance to quantify vasomotor responses (70). It is difficult to compare changes in resistance between resting and exercising skeletal muscle because resistance (pressure/flow) is inversely and therefore nonlinearly related to flow (47, 57). Thus a given change in blood flow will produce a much smaller change in calculated resistance when superimposed on a high baseline flow vs. a low baseline flow, which leads to an underestimation of the true magnitude of the vascular response under high-flow conditions. In contrast, vascular conductance (flow/pressure) is related linearly to blood flow. In this case, a given change in flow produces the same change in conductance irrespective of the baseline level of flow. However, even though conductance provides a more accurate assessment of vascular responsiveness when baseline flows differ, it does not solve all of the problems associated with comparing responses between conditions of low and high muscle blood flows.

Another key concern is whether vasomotor responses are expressed as absolute or relative changes from baseline. For example, when a given increase in SNA evokes the same absolute decrease in conductance in resting and exercising muscle, the relative decrease is smaller in exercising muscle.
MECHANISMS UNDERLYING FUNCTIONAL SYMPATHOLYSIS

During exercise, sympathetic vasoconstriction is diminished in the active muscles but preserved in the inactive muscles (65, 87). This regional selectivity indicates that, akin to the intrinsic coupling between muscle fiber recruitment and blood flow described in the introduction, functional sympatholysis is mediated by local events that are confined to the active muscles and not by humoral factors carried in the systemic circulation (Fig. 2). Our understanding of the nature of these local events has been facilitated greatly in recent years by the work of numerous investigators using a variety of experimental models.

Key findings from these experiments are now summarized in light of future directions for research efforts.

**Sympathetic neuromuscular transmission.** The attenuation of sympathetic vasoconstriction may occur prejunctionally by reducing neurotransmitter release as well as postjunctionally by interfering with its actions on smooth muscle cells. A prejunctional mechanism is suggested by studies in which exercise attenuated the vasoconstrictor response to SNA but not to the infusion of norepinephrine (11). Remarkably, little is presently known about the ability of exercise to modulate the release, reuptake, or metabolism of sympathetic neurotransmitters. In contrast, a role for a postjunctional mechanism is supported strongly by studies in both animals and humans showing attenuated vasoconstrictor responses to exogenously administered norepinephrine or other α-adrenoceptor agonists in exercising muscle (3, 4, 9, 20, 65, 68, 87, 88). These findings collectively suggest that a major locus of functional sympatholysis is at the level of the postjunctional vascular α-adrenoceptors and/or their underlying intracellular signaling pathways in smooth muscle cells.

It is unlikely that β-adrenoceptors play a significant role in functional sympatholysis because their blockade has no effect on functional sympatholysis in mice (89) and the vasodilation produced by infusion of the β-agonist isoproterenol in resting muscle does not attenuate sympathetic vasoconstriction in rats (86). In addition to norepinephrine, sympathetic nerves also release ATP, which causes vasoconstriction by activating P2X purinoreceptors. A recent study in dogs suggests that P2X purinoreceptor vasoconstriction also is attenuated in exercising muscle (7). Whether similar mechanisms modulate P2X purinoreceptor and α-adrenoceptor vasoconstriction in active muscle remains to be determined.

**Spatial relationships.** The interaction between muscle contraction and SNA in controlling vessel diameter is graded with the intensity of the respective stimuli and with the location of vessel branches within the resistance network (27, 52, 95). In
contracting muscle of cats and hamsters, the vasoconstrictor response to SNA is attenuated to a greater extent in distal vs. proximal resistance microvessels (27, 95). The physiological importance of this proximal shift in resistance, from downstream to upstream arterioles, is that the dilation of distal vessels promotes maximal extraction of oxygen when flow is restricted in proximal segments. In consonance with these observations, the vasoconstriction mediated by \( \alpha_2 \)-adrenoreceptors is more susceptible to attenuation than that of \( \alpha_1 \)-adrenoreceptors in exercising muscle of rats and dogs (3, 9, 87), which closely corresponds to the preferential expression of \( \alpha_2 \)-adrenoreceptors on the distal arterioles described earlier for the rat cremaster muscle (24). In humans, a greater susceptibility of \( \alpha_2 \)- vs. \( \alpha_1 \)-adrenoreceptor-mediated vasoconstriction to attenuation is apparent in exercising leg muscles (100) but not in exercising forearm muscles (68). Other factors that may contribute to regional differences in microvascular reactivity in exercising muscle include differences in vessel wall stress (28), the nature of smooth muscle coupling to endothelium (74), and physical proximity to vasodilator metabolites.

Temporal aspects. Both motor unit recruitment and SNA increase with exercise; however, this synchrony has been difficult to study with experimental models. Therefore, in most studies examining functional sympatholysis, the vasoconstrictor stimulus is superimposed during steady-state exercise, which precludes evaluation of the time required for muscle contractions to modulate sympathetic vasoconstriction. Two recent studies in humans in which SNA was increased before the start of exercise suggest that sympathetic vasoconstriction may be attenuated within the first 30 s of muscle contractions (18, 92). Studies in dogs have also found that sympathetic vasoconstriction was reduced during contractions of durations as brief as 4 s (43) and that the modulation of vasoconstriction in active muscle was transient, paralleling increases in arterial \( K^+ \) concentration, but not \( H^+ \) concentration or osmolality (4).

In light of recognized differences in the mediators responsible for the onset vs. maintenance of functional vasodilation (33), these findings raise the question whether different mechanisms modulate sympathetic vasoconstriction during the course of an exercise bout. Additional work is needed to resolve such “components” of functional sympatholysis.

Metabolic mechanisms. Because functional sympatholysis is confined to the active muscles and is graded to the intensity of the exercise, the search for the underlying mechanisms has focused primarily on local factors related to changes in muscle metabolism. Approaches commonly used to identify potential mechanisms include 1) establishing temporal associations between metabolite concentrations and functional sympatholysis; 2) determining whether sympathetic vasoconstriction in resting muscle is attenuated by mimicking exercise-induced changes in the local metabolic environment; and 3) determining whether functional sympatholysis is impaired either by inhibiting the production of particular metabolites in active muscle or the action of these metabolites on specific cellular signaling pathways. The regulation of smooth muscle cell contraction during SNA is summarized briefly first for reference.

Activation of \( \alpha \)-adrenoreceptors causes contraction of vascular smooth muscle by a depolarization-induced increase in intracellular \( Ca^{2+} \) that is derived from the extracellular fluid through voltage-dependent L-type \( Ca^{2+} \) channels and internally from the sarcoplasmic reticulum via inositol 1,4,5-trisphosphate receptors (32, 53). Smooth muscle contraction also can be altered independent of \( Ca^{2+} \) via thin-filament regulation and phosphorylation of various regulatory proteins (82, 99). Whereas \( \alpha_1 \)-adrenoreceptor signaling mobilizes both intra- and extracellular \( Ca^{2+} \), \( \alpha_2 \)-adrenoreceptors rely mainly on extracellular \( Ca^{2+} \) (53, 54). Thus contraction mediated by \( \alpha_2 \)-adrenoreceptors is susceptible to modulation by events that preferentially inhibit influx of extracellular \( Ca^{2+} \). One such event may be the activation of membrane \( K^+ \) channels, which hyperpolarize smooth muscle cells, thereby reducing \( Ca^{2+} \) entry through the voltage-dependent \( Ca^{2+} \) channels (39).

During muscle contraction, \( K^+ \) is released from the active skeletal muscle cells. Increases in extracellular \( K^+ \) concentration ([\( K^+ \])\text{cell} \) can promote smooth muscle hyperpolarization by activating inward-rectifying \( K^+ \) channels and stimulating \( Na^+\text{-}K^+ \) pump activity in the plasma membrane (62). These actions of elevated [\( K^+ \])\text{cell} \) may explain the impaired sympathetic vasoconstriction observed in the resting skeletal muscle of dogs perfused with blood made hyperkalemic to reflect the exercise-induced increase in [\( K^+ \])_o (4, 11). Alternatively, increased [\( K^+ \])_o may act to inhibit norepinephrine release from sympathetic nerves. Of the various \( K^+ \) channels expressed in vascular smooth muscle, the ATP-sensitive \( K^+ \) (\( K_{\text{ATP}} \)) channel is uniquely regulated by cellular metabolism and is activated by hypoxia, ischemia, acidosis, and by endogenous vasodilators such as prostacyclin, adenosine, and NO (62). Pharmacological activation of \( K_{\text{ATP}} \) channels has a greater inhibitory effect on the vasoconstrictor response to \( \alpha_2 \)- vs. \( \alpha_1 \)-adrenoreceptor activation (85, 86), making this an attractive candidate for mediating functional sympatholysis. Indeed, \( K_{\text{ATP}} \) channel blockade has been shown to enhance sympathetic vasoconstriction in the contracting hindlimb of rats (86) and augment spontaneous vasomotor tone in arterioles of the hamster cremaster muscle (38). However, a concern in defining the role of specific ion channels in the regulation of vascular resistance is resolving which of the cell types expressing the channel of interest mediates the vascular response. For example, \( K_{\text{ATP}} \) channels are expressed in smooth muscle, endothelial cells, and skeletal muscle (62). Although this resolution is difficult to achieve by conventional pharmacological interventions, such limitations open the doors for selective genetic and molecular interventions.

Of the numerous metabolic signals generated in exercising muscle, only a few have been examined as potential mediators of functional sympatholysis. At present, neither adenosine nor prostaglandins appear to be obligatory for functional sympatholysis (20, 34, 69, 90, 93). In contrast, a study in humans has implicated local tissue hypoxia as an important factor in the attenuated vasoconstrictor response to SNA in exercising muscle (34). This effect of hypoxia may be enhanced by physiologically relevant increases in [\( K^+ \])_o (81), indicating the potential for additive or synergistic effects of metabolic signals on vascular regulation in exercising muscle. Another factor that is reported to mediate functional sympatholysis in rodents (88–90) and in some (13, 73), but not all (20), human studies is NO. The predominant source of NO that modulates sympathetic vasoconstriction appears to be the neuronal isoform of NO synthase (29, 88, 89), which is abundantly expressed in skeletal muscle fibers. NO may act to antagonize sympathetic vasoconstriction by a variety of mechanisms such as facilitating \( K_{\text{ATP}} \) channel activation (56, 90) or reducing phosphory-
lation of regulatory myosin light chain (29), which is a key determinant of smooth muscle contraction (99).

Additional mechanisms for modulating sympathetic vasoconstriction. Negative feedback from the endothelium (e.g., NO release) during α-adrenoceptor activation of adjacent smooth muscle cells can attenuate sympathetic vasoconstriction in isolated arterioles (22, 101). Stimulation of endothelial cells can also produce smooth muscle cell hyperpolarization through release of autacoids that activate K⁺ channels in smooth muscle (12). Furthermore, the conduction of vasodilatation can attenuate sympathetic vasoconstriction (45), with hyperpolarization initiated and conducted along the endothelium and into the surrounding smooth muscle cells through myoendothelial gap junctions (23, 78). These signaling pathways provide alternative mechanisms through which exercise-induced increases in metabolites and blood flow can influence smooth muscle contraction. Although many of these regulatory events have been defined in isolated vessels and cellular preparations, a great deal remains to be learned with respect to how and where vasoactive signals produced during exercise actually modulate the ability of SNA to produce vasoconstriction.

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

There is growing consensus that, in both animal and human skeletal muscle, the vasoconstrictor response to activation of sympathetic nerves is attenuated during the activation of somatic motor nerves. Nevertheless, a great deal remains to be learned about how these two neural control systems interact to facilitate the coupling of muscle blood flow to the metabolic demand of active motor units. Issues that have yet to be studied systematically include (but are not limited to) the roles of α-adrenoceptor subtypes, skeletal muscle fiber types, active muscle mass, aging, and training status. In accord with the regulation of functional hyperemia (33, 46), it is likely that the modulation of sympathetic vasoconstriction by exercising muscle does not depend on any single mechanism but reflects the spatial and temporal interactions of multiple signaling events that work in concert to modulate vascular responsiveness. Furthermore, the findings that functional sympatholysis is impaired in several diseases, including muscular dystrophy (73, 88) and experimental heart failure (91), lead to the hypothesis that derangements of sympathetic neural control may contribute to the exercise intolerance observed in these and other pathophysiological conditions. Innovative approaches in both animals and humans are required to address these unresolved issues and to fully appreciate the integrative nature of the interaction between local vasodilatory factors and sympathetic vasoconstrictor activity in exercising muscle.

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