Vasoconstriction in exercising skeletal muscles: a potential role for neuropeptide Y?

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Buckwalter, John B., Jason J. Hamann, Heidi A. Kluess, and Philip S. Clifford. Vasoconstriction in exercising skeletal muscles: a potential role for neuropeptide Y? Am J Physiol Heart Circ Physiol 287: H144–H149, 2004. 10.1152/ajpheart.00071.2004.—There is evidence that neuropeptide Y (NPY) acts as a neurotransmitter in vascular smooth muscle and is released with noradrenaline from sympathetic nerves. We hypothesized that NPY Y1 receptor stimulation would produce vasoconstriction in resting and exercising skeletal muscle. Nine mongrel dogs were instrumented chronically with flow probes on the external iliac arteries of both hindlimbs and a cathether in one femoral artery. The selective NPY Y1 receptor agonist [Leu31,Pro34]NPY was infused as a bolus into the femoral artery at rest and during mild, moderate, and heavy exercise. The selective NPY Y1 receptor agonist [Leu31,Pro34]NPY elicited reductions (P < 0.05) in vascular conductance of 38 ± 3, 25 ± 2, 17 ± 1, and 11 ± 1% at rest, 3 miles/h, 6 miles/h, and 6 miles/h and 10% grade, respectively. The agonist infusions did not affect (P > 0.05) blood flow in the centralateral iliac iliac artery. To examine whether nitric oxide (NO) is responsible for the attenuated vasoconstrictor response during exercise to NPY Y1 receptor stimulation, the infusions were repeated after NO syntheis blockade. These infusions yielded reductions (P < 0.05) in vascular conductance of 47 ± 3, 23 ± 2, 19 ± 3, and 12 ± 2% at rest, 3 miles/h, 6 miles/h, and 6 miles/h and 10% grade, respectively. NPY Y1 receptor responsiveness was attenuated (P < 0.05) during exercise compared with rest. Blockade of NO production did not affect (P > 0.05) the attenuation of NPY Y1 receptor responsiveness during exercise. These data support the hypothesis that NPY Y1 receptors can produce vasoconstriction in exercising skeletal muscle.

Vasogenic constriction in exercising skeletal muscles is potentially regulated by a role for neuropeptide Y. The purpose of this study was to examine the effect of NPY Y1 receptor stimulation on the skeletal muscle vasculature of conscious dogs at rest and during exercise. We hypothesized that NPY Y1 receptor stimulation would elicit vasoconstriction in resting and exercising skeletal muscle. Furthermore, we hypothesized that NPY Y1 receptor responsiveness would be attenuated from rest to exercise in an exercise intensity-dependent manner by the production of NO.

MATERIALS AND METHODS

The experimental procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the American Physiological Society guidelines for the care and use of laboratory animals. Mongrel dogs (n = 9, 18–23 kg) were chosen for the sympathetic nerve terminal, which stimulates α-adrenergic receptors to contract vascular smooth muscle. However, there is strong evidence that a number of other neurotransmitters are released along with noradrenaline from sympathetic nerves (19, 22, 26, 39). One of the most well-described cotransmitters is neuropeptide Y (NPY). In humans and animals, NPY is present in the perivascular noradrenergic neurons innervating the vasculature of skeletal muscle (39). NPY produces vasoconstriction in resting skeletal muscle in a number of species, including the dog (20, 26, 33, 37). In a recent study, intraarterial infusion of NPY elicited a substantial increase in resting forearm vascular resistance of human volunteers (33).

Interestingly, there is evidence for a substantial increase in plasma concentrations of NPY during dynamic exercise (25, 38), suggesting that the increase in sympathetic nerve activity associated with exercise results in an increased release of NPY from the sympathetic nerve terminal. Although previous studies indicate that NPY can elicit vasoconstriction in skeletal muscle at rest, the ability of NPY to produce vasoconstriction in exercising skeletal muscle remains unknown.

Although there is clear and convincing evidence that the sympathetic nervous system restrains skeletal muscle hyperemia during exercise (3, 7, 17, 21, 36), it appears that there is an attenuation in the ability of sympathetic stimulation to produce vasoconstriction in the arterial vasculature of exercising skeletal muscle (8, 23, 40, 41, 43, 44, 49). This diminished vascular responsiveness to sympathetic stimulation during muscular contraction was termed “functional sympatholysis” by Remensnyder et al. (40). Recently, studies by Thomas and colleagues (11, 45, 47, 48) provided evidence that the mechanism by which sympatholysis occurs is related to the production of nitric oxide (NO). There is also evidence that NPY-mediated vasoconstriction is attenuated by NO production (29).

The purpose of this study was to examine the effect of NPY Y1 receptor stimulation on the skeletal muscle vasculature of conscious dogs at rest and during exercise. We hypothesized that NPY Y1 receptor stimulation would elicit vasoconstriction in resting and exercising skeletal muscle. Furthermore, we hypothesized that NPY Y1 receptor responsiveness would be attenuated from rest to exercise in an exercise intensity-dependent manner by the production of NO.
their willingness to run on a motorized treadmill with minimal training. The dogs were chronically instrumented in a series of sterile surgeries. For all surgical procedures, anesthesia was induced with thiopental sodium (15–30 mg/kg; Genesia Pharmaceuticals, Irvine, CA). After intubation with a cuffed endotracheal tube, a surgical level of anesthesia was maintained through mechanical ventilation with 1.5% halothane (Halocarbon Laboratories, River Edge, NJ) and 98.5% oxygen. Antibiotics (cefa-zolin sodium; Apothecon, Princeton, NJ) and analgesics (buprenorphine hydrochloride, 0.3 mg; Rec-kitt and Coleman, Kingston-upon-Hull, UK) were given postopera-
tively.

In the first surgical procedure, the carotid arteries were placed in skin tubes on the neck so that they could be cannulated percutaneously to measure arterial blood pressure (32, 34). During the second surgery, the dogs were instrumented with 4-mm ultrasonic transit-time flow probes (Transonic Systems, Ithaca, NY) around the external iliac arteries for measurement of skeletal muscle blood flow in each hindlimb independently. The cables were then tunneled under the skin to the back. In the final surgery, a heparinized catheter (0.045 in. OD, 0.015 in. ID, 60 cm long; Data Science International, St. Paul, MN) was implanted in one hindlimb. This catheter was inserted through a side branch into the femoral artery distal to the flow probes and tunneled to the back of the dog. After recovery, this catheter allowed infusion of drugs into the arterial vasculature of one hindlimb at rest and during exercise. To maintain patency, the femoral catheter was flushed daily with saline and filled with a heparin solution (100 IU heparin/ml in 50% dextrose solution). The dogs were given ≈2 days to recover from the final surgery before any experiments were performed.

All experiments were performed in a laboratory in which the temperature was maintained at ≈20°C. On the day of the experiment, the dog was brought to the laboratory and a 20-gauge intravascular catheter (Insysyte, Becton Dickinson, Sandy, UT) was inserted retro-
gradely into the lumen of the carotid artery. The carotid catheter was attached to a solid-state pressure transducer (Ohmeda, Madison, WI), and the flow probes were connected to a transit-time flowmeter (Transonic Systems).

To examine the effect of NPY Y₁ receptor stimulation on skeletal muscle vascular tone, we chose to employ a selective Y₁ agonist instead of NPY. The use of a Y₁ agonist eliminates the confounding effects of Y₂ stimulation, which would inhibit the release of nor-epinephrine. [Leu¹¹,Pro³⁴]NPY (Bachem, King of Prussia, PA), a selec-
tive NPY Y₁ receptor agonist for the dog (30), was infused into one hindlimb at rest and during exercise. This agonist was chosen for its selectivity and potency and because it can be dissolved easily in aqueous solution. We reasoned that because hindlimb blood flow increases in an exercise intensity-dependent manner, administration of an identical amount of agonist at rest and during exercise would result in a lower effective concentration of the drug during exercise. Therefore, as in previous investigations (5, 6, 8, 44, 49), the dose of the agonist administered during exercise was increased from rest in proportion to the increase in blood flow. The dose of [Leu¹¹,Pro³⁴] NPY given throughout this study was equal to 0.1 μg/ml of external iliac blood flow. Infusions were performed at rest and during steady-
state exercise while the dogs ran on the treadmill at three different intensities: a mild exercise intensity of 3 miles/h (4.8 km/h) and 0% grade, a moderate exercise intensity of 6 miles/h (9.7 km/h), and a heavy exercise intensity of 6 miles/h (9.7 km/h) and 10% grade. Each exercise intensity was performed on a separate day. For each exercise intensity, there were two infusions of [Leu¹¹,Pro³⁴]NPY. The dog performed one bout of exercise at a given intensity during which [Leu¹¹,Pro³⁴]NPY was infused. After 10 min of rest, the bout of exercise was repeated. The data from the two infusions were averaged for determination of NPY Y₁ receptor responsiveness under each condition. During preliminary studies to examine the reproducibility of repeated infusions of [Leu¹¹,Pro³⁴]NPY, it was determined that a 10-min interval between the infusions was sufficient to avoid any tachyphylaxis.

To determine whether NO production was responsible for the attenuation of NPY Y₁ receptor responsiveness from rest to exercise, additional experiments were performed in five of the animals. NO production was inhibited with an intravenous infusion of N-nitro-l-arginine methyl ester (l-NAME; Sigma Chemical, St. Louis, MO) at 15 mg/kg. Effective NO synthase blockade was inferred from a rise in resting mean arterial pressure. At least 10 min after administration of l-NAME, NPY Y₁ receptor responsiveness was determined with intra-arterial infusions of [Leu¹¹,Pro³⁴]NPY at rest and during exercise at 3 miles/h (4.8 km/h) and 0% grade, 6 miles/h (9.7 km/h), and 6 miles/h (9.7 km/h) and 10% grade. These data were collected in the same manner as the data without NO synthase inhibition (see above).

A computer (Apple G3 Power PC) using a PowerLab system (ADInstruments, Castle Hill, Australia) was used to record (at 100 Hz) arterial blood pressure and right and left external iliac blood flow during all experiments. Data were analyzed offline using MacLab software to calculate mean arterial pressure, heart rate, iliac blood flow, and iliac vascular conductance (blood flow/mean arterial pressure). Vascular conductance, rather than vascular resistance, was calculated, because conductance better reflects vascular tone when the experimental manipulation causes a change primarily in flow and not pressure (24). Control measurements were averaged over 30 s before
agonist infusion. After agonist infusion, all variables were averaged over 1-s intervals (100 consecutive data points), and the nadir 1-s average for vascular conductance was chosen as the peak response.

An α level of P < 0.05 was used to establish statistical significance during all analysis. Statistical analyses of the data were performed with a repeated-measures analysis of variance. Where significant F ratios were found, Tukey’s post hoc test was performed. Values are means ± SE.

RESULTS

Intra-arterial infusion of [Leu11,Pro34]NPY at rest and during exercise produced a localized vasoconstriction in the experimental limb without corresponding changes in blood flow or conductance in the contralateral limb. Original traces in Fig. 1 show the response in one dog to NPY Y1 receptor stimulation during heavy exercise. Hemodynamic values before and after intra-arterial infusion of [Leu11,Pro34]NPY for the group of animals are provided in Table 1. In addition, the absolute changes in experimental limb blood flow and conductance are provided in Table 2. To examine vascular responsiveness of the arterial vasculature, the data are expressed as a percent change in vascular conductance from baseline (2). Figure 2 shows the responsiveness of the arterial vasculature of skeletal muscle to NPY Y1 receptor stimulation at rest and during exercise at the three intensities. The vasoconstrictor response to intra-arterial infusions of [Leu11,Pro34]NPY was attenuated from rest to exercise in an exercise intensity-dependent manner.

To test the hypothesis that attenuation of NPY Y1 receptor responsiveness during exercise was due to NO production, infusions were repeated after NO synthase inhibition with L-NAME in five of the animals. Intra-arterial infusions of [Leu11,Pro34]NPY at rest and during exercise elicited significant (P < 0.05) reductions in experimental limb blood flow and conductance with and without L-NAME. Hemodynamic values before and after intra-arterial infusion of [Leu11,Pro34]NPY with and without L-NAME are found in Table 3. In addition, the absolute changes in experimental limb blood flow and conductance are provided in Table 2. Administration of L-NAME caused significant elevations in baseline mean arterial pressure (P < 0.05) but did not alter the magnitude of the vasoconstriction evoked by [Leu11,Pro34]NPY compared with the control condition (Fig. 3; P > 0.05). After L-NAME administration, the vasoconstrictor effects of [Leu11,Pro34]NPY with and without L-NAME were not different from control (Fig. 3; P > 0.05).

Table 1. Baseline hemodynamic measurements at each workload before and after intra-arterial infusion of [Leu11,Pro34]NPY

<table>
<thead>
<tr>
<th>Workload</th>
<th>HR, beats/min</th>
<th>MAP, mmHg</th>
<th>Control limb Blood Flow, ml/min</th>
<th>Experimental limb Blood Flow, ml/min</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Rest</td>
<td>84 ± 6</td>
<td>81 ± 7</td>
<td>110 ± 4</td>
<td>106 ± 4</td>
</tr>
<tr>
<td>3 miles/h</td>
<td>146 ± 5</td>
<td>145 ± 7</td>
<td>118 ± 6</td>
<td>117 ± 5</td>
</tr>
<tr>
<td>6 miles/h</td>
<td>177 ± 8</td>
<td>168 ± 9</td>
<td>123 ± 5</td>
<td>121 ± 5</td>
</tr>
<tr>
<td>6 miles/h/10%</td>
<td>226 ± 10</td>
<td>225 ± 11</td>
<td>127 ± 5</td>
<td>128 ± 5</td>
</tr>
</tbody>
</table>

Table 2. Absolute change in blood flow and conductance after intra-arterial infusion of [Leu11,Pro34]NPY

<table>
<thead>
<tr>
<th>Workload</th>
<th>NPY Y1 agonist (n = 9)</th>
<th>NPY Y1 agonist (n = 5)</th>
<th>NPY Y1 agonist + L-NAME (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>61 ± 6</td>
<td>51 ± 7</td>
<td>31 ± 4</td>
</tr>
<tr>
<td>3 miles/h</td>
<td>124 ± 18</td>
<td>110 ± 26</td>
<td>84 ± 12</td>
</tr>
<tr>
<td>6 miles/h</td>
<td>105 ± 6</td>
<td>96 ± 9</td>
<td>92 ± 11</td>
</tr>
<tr>
<td>6 miles/h/10%</td>
<td>96 ± 11</td>
<td>81 ± 10</td>
<td>93 ± 11</td>
</tr>
</tbody>
</table>

Values (means ± SE) are expressed as absolute change. NPY Y1 agonist ([Leu11,Pro34]NPY) was infused intra-arterially at 0.1 μg/ml external iliac blood flow. N-nitro-L-arginine methyl ester (L-NAME) was infused at 15 mg/kg iv.
NPY-induced vasoconstriction in skeletal muscle

**DISCUSSION**

There are three major new findings in this study. First, stimulation of NPY Y₁ receptors in the arterial vasculature of skeletal muscle elicited vasoconstriction in resting and active skeletal muscle. Second, the responsiveness of NPY Y₁ receptors was attenuated from rest to exercise, such that stimulation with the selective NPY Y₁ agonist [Leu³¹,Pro³⁴]NPY produced less vasoconstriction at each exercise intensity than at rest. Finally, NO production does not appear to be responsible for the reduction in NPY Y₁ receptor responsiveness during exercise. To our knowledge, this is the first demonstration in conscious animals that stimulation of NPY Y₁ receptors produces vasoconstriction in resting and exercising skeletal muscle.

For years, sympathetic vasoconstriction was thought to be mediated entirely by norepinephrine released from sympathetic nerve terminals. However, there is strong evidence that other neurotransmitters are released along with norepinephrine from sympathetic nerves (19, 22, 26, 39). The most well described of these sympathetic cotransmitters are ATP and NPY. Recently, our laboratory provided evidence for a role for P2X receptors in the regulation of skeletal muscle blood flow at rest and during exercise (5, 10). The present study was undertaken to examine whether NPY may also have a role in the control of blood flow to exercising skeletal muscle. Along with pancreatic polypeptide and peptide YY, NPY is a member of the PP-fold family of peptides (1). These peptides bind G protein-coupled receptors. However, unlike pancreatic polypeptide and peptide YY, which are mainly found in endocrine cells in the gut, NPY is strictly localized in neurons (1). Although a number of different populations of NPY Y receptors exist, the Y₁ and Y₂ receptors appear to play the most prominent roles in the cardiovascular system. The Y₁ receptor is primarily postjunctionally on vascular smooth muscle, where it mediates vasoconstriction (50). The Y₂ receptor is mainly postjunctional and inhibits the release of norepinephrine (50). In the present study, we chose to infuse a selective Y₁ receptor agonist, instead of NPY, to eliminate the confounding effects of Y₂ receptor stimulation. In humans and animals, NPY has been shown to be present in the perivascular noradrenergic neurons innervating the vasculature of skeletal muscle (39). Pernow and colleagues (39) showed that NPY is a potent constrictor of small (0.2 to 0.4 mm) human arteries. Indeed, in these arteries, NPY was a more potent constrictor than norepinephrine. Although the present investigation is in agreement with other studies (20, 26, 33, 37) that show that NPY can produce vasoconstriction in resting skeletal muscle, these results extend those findings by demonstrating that Y₁ receptor stimulation can elicit vasoconstriction in exercising skeletal muscle. These results raise the possibility that the NPY Y₁ receptor may regulate skeletal muscle vascular tone during exercise, which has important implications for the regulation of blood pressure during exercise.

**Table 3. Baseline hemodynamic measurements at each workload before and after intra-arterial infusion of [Leu³¹,Pro³⁴]NPY**

<table>
<thead>
<tr>
<th></th>
<th>Blood Flow, ml/min</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>HR, beats/min MAP, mmHg</td>
</tr>
<tr>
<td>Rest</td>
<td>82±6</td>
</tr>
<tr>
<td>3 miles/h</td>
<td>141±8</td>
</tr>
<tr>
<td>6 miles/h</td>
<td>167±10</td>
</tr>
<tr>
<td>6 miles/h 10%</td>
<td>210±8</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR, MAP and blood flow increased as exercise intensity increased (P < 0.05). After l-NAME infusion, MAP was significantly elevated (P < 0.05). Intra-arterial infusion of [Leu³¹,Pro³⁴]NPY significantly reduced experimental limb blood flow (P < 0.05).

NPY were still attenuated at each exercise intensity compared with rest (P < 0.05).

Fig. 3. Percent changes from baseline in iliac conductance resulting from intra-arterial infusion of [Leu³¹,Pro³⁴]NPY with and without nitric oxide synthase blockade (n = 5). Amount of vasoconstriction produced with NPY Y₁ receptor stimulation was significantly attenuated at each exercise intensity compared with rest (*P < 0.05) under both conditions. There were no significant differences (P > 0.05) in magnitude of vasoconstriction produced in control compared with N-nitro-L-arginine methyl ester (l-NAME). Values are means ± SE.
Interestingly, there is evidence for a substantial increase in plasma concentration of NPY during dynamic exercise (25, 38). It is well known that exercise increases sympathetic nerve activity. Venous levels of NPY appear to increase in an exercise intensity-dependent manner similar to that in which plasma norepinephrine levels increase during exercise (25). This suggests that the increase in sympathetic nerve activity associated with exercise results in an increased release of norepinephrine and NPY from sympathetic nerve terminals. The increase in circulating NPY levels, coupled with the results from the present study showing vasoconstriction evoked by Y1 receptor stimulation, suggests a potential role for NPY in the tonic regulation of blood flow to exercising skeletal muscle. Further studies are warranted to elucidate the role of Y1 receptors in the tonic regulation of vascular function during exercise.

There is substantial evidence that α-adrenergic receptors tonically restrain blood flow to exercising skeletal muscle, even during intense exercise (3, 7, 36). Previously, our laboratory demonstrated that intra-arterial infusions of α1- and α2-adrenergic agonists produce vasoconstriction at rest and during exercise (6, 8). Furthermore, our laboratory and others demonstrated that α-adrenergic receptor responsiveness in the arterial vasculature of skeletal muscle is attenuated during exercise (8, 48), with the α2-adrenergic receptor being especially sensitive to attenuation (8, 48). A diminished vascular responsiveness to sympathetic stimulation during muscular contraction (or “sympatholysis”) has been described by a number of different laboratories (23, 40, 41, 43, 44, 49). However, the present study is the first to demonstrate that NPY Y1 receptor responsiveness is attenuated during exercise compared with rest. The results from the present study show that NPY Y1 receptor responsiveness in the arterial vasculature of skeletal muscle is attenuated in an exercise intensity-dependent manner. Interestingly, although α1-adrenergic receptor responsiveness is only attenuated during intense exercise, NPY Y1 receptor responsiveness, such as α2-adrenergic receptor responsiveness, is attenuated in an exercise intensity-dependent manner (8). Another interesting similarity between α2-adrenergic and Y1 receptors is their primary role in the constriction of small arteries in skeletal muscle. Faber (15) demonstrated that α2-receptors are the primary mediators of adrenergic vasoconstriction for small arterioles in skeletal muscle. A similar role has been suggested by Pernow and colleagues (39) for NPY Y1 receptors. NPY appears to produce substantial vasoconstriction at the arteriolar level, but not in larger conduit vessels. The relative contribution of α2-adrenergic receptors and NPY Y1 receptors to the regulation of vascular tone in the microvasculature of skeletal muscle remains to be determined.

Although the ability of sympathetic stimulation to produce vasoconstriction is attenuated in the arterial vasculature of exercising skeletal muscle (23, 40, 41, 43, 44, 49), the exact mechanism responsible for exercise sympatholysis remains to be definitively determined. It is thought that the reduction in α-adrenergic receptor responsiveness is the result of alterations in the chemical environment of the vascular smooth muscle. In addition to exercise, postsynaptic α2-adrenergic receptor-mediated vasoconstriction appears to be readily attenuated by modest reductions in pH (27, 31, 46), hypoxia (27, 46), elevated temperature (12), and ischemia (28). It unknown whether NPY Y1 receptor-mediated vasoconstriction is susceptible to attenuation by similar factors.

NO production in exercising skeletal muscle is another localized factor that has been hypothesized to alter the chemical environment of vascular smooth muscle and mediate functional sympatholysis (11, 45, 47, 48). Since Thomas and Victor (48) first demonstrated that acute inhibition of NO synthase partially restored sympathetic vasoconstriction in contracting rat limbs, their laboratory provided convincing evidence in human (11, 45) and animal studies (47) that NO production is critical for sympatholysis. In addition, endogenous NO has been shown to modulate the vasoconstrictor response to NPY in the renal vasculature (29). Therefore, in the present study, we hypothesized that attenuation of NPY Y1 receptor responsiveness in the arterial vasculature of skeletal muscle would be related to NO production. Surprisingly, we found no evidence that NO production was responsible for the attenuation in NPY Y1 receptor responsiveness. Acute inhibition of NO synthase did not restore NPY Y1 receptor-mediated vasoconstriction in the exercising limb of the dog. This suggests that the mechanism for exercising sympatholysis involving the NPY Y1 receptor is different from the mechanism involved in α-adrenergic receptor attenuation, although a recent study in humans also questioned the involvement of NO in exercise sympatholysis involving the α-adrenergic receptor (14). Nonetheless, NO production does not appear to be obligatory for exercise sympatholysis involving the NPY Y1 receptor in contracting canine skeletal muscles. One might also speculate from the present results that NO may play a different role in the modulation of NPY Y1 vascular tone in skeletal muscle compared with the kidney (29).

The results from the present study reveal that stimulation of NPY Y1 receptors in the arterial vasculature of skeletal muscle elicited vasoconstriction in resting and active skeletal muscle. In addition, the responsiveness of NPY Y1 receptors was attenuated from rest to exercise, such that stimulation with the selective NPY Y1 agonist [Leu31,Pro34]NPY elicited less vasoconstriction at each exercise intensity than at rest. Surprisingly, NO production does not appear to be responsible for the reduction in NPY Y1 receptor responsiveness during exercise compared with rest. These results suggest the possibility that NPY Y1 receptors regulate skeletal muscle vascular tone during exercise.

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REFERENCES


