The Paradox of Sympathetic Vasoconstriction in Exercising Skeletal Muscle

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BUCKWALTER, J.B., and P.S. CLIFFORD. The paradox of sympathetic vasoconstriction in exercising skeletal muscle. *Exerc. Sport Sci. Rev.*, Vol. 29, No. 4, pp. 159–163, 2001. *Is there sympathetic vasoconstriction in exercising skeletal muscle? Although convincing evidence exists that demonstrates vasoconstriction in active muscle, the proposition that the sympathetic nervous system constricts skeletal muscle during exercise poses a paradox, given the robust vasodilation that occurs in muscle during exercise. Ultimately, muscle perfusion is a balance between metabolic vasodilation and sympathetic vasoconstriction.* **Keywords:** blood flow, blood pressure, autonomic nervous system, adrenergic receptors, contraction, sympatholysis

INTRODUCTION

At the onset of exercise, substantial cardiovascular adjustments are needed if the bout of exercise is to continue for more than a few seconds. The increase in metabolism in the contracting muscle necessitates an increase in oxygen delivery, which in turn requires an abrupt increase in cardiac output (characterized by an increase in heart rate and stroke volume) and pronounced dilation in the vasculature of exercising skeletal muscle. The proportion of cardiac output directed toward exercising and nonexercising tissue must be reapportioned such that active skeletal muscle receives the vast majority of cardiac output. Skeletal muscle, which receives 10%–20% of cardiac output at rest, may receive as much as 85% of cardiac output during maximal exercise. In contrast, the kidneys (as an example of nonexercising tissue), which receive approximately 20% of cardiac output at rest, receive only 1%–2% of cardiac output during maximal exercise. The sympathetic nervous system is essential for this redistribution of cardiac output because an increase in sympathetic outflow shunts blood flow away from nonexercising tissue and toward exercising skeletal muscle to meet the increased oxygen demands of the contracting muscle (12). Though the sympathetic nervous system is known to cause vasoconstriction in nonexercising tissues, does it also exert control over the arterial vasculature of exercising skeletal muscle?

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On the surface, the proposition that the sympathetic nervous system constricts active skeletal muscle during exercise seems counterintuitive, given the robust vasodilation that occurs in skeletal muscle from rest to exercise. This conundrum is represented schematically in Figure 1. Large increases in skeletal muscle vascular conductance persist during exercise despite the evidence provided by DiCarlo and colleagues (5) that sympathetic nerve activity to skeletal muscle increases as the animal begins to exercise and is augmented as exercise intensity increases. Although one might speculate that this increase in sympathetic nerve activity produces vasodilation in the active muscle, recent data from our laboratory run counter to this hypothesis (3). Thus, the increase in sympathetic nerve activity is almost certainly vasoconstrictive in nature and opposes the profound vasodilation in active muscle. These intriguing observations have led investigators to examine the influence of the sympathetic nervous system on the control of skeletal muscle blood flow during exercise.

BLOOD PRESSURE REGULATION DURING EXERCISE

The maintenance of a stable arterial pressure is of paramount importance during exercise. Short-term adjustments to blood pressure, initiated by the arterial baroreceptors, are primarily the result of alterations in sympathetic outflow. Indeed, in the absence of sympathetic outflow, the initiation of exercise results in a decrease in blood pressure. Blood pressure at rest and during exercise is determined by two factors, cardiac output and vascular conductance, both of which are greatly influenced by the sympathetic nervous system. The mathematical relationship between these variables is described in Equation 1:
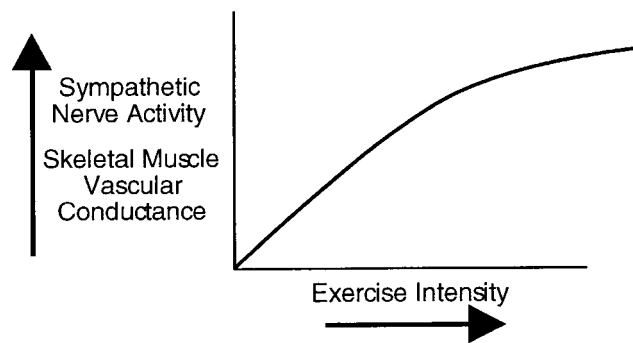
Figure 1. Paradox of concomitant increases in sympathetic nerve activity and vasodilation in skeletal muscle with increases in exercise intensity.

Mean arterial pressure (MAP) = Cardiac output (Q)/ Total vascular conductance (TVC)

Cardiac output represents the total amount of blood pumped by the heart, whereas total vascular conductance represents the relative amount of constriction or dilation exhibited by the systemic arterial vasculature. Unlike cardiac output and mean arterial pressure, vascular conductance cannot be measured directly. Nevertheless, this calculated value provides a useful assessment of vascular tone because an increase in total vascular conductance always represents a net dilation of the systemic vasculature whereas a decrease in total vascular conductance always represents a net constriction of the systemic vasculature. From rest to exercise there is a substantial increase in total vascular conductance even though there is simultaneous vasoconstriction in nonexercising tissue. This vasoconstriction is produced by the sympathetic nervous system and not only directs cardiac output toward exercising skeletal muscle; it also contributes to the maintenance of arterial pressure during exercise. However, because nonexercising tissue receives such a small proportion of cardiac output during exercise, it has been argued that the contribution of vasoconstriction in nonexercising tissue to blood pressure regulation during exercise must be relatively small (12). For example, if the renal bed receives 1% of cardiac output during exercise, total constriction of the renal vasculature without any other hemodynamic changes will result in only a small increase in mean arterial pressure (Figure 2). In contrast, a modest reduction in skeletal muscle vascular conductance when exercising skeletal muscle is receiving 85% of cardiac output will result in a substantial increase in mean arterial pressure. The *prima facie* evidence that the vasculature of exercising skeletal muscle is the most important target to produce increases in blood pressure via sympathetic vasoconstriction poses a dilemma. Whereas sympathetic vasoconstriction of active skeletal muscle may be essential to maintain a stable blood pressure during exercise, sympathetic tone, which restricts blood flow and compromises essential oxygen delivery to the exercising skeletal muscle, severely limits the intensity and duration of exercise that can be performed.

INVESTIGATING THE INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON THE ARTERIAL VASCULATURE OF SKELETAL MUSCLE.

Figure 3 is a schematic representation of a sympathetic nerve terminal. There are a number of experimental approaches that can be used to examine sympathetic outflow to skeletal muscle. The most straightforward method is to place an electrode on sympathetic nerve fibers innervating skeletal muscle and directly measure sympathetic nerve activity at rest and during exercise (as discussed above). However, movement of the electrode due to the motion associated with exercise can produce mechanical artifacts, which makes these types of recordings difficult in animal studies and technically challenging in humans. Sympathetic nerve recordings during exercise in humans are generally limited to nerves innervating nonexercising muscles. Indirect assessment of sympathetic nerve activity can be accomplished by measuring norepinephrine spillover from the
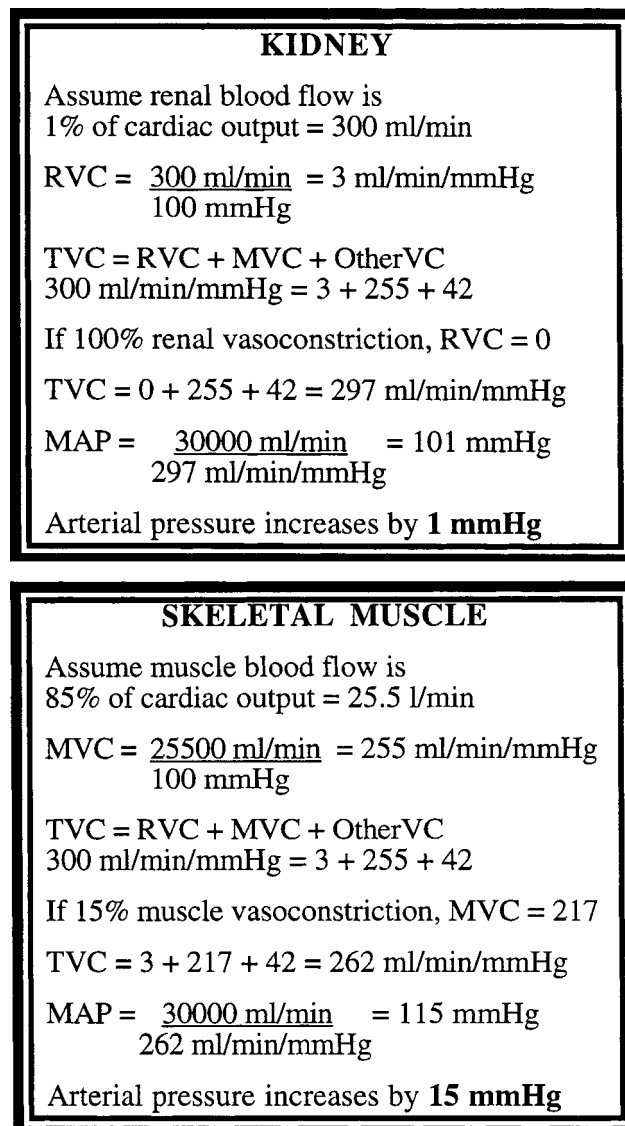

KIDNEY

Assume renal blood flow is 1% of cardiac output = 300 ml/min

RVC = $\frac{300 \text{ ml/min}}{100 \text{ mmHg}}$ = 3 ml/min/mmHg

TVC = RVC + MVC + OtherVC
300 ml/min/mmHg = 3 + 255 + 42

If 100% renal vasoconstriction, RVC = 0

TVC = 0 + 255 + 42 = 297 ml/min/mmHg

MAP = $\frac{30000 \text{ ml/min}}{297 \text{ ml/min/mmHg}}$ = 101 mmHg

Arterial pressure increases by **1 mmHg**

SKELETAL MUSCLE

Assume muscle blood flow is 85% of cardiac output = 25.5 l/min

MVC = $\frac{25500 \text{ ml/min}}{100 \text{ mmHg}}$ = 255 ml/min/mmHg

TVC = RVC + MVC + OtherVC
300 ml/min/mmHg = 3 + 255 + 42

If 15% muscle vasoconstriction, MVC = 217

TVC = 3 + 217 + 42 = 262 ml/min/mmHg

MAP = $\frac{30000 \text{ ml/min}}{262 \text{ ml/min/mmHg}}$ = 115 mmHg

Arterial pressure increases by **15 mmHg**

Figure 2. Illustration of the potential influence on arterial blood pressure of vasoconstriction in representative nonexercising tissue (kidney) and skeletal muscle at maximal exercise. Calculations were performed using Equation 1, assuming a mean arterial pressure of 100 mm Hg and a cardiac output of 30 L·min^{-1}. Regional vascular conductances were calculated by substituting regional flow for cardiac output. The results show that total renal vasoconstriction produces only a 1 mm Hg increases in pressure compared with a 15 mm Hg increase with a modest (15%) reduction in muscle vascular conductance. RVC=Renal Vascular Conductance, MVC=Muscle Vascular Conductance, TVC=Total Vascular Conductance, MAP=Mean Arterial Pressure
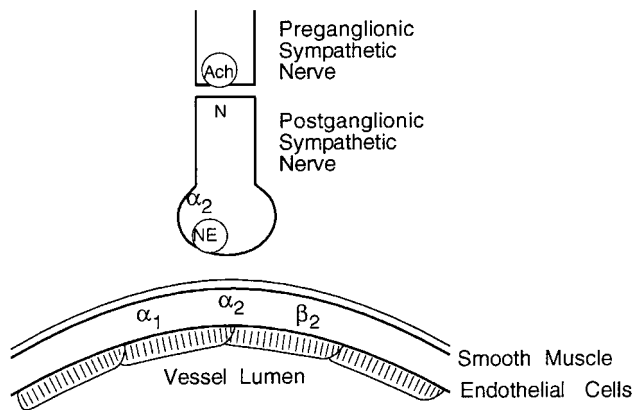
Figure 3. Sympathetic nerve terminal in close apposition to abluminal surface of an arteriole. Propagation of an action potential along preganglionic fibers causes release of acetylcholine (Ach) that binds to nicotinic receptor (N) to produce an excitatory postsynaptic potential in the postganglionic nerve fibers with subsequent release of norepinephrine (NE). After diffusion across the synaptic cleft, NE binds to α-adrenergic (α_1 and α_2) receptors to elicit contraction of vascular smooth muscle cells and ensuing vasoconstriction. Postsynaptic β-adrenergic receptors (β_2) can cause vasodilation and presynaptic α_2 receptors can inhibit release of NE.

sympathetic nerve terminal. As sympathetic nerve activity increases, more norepinephrine is released from the nerve terminal and more norepinephrine diffuses away from the synaptic cleft into the blood where it can be detected. Although both of these methods provide an indication of the magnitude of sympathetic outflow to the vasculature of skeletal muscle, they provide no information as to whether the sympathetic nerve activity has a functional effect and produces vasoconstriction. Several approaches can be used to directly examine the functional effect of sympathetic outflow on the arterial vasculature of skeletal muscle. One approach is to examine skeletal muscle vascular conductance during exercise before and after surgically severing the sympathetic nerve to the muscle. Obviously, this experimental approach is practical in animal models but ill suited for use in human subjects. However, a reversible block of sympathetic nerves can be accomplished by application of local anesthetics in humans. Another approach is to block transmission between the preganglionic and postganglionic sympathetic nerves (Figure 3) with a nicotinic neuronal receptor antagonist. Unfortunately, this approach does not have a localized effect and also abolishes parasympathetic outflow. The use of α_1- and α_2-adrenergic adrenergic receptor antagonists will competitively block the receptors that produce sympathetic vasoconstriction. These drugs can be infused intraarterially into the vascular bed of interest so that they have a localized affect. However, this technique will also block the effects of circulating catecholamines, which leaves the source of the sympathetic vasoconstrictor stimulus in doubt. Each of these experimental paradigms has been used to study sympathetic vasoconstriction in exercising skeletal muscle.

IS THERE SYMPATHETIC VASOCONSTRICTION IN EXERCISING SKELETAL MUSCLE?

Convincing evidence of sympathetic restraint of blood flow to active skeletal muscle has only recently been obtained. In

fact, one of the landmark studies on neural control of blood flow to exercising skeletal muscle argued quite convincingly that sympathetic innervation of skeletal muscle exerted no effect on blood flow to contracting skeletal muscle. Donald and colleagues (6) examined the influence of the sympathetic nervous system on canine skeletal muscle blood flow. They instrumented dogs with electromagnetic flow probes to measure hindlimb blood flow, then measured skeletal muscle blood flow at various exercise intensities on a motorized treadmill. After another surgical procedure to sever the sympathetic nerves to the hindlimb, the bouts of exercise were repeated and the blood flow response was compared to that before sympathectomy. Under the two conditions, Donald and colleagues found virtually identical skeletal muscle blood flow responses to exercise. Thus, the authors logically concluded that the sympathetic nervous system did not influence blood flow to active skeletal muscle.

Using a slightly different experimental approach, three recent studies (1,7,10) revisited the question of the existence of sympathetic restraint of blood flow to active skeletal muscle. Instead of chronically abolishing sympathetic outflow, these investigators used pharmacological agents to acutely interrupt sympathetic vasoconstriction. Joyner and colleagues (7) examined sympathetic vasoconstriction in the active skeletal muscles of the human forearm by using the local anesthetic lidocaine to interrupt sympathetic outflow to the forearm during exercise. In contrast to Donald and colleagues (6), these investigators showed substantial vasoconstriction in exercising skeletal muscle. The difference between these two studies does not appear to be related to species as two other laboratories have shown substantial vasoconstriction in exercising canine muscles (1,10) by using the α_1-adrenergic antagonist prazosin to acutely interrupt tonic sympathetic vasoconstriction during dynamic exercise. Not only did these independent groups demonstrate α_1-adrenergic receptor mediated tone in exercising skeletal muscle but they also found sympathetic vasoconstriction even at heavy exercise intensities. Furthermore, Buckwalter and colleagues (1) provided convincing evidence of α_2-adrenergic receptor mediated vasoconstriction in dynamically exercising muscle. These latter studies demonstrate that there is sympathetic restraint of blood flow during exercise. However, questions remain in regard to the site of the vasoconstriction within the arterial network in skeletal muscle and the magnitude of the sympathetic vasoconstriction in exercising skeletal muscle and how it relates to exercise intensity. Whereas sympathetic vasoconstriction in active skeletal muscle almost certainly exists, sympathetic tone of the magnitude that would restrict blood flow and compromise essential oxygen delivery to the exercising skeletal muscle would be counterproductive and have a detrimental effect on the ability of the muscle to sustain contractions. Ultimately, perfusion of contracting skeletal muscle is a balance between metabolic vasodilation and sympathetic vasoconstriction (Figure 4).

SYMPATHETIC VASOCONSTRICTION IN ACTIVE SKELETAL MUSCLE AND EXERCISE INTENSITY

Although there is good evidence that there is sympathetic vasoconstriction in exercising skeletal muscle even during heavy exercise (1,7,10), the relationship between exercise intensity and the magnitude of the vasoconstriction has been the
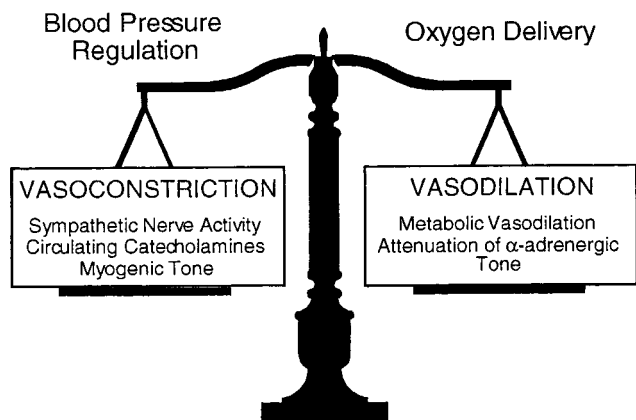
Figure 4. Blood flow in skeletal muscle subserves two sometimes competing functions—blood pressure regulation and oxygen delivery. Blood pressure regulation requires constriction of the skeletal muscle vasculature, whereas increasing oxygen delivery demands vasodilation.

topic of longstanding debate. A number of investigators have reported an attenuation of sympathetic vasoconstriction from rest to exercise, with greater attenuation as the intensity of the exercise increases. A decreased sensitivity to sympathetic stimulation or adrenergic agonists in the skeletal muscle vasculature during exercise was first termed "functional sympatholysis" by Remensnyder et al (11). This term has been misinterpreted to mean an abolition of sympathetic control in active skeletal muscle. As described in the previous section, the sympathetic nervous system clearly exerts control over vascular tone in exercising skeletal muscle. Exercise sympatholysis represents an attenuation of the vascular response to an augmented sympathetic outflow.

Inappropriate expression of data concerning vasomotor function has added to some of the controversy in the literature regarding sympathetic vasoconstriction in active skeletal muscle. Because of the reciprocal relationship between vascular conductance and vascular resistance, conductance exhibits a linear relationship with flow whereas resistance exhibits a curvilinear relationship with flow. The inappropriate use of resistance to describe an increase in constriction in vasculature of skeletal muscle during exercise could lead one to erroneously conclude that there was modest vasoconstriction when in fact there was a substantial decrease in conductance (for a more complete discussion, see 9). It is important to express the data as conductance rather than resistance, and when comparing the magnitude of vasoconstriction across widely different baseline flows, expression of the data as a percent change in conductance is most appropriate. By definition, vasoconstriction or vasodilation in a vascular bed reflects a change in the vessel radius. According to Poiseuille's Law, small changes in radius can have large effects on blood flow (flow $\propto r^4$). Despite differing baseline blood flows, a given percent reduction in conductance will always reflect a predictable percent reduction in the radius of the vessel (Table 1). On the other hand, absolute changes in conductance can vary considerably when identical percent changes in vessel radius are imposed on differing baseline blood flows. If an investigator is primarily interested in how exercise affects the responsiveness of the arterial vasculature of skeletal muscle to sympathetic stimulation, expressing the data as a percent change in vascular conductance is most appropriate.

There is considerable evidence to support the idea that responsiveness of the arterial vasculature of active skeletal muscle is attenuated during exercise. A convincing demonstration of attenuation of sympathetic vasoconstriction was provided by Thomas et al (13) in an anesthetized rat model. Blood pressure and blood flow to hindlimb skeletal muscle were recorded at rest and during electrically stimulated muscle contractions. Lumbar sympathetic nerve stimulation and intraarterial infusions of α-adrenergic agonists into the hindlimb produced substantial vasoconstriction of the hindlimb at rest. However, during muscle contractions, the vasoconstrictive effect of lumbar sympathetic nerve stimulation and α_2-adrenergic receptor stimulation were significantly attenuated. Our laboratory has recently reported similar findings in conscious, dynamically exercising dogs in which selective α adrenergic receptor agonists were infused locally into the hindlimb arterial circulation (2). The vasoconstrictor effect of an α_2-adrenergic agonist in exercising skeletal muscle was attenuated from rest in an exercise intensity dependent manner (Figure 5). Because of the potentially confounding effects of stimulating presynaptic α_2 receptors, which function in an autoregulatory manner to decrease norepinephrine release, the α_2 agonist infusions were repeated in dogs with sympathectomized hindlimbs. Since similar results were found in the sympathectomized animals, the attenuated vasoconstriction during exercise can be attributed to changes in postsynaptic α_2 receptor responsiveness. In contrast to the data of Thomas and colleagues, our data also show diminished vascular responses to an α_1-adrenergic agonist during heavy exercise. This difference may be attributable to limited ability to reproduce intense exercise with electrically stimulated muscle contractions. The results of both studies are congruous, though, in that they demonstrated a differential sensitivity to attenuation by the postjunctional α_1- and α_2-adrenergic receptors. These results are consistent with microcirculatory studies that reported α_2-adrenergic receptor mediated vasoconstriction in skeletal muscle to be particularly sensitive to modest reductions in pH, while α_1-adrenergic receptor mediated vasoconstriction was relatively resistant to attenuation (8). Interestingly, α_1- and α_2-adrenergic receptors appear to have a different anatomical distribution in the arterial vasculature of skeletal muscle with both α_1 and

Table 1

Influence of decreases and increases in vessel radius on blood flow and conductance in vessels with markedly different baseline blood flows.

Blood Flow	% Δ Radius	Δ BF	COND	Δ COND	% Δ COND
100 m./min	↑ 10%	+46	1	+0.46	↑ 46%
	↓ 10%	-34	1	-0.34	↓ 34%
	↑ 50%	+406	1	+4.06	↑ 406%
	↓ 50%	-94	1	-0.94	↓ 94%
1000 ml/min	↑ 10%	+464	10	+4.64	↑ 46%
	↓ 10%	-344	10	-3.44	↓ 34%
	↑ 50%	+4063	10	+40.63	↑ 406%
	↓ 50%	-937	10	-9.37	↓ 94%

Values were calculated from Poiseuille's Law assuming a constant mean perfusion pressure of 100 mm Hg. A given percent change in radius always produces the same percent change in conductance, regardless of the initial baseline flow. COND=conductance
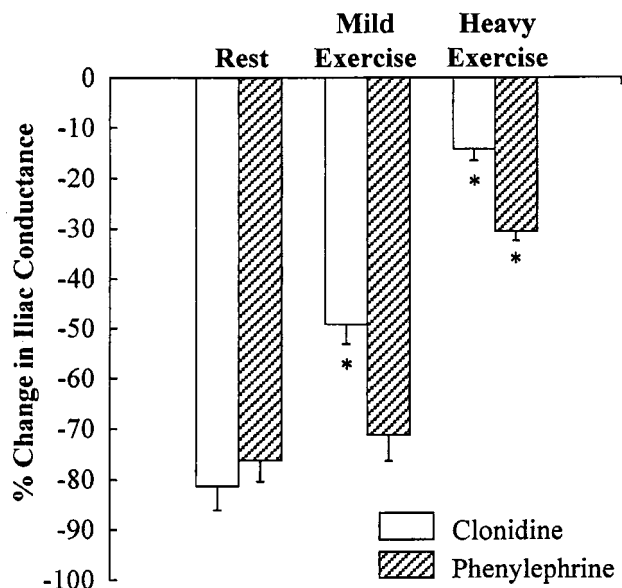
Figure 5. Changes in skeletal muscle vascular conductance due to infusion of selective α_1 (phenylephrine) and α_2 (clonidine) agonists. Note that the response to phenylephrine was only attenuated at the higher exercise intensity, whereas the response to clonidine was diminished even at the lower workload.

α_2 adrenergic receptors present on large arterioles, but only α_2 receptors on the terminal arterioles. The functional importance of a differential distribution and sensitivity of α-adrenergic receptors may be to provide a selective means of directing blood flow to areas of high metabolic activity in active skeletal muscle during exercise.

The mechanism of exercise sympatholysis has not been fully elucidated. It appears that presynaptic release of norepinephrine may be diminished by products of muscle contraction, but there is stronger evidence for an exercise-induced reduction in postsynaptic receptor responsiveness. The reduction in postsynaptic responsiveness to sympathoactivation is most likely mediated by: 1) metabolite production, 2) release of nitric oxide, or 3) temperature. Skeletal muscle contractions may produce acidosis, regional hypoxia, and localized ischemia - all factors which have been shown to inhibit adrenergic vasoconstriction. In addition to metabolites, there is increasing evidence for nitric oxide as a modulator of vascular responsiveness to α-adrenergic agonists. Mice with deficiencies in NO synthase do not exhibit sympatholysis (14), and acute inhibition of nitric oxide synthase partially restores sympathetic vasoconstriction in contracting limbs (15). Finally, muscle temperature could play a role since α_2-receptors become less responsive as muscle temperature increases (4).

CONCLUSION

At the onset of exercise there is an increase in blood flow and vascular conductance to active skeletal muscle. In addition there is an increase in sympathetic nerve activity to exercising skeletal muscle that produces skeletal muscle vasoconstriction even during heavy exercise. It is likely that

sympathetic vasoconstrictor influences acting on the arterial vasculature of contracting skeletal muscle are attenuated. The attenuation appears more severe as exercise intensity increases, with α_2-adrenergic receptor mediated vasoconstriction being especially sensitive to attenuation. However, this does not mean that sympathetic vasoconstriction of active skeletal muscle is not important for the maintenance of a stable arterial pressure during exercise. Indeed, because of the large conductance in active skeletal muscle, a small percentage decrease in vascular conductance could produce a substantial pressor response. Ultimately, perfusion of contracting skeletal muscle is a balance between metabolic vasodilation and sympathetic vasoconstriction.

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