Responses of group III and IV muscle afferents to distension of the peripheral vascular bed

PHILIPPE HAOUZI,1 JANEEN M. HILL,2 BROCK K. LEWIS,2 AND MARC P. KAUFMAN2
1Laboratoire de Physiologie, Faculté de Médecine de Nancy, 54505 Vandœuvre-lès-Nancy, France; and 2Division of Cardiovascular Medicine, Department of Internal Medicine, University of California, Davis 95616

Haouzi, Philippe, J aneen M. Hill, Brock K. Lewis, and Marc P. Kaufman. Responses of group III and IV muscle afferents to distension of the peripheral vascular bed. J. Appl. Physiol. 87(2): 545–553, 1999.—This study was undertaken to test the hypothesis that group III and IV afferents with endings in skeletal muscle signal the distension of the peripheral vascular network. The responses of these slowly conducting afferents to pharmacologically induced vasodilation and to acute obstruction of the venous drainage of the hindlimbs were studied in barbiturate-anesthetized cats. Afferent impulses arising from endings in the triceps surae muscles were recorded from the L7 and S1 dorsal roots. Fifteen of the 48 group IV and 3 of the 19 group III afferents tested were stimulated by intra-aortic injections of papaverine (2–2.5 mg/kg). Sixty-two percent of the afferents that responded to papaverine also responded to isoproterenol (50 µg/kg). Seven of the 36 group IV and 2 of the 12 group III afferents tested were excited by acute distension of the hindlimb venous system. Four of the seven group IV afferents responding to venous distension also responded to papaverine (57 vs. 13% for the nonresponding). Finally, we observed that most of the group IV afferents that were excited by dynamic contractions of the triceps surae muscles also responded either to venous distension or to vasodilatory agents. These results are consistent with the histological findings that a large number of group IV endings have their receptive fields close to the venules and suggest that they can be stimulated by the deformation of these vascular structures when peripheral conductance increases. Moreover, such a mechanism offers the possibility of encoding both the effects of muscle contraction through intramuscular pressure changes and the distension of the venular system, thereby monitoring the activity of the veno-muscular pump.

ventilation; muscle vasodilation; ventilatory and circulatory control; gas-exchange regulation

STIMULATION OF THINLY MYELINATED (i.e., group III) or unmyelinated (i.e., group IV) muscle afferents has long been shown to provoke powerful ventilatory and circulatory effects (16, 20, 29). Because some of these slowly conducting afferents respond to mechanical, chemical, and thermal stimuli (see Refs. 9, 11, 17, and 20 for reviews), the traditional view is that contraction-induced deformation of their receptive fields (mechanoreception), as well as the accumulation of metabolic by-products (metaboreception), represents the adequate stimuli that evoke some of the cardiovascular and respiratory adjustments to static (13) and dynamic (1, 23) exercise.

Recently, group III and IV afferents have been proposed to possess the ability to signal the degree of muscular hyperemia (10). Specifically, the hypothesis is that the increased volume of the venular and venous compartment stimulates mechanosensitive free nerve endings located close to the vascular network (6–8). This circulatory-related signal originating in the muscular circulation offers an additional control mechanism that could link the ventilatory and the cardiovascular control systems to metabolic demand during a dynamic exercise (4, 31). In other words, the immediate and massive local vascular response to any contraction-induced increase in muscle metabolism could be a source of stimulation to these endings. This stimulation would, in turn, increase reflexively ventilation and cardiac output in proportion to the level of gas exchange in the exercising muscle.

The possibility that local vascular changes can be detected in the muscles has never been investigated. Nevertheless, anatomic evidence for such a mechanism exists (2, 28, 30). For example, Stacey (28) reported that terminals of many fine afferent fibers were found in the interstitial space of skeletal muscle close to or within the adventitia of arterioles and venules. More recently, Von Düring and Andres (30) found that group IV endings originated in the adventitia of the small veins and the lymphatic vessels. Although they are not homogeneous with respect to their discharge properties (18), many group III and IV afferents respond to mechanical stimuli of light intensity (20, 22). This raises the possibility that they respond to the distortion of their receptive fields because of local vascular distension, as was demonstrated for many other mechanosensitive nerve endings located close to vascular structures (3, 19).

Finally, several observations point to the existence of a neural link between the degree of distension of the peripheral vascular bed in the skeletal muscles and ventilatory (6–8, 10) or circulatory (15) control in exercise. For instance, impeding the venous return from the postexercising muscle in dogs (10) provokes ventilatory changes that follow the expected change in hindlimb peripheral vascular distension or volume, regardless of the time course of the arterial blood pressure (BP). Oren et al. (21) have shown that injection of isoproterenol in the hindlimb arterial supply increases ventilation faster than did a venous injection. Similar results were reported with the use of an injection of papaverine (6). The degree of distension of the venular system and, therefore, of the increased pressure of the surrounding perivascular space was hypothesized to be the stimulating factor.
The first aim of this study was to test the hypothesis that some slowly conducting afferents with endings in the triceps surae muscles respond to the vasodilation induced by intra-arterial injection of papaverine and isoprotenerol (6, 21). Because the venous compartment may be an important site of mediation for this response (6, 10), the existence of afferents that could respond to acute blocking of the venous return from the hindlimbs was also examined. In addition, the activity of group III and IV afferents responsive to vasodilatory agents or venous occlusion was analyzed during electrically induced rhythmic contractions of the triceps surae muscles.

METHODS

Twenty-nine cats (weight range 2.9–5.2 kg, median 3.1 kg) of both sexes were studied. The cats were anesthetized initially with a gas mixture of halothane (3–5%) and O2-N2O (4:1). The left jugular vein was cannulated, and a loading dose of pentobarbital sodium was slowly injected (30 mg/kg, iv). Anesthesia was maintained with 7.5 mg/kg doses of pentobarbital sodium and was repeated as required throughout the experiment. The trachea was cannulated, and the lungs were artificially ventilated with room air by using a Harvard respirator (model 660). Heating lamps and pad were used to maintain the temperature of the cat at ~38°C. Arterial BP was measured from the right carotid artery. A catheter was placed into this artery and was connected in turn to a Statham P23dB transducer. A nonobstructive catheter was placed into the right femoral artery. Its tip was advanced just above the iliac bifurcation for intra-aortic injections of vasodilatory agents. Finally, a balloon-tipped catheter (French 3, Arrows) was placed in the inferior vena cava above the iliac bifurcation via the right femoral vein. Placing the tip of the balloon catheter at this relatively low level allowed us to impede the venous drainage from the hindlimb circulation without dramatically affecting the systemic arterial pressure (8). The venous pressure, below the occlusion, was monitored either through a small catheter placed in a superficial vein of the left hindlimb or directly via the balloon-tipped catheter modified for this purpose.

The peroneal, femoral, sural, and obdurator nerves, as well as all visible branches of the sciatic nerves, except those supplying the triceps surae muscles, were cut. The left triceps surae muscles were exposed, covered with gauze soaked in warm Ringer solution, and continuously warmed with the use of a heating lamp. The calcaneal tendon was cut and attached to a force-displacement transducer (model FT10, Grass Instruments). The resting tension of the triceps surae muscles was set at 0.5–1 kg by using a rack and pinion. A lumbar-sacral laminectomy was performed (12), and the cat was placed in a Kopf spinal unit. A pool was made by tying the skin flaps of the laminectomy incision to a metal frame and filling it with warm mineral oil (37–38°C). The dura was opened, and L7 and S1 left dorsal roots were then identified.

A 1-mm ultrasonic flow probe (Transonic Systems) was placed around the left popliteal artery and connected to a flowmeter (T206, Transonic Systems). The carotid BP, peripheral venous pressure, popliteal blood flow, and muscle tension signal were displayed on-line on a monitor (Gould V1000) and a chart recorder (Gould ES 1000).

Afferent Identification

Afferent impulses arising from fine filaments split from either the left L7 or S1 dorsal roots were recorded. The roots were cut at their level of entrance into the spinal cord and gently separated into several fine filaments, which were placed, one at a time, on a platinum wire of a bipolar electrode. The other wire was used as a reference. The animal and the recording apparatus were grounded to reduce the electrical noise. The gastrocnemius muscles were then poked and stretched to study the response of spontaneously active fibers or eliciting activity from silent fibers. The filaments were further split to obtain a single or a few fiber preparation (12). The neural signals were passed through a high-impedance probe (model HIP511, Grass Instruments), amplified, and filtered (100–3,000 Hz). The conduction time was determined by electrically stimulating the tibial nerve, as previously described (1). The conduction velocity was then calculated by dividing the conduction distance between the stimulating and the recording electrodes by the conduction time. Afferents conducting impulses between 2.5 and 30 m/s were classified as group III afferent, and those conducting impulses at <2.5 m/s were classified as group IV afferents. The conduction time was redetermined at the end of the protocol after the cat was paralyzed. Afferents conducting impulses >30 m/s were discarded. The action potentials were displayed and stored on an oscilloscope (HP 54603B, Hewlett-Packard) and visualized on-line on the chart recorder.

Protocol

The activity of group III and IV afferents was studied in the following situations: 1) during rhythmic contractions of the triceps surae muscles; 2) after intra-aortic injection of papaverine and isoprotenerol; and 3) during occlusion of the inferior vena cava.

Rhythmic contractions. Dynamic contractions of left triceps surae muscles were induced by stimulating the tibial nerve for 400 ms (20 Hz, 0.025 ms) at two times motor threshold. Two distinct phases were described: the “contracting” phase (400 ms), during which the muscle tension increased and remained elevated, and the “relaxing” phase (600 ms), during which the muscle tension returned to its resting level. The brief transitional period just at the cessation of the stimulation was regarded as part of the relaxing phase. Following the behavioral and morphological and mechanical manipulation of the hindlimb circulation. Approximately 15–20 min after the end of the contractions, the cat was paralyzed (vecuronium bromide, 0.1 mg/kg). Papaverine was used as the primary vasodilatory stimulus because it has a direct and potent relaxing effect on the vascular smooth muscle. Papaverine (papaverine chloride) was diluted in saline to a volume of 2 ml and was injected into the abdominal aorta at a dose of 2–2.5 mg/kg. The injections of the drug and flushing of the arterial line with normal saline (2 ml) were done within 3–5 s. Injections of the vehicle solution, which had a similar pH (pH = 3), and volume (2 ml), was used as control, and it was injected several minutes before the papaverine. To test whether the activity depended on some nonspecific (drug-unrelated) effects of papaverine, another vasodilator agent, isoproterenol (50 µg/kg), was tested. This β-adrenergic agonist was diluted in saline to a volume of 2 ml and was injected by using the same protocol as that used for papaverine. Sufficient time was given between two different injections of the two vasodilators for blood flow and BP to return to their preinjection values. This time was usually ~15–30 min after papaverine injection but was much longer after isoproterenol injection (from 45 to >90 min). Thus papaverine was usually injected first. Finally, the effect of venous obstruction on group III and IV afferent discharge was examined. The caval balloon was inflated with 2 ml of air for 1 min, and the occlusion was performed in...
Data Analysis

We compared activity for the 1 min preceding a maneuver with that for 1 min after the onset of a maneuver. Activity was expressed as impulses per minute. An afferent was regarded as responding if its activity increased over baseline levels by at least 100% during either the minute of contraction or venous occlusion. Similarly, the afferent was regarded as responding to injection of a vasodilator substance if its activity increased by at least 100% during the first minute after the end of the injection period. To describe the temporal profile of the change in activity, we computed the discharge rate of the responding group III and IV afferents every 2 s for both the injections and venous occlusion and every 1 s for the rhythmic contractions. Similarly, the BP and the popliteal blood flow were measured every 2 s after the injection of a vasodilatory agent or the vehicle solution. Whenever the hemodynamic variables did not return to control levels at the end of the first minute, afferent activity was computed every minute up to the fifth minute. To estimate the chance-corrected agreement between the responses to two stimuli (papaverine vs. venous occlusion, papaverine vs. isoproterenol, and isoproterenol vs. papaverine), we used the kappa statistic, where a kappa coefficient of 1 indicates total agreement between two stimuli and a kappa value of 0 indicates only chance agreement. This approach was used to determine whether the observation that a fiber responded, for instance, to both vasodilatory agents or to neither drugs was not due to chance. The kappa coefficient (k) was computed as K = Po – Pc/(1 – Po) where Po is the proportion of observed agreement (number of fibers both responding to the 2 stimuli and to neither of them) and Pc is the expected agreement (2). A kappa coefficient >0.6 was regarded as the marker of a good agreement, one between 0.4 and 0.6 reflected a moderate level of agreement, whereas one <0.2 was regarded as a marker of bad agreement between two stimuli. In other words, we considered that a kappa coefficient <0.2 indicated only chance agreement. In addition, a paired t-test was used to compare the effect of injections and occlusion on blood flow and BP (values before the test vs. the peak response). All values are reported as means ± SE. The criterion for significance was P < 0.05.

RESULTS

We recorded the impulse activity of 48 group IV and 19 group III afferents. Receptive fields were localized by mechanical stimulation of the triceps surae muscles in 36 of the 48 group IV afferents and in each of the group III afferents. The effects of papaverine were studied in each of these afferents, whereas those of isoproterenol were studied in 21 group IV and 8 group III afferents. The effects of venous occlusion were studied in 36 group IV and 15 group III afferents. Finally, the effects of rhythmic contraction on the activity of 33 group IV and 10 group III afferents were studied.

Responses to Papaverine

Circulatory responses to papaverine. Intra-arterial injection of papaverine produced an immediate increase in popliteal arterial blood flow. On average, blood flow rose from 6.4 ± 0.5 to 16.3 ± 1.0 ml/min (P < 0.01). The peak effect was reached 13 ± 0.5 s after the end of injection (Fig. 1). Blood flow then returned to preinjection levels (range 30 to >300 s, which was the maximum period of computation). On several occasions, the initial increase in flow had two phases (Fig. 1): after 32–50 s, a second increase in flow occurred so that its level remained above control well beyond the 5-min period of computation. Arterial BP decreased 10 s after the end of injection and remained significantly lower than control levels beyond the period of computation. At the nadir of the response, systolic and diastolic BPs were decreased by 26 ± 4 and 36 ± 4 mmHg, respectively (P < 0.01). Interestingly, a slight but clear increase in BP was observed in many tests during the first 10 s after the intra-arterial injection. This occurred at a time when popliteal blood flow was elevated (Fig. 1).

Afferent response. In response to papaverine injection, 15 of the 48 group IV afferents increased their discharge rate (from 6.5 ± 2.3 to 45.9 ± 16.0 imp/min). The temporal profile of the responses varied between afferents (Fig. 1) and could be described as follows. In four afferents, the increase was temporally associated with the sudden and prolonged rise in popliteal blood flow. For one of these afferents, the activity remained elevated as long as the BP and, therefore, the peripheral resistance remained reduced despite the fact that the popliteal flow returned to, or was slightly below, the preinjection levels. In five other afferents, the activity increased after a delay (30–48 s). This delayed increase in activity was associated with the second rise in flow in three of these afferents (Fig. 1) and with the rise in pulse pressure in the two others. The six remaining afferents displayed an immediate but transient increase in activity that was associated with the initial rise in flow. In these, the activity was not sustained despite a persistently elevated blood flow. The receptive fields of 13 of the 15 group IV afferents responding to papaverine were localized by probing the triceps surae muscles.

Of the 19 group III afferents, 3 were excited by papaverine injections. In contrast to the group IV afferents, the activity of the group III afferents increased in all instances after a delay (18–20 s) that in one case was clearly associated with the rise in pulse pressure. Analysis of the cumulative activity of the group III and IV afferents responding to papaverine (Fig. 2) revealed that the activity increased as soon as popliteal blood flow started to rise and with a temporal profile that was clearly biphasic.

Response to the Vehicle Solution

The activity of 42 group IV and 15 group III afferents was recorded while the vehicle solution was injected. Each of the afferents responding to papaverine was tested. Only one group IV afferent, which also responded to papaverine, displayed a brief and transient increase in activity. This increase was much smaller than that evoked by papaverine, which elicited an intense and prolonged discharge. Interestingly, this brief response to the vehicle was associated with a rise
in popliteal blood flow and a small decrease in systemic BP. None of the other afferents tested responded to injection of the vehicle.

Response to Isoproterenol

On average, isoproterenol injection increased popliteal blood flow from 6.7 ± 1.1 to 18 ± 2.5 ml/min. This increase was not significantly different from that caused by papaverine, in terms of both magnitude and onset. Of the 21 group IV muscle afferents tested, 5 responded to isoproterenol. Two of these five afferents were stimulated with no delay (Fig. 1), whereas the remaining afferents increased their discharge rates after a delay of >40 s. On average, their discharge rate increased from 6.6 ± 4.6 to 21.6 ± 8.5 imp/min (Fig. 3). Each of the five afferents responding to isoproterenol also responded to papaverine injection. The frequency of occurrence of positive and negative responses to papaverine and isoproterenol for the 21 fibers that were tested with these two agents is shown in Table 1. We found a high level of agreement between the fibers responding to papaverine and isoproterenol (kappa coefficient = 0.77, with PC = 0.58 and Po = 0.91). None of the eight group III afferents that were tested was excited by isoproterenol injection.
Venous Occlusion

Obstruction of the inferior vena cava increased peripheral venous pressure by 29 ± 2 mmHg but had little effect on mean arterial BP (>25 ± 1 mmHg). Of the 36 group IV afferents tested, 7 were excited by this maneuver. Their discharge rates increased from 2.7 ± 1.7 to 21.5 ± 9.3 imp/min. In all except one, activity was evoked by probing the belly of the triceps surae muscles. Two types of responses to occlusion were observed. In four afferents, the activity increased after a 15- to 40-s delay and remained elevated throughout the period of occlusion. Typically, activity decreased after the release of occlusion, but on one occasion a transient excitation was observed. The three remaining afferents adapted to venous distension (Fig. 4). They were excited with no delay, but this stimulation was followed by a rapid decrease in activity that disappeared in one afferent before the end of the minute of occlusion. Four of these seven afferents also responded to papaverine injection. An example is shown in Fig. 4, and the distribution of response types among the group IV afferents tested during both venous occlusion and papaverine injection (38 fibers) and during venous occlusion and isoproterenol administration (20 fibers) is displayed in Table 1. Although poorer than for isoproterenol and papaverine, the level of agreement between the responses to venous occlusion and papaverine remained good (kappa coefficient = 0.41, with Po = 0.67 and Pc = 0.81) but was found to be too low for isoproterenol and venous occlusion because of an insufficient number of fibers responding to isoproterenol in the group of fibers tested by venous occlusion. Of the 15 group III afferents tested, 2 increased their activity in response to venous occlusion (from 0 to 7 imp/min for one and from 0 to 8 imp/min for the other). The cumulative activity of the group III and IV afferents responding to venous occlusion is shown in Fig. 5.

Response to Dynamic Contractions

The developed tension during the contraction averaged 3.6 ± 0.8 kg. Six of the 33 group IV (18%) and 4 of the 10 group III (40%) afferents tested were stimulated by rhythmic contractions of the triceps surae muscles. For the group III afferents, responses were exclusively observed during the contracting phase, and in many instances adaptation occurred as already reported during static contraction (12). In contrast, the activity of the group IV afferents, which increased from 6.3 ± 3.5 to 23 ± 7.2 imp/min, was observed during both the relaxing (after correction for the conduction time) and the contracting phases. Four of the six group IV afferents that were stimulated during dynamic contractions also responded to papaverine, and two of them responded to venous distension (Fig. 4).

**DISCUSSION**

We found that some of the group III and IV afferents with endings in the triceps surae muscles were stimulated by intra-arterial injection of vasodilatory agents and by occlusion of the hindlimb venous return. Specifically, 31% of the group IV and 16% of the group III afferents tested were excited by the vascular smooth muscle relaxant papaverine. In addition, 23% of the group IV and none of the group III afferents were stimulated by the β-adrenergic agonist isoproterenol.
Moreover, distending by mechanical means the venous and venular system of the triceps surae muscles stimulated 20% of the group IV and 13% of group III afferents tested.

Response to Papaverine and Venous Occlusion

Various substances injected into the arterial supply of the hindlimb circulation have already been shown to stimulate both group III and IV muscle afferent fibers. These agents, such as potassium (26), lactic acid (22), or prostaglandins (25), were used to mimic the effect of metabolic by-products of contraction on the discharge of group III and IV afferents (see also Refs. 11, 17, and 20 for reviews). Several elements point, however, to the fact that most of the group III and IV afferent fibers that responded to papaverine were stimulated by the deformation or the distortion of the vascular structures located close to their endings rather than through any kind of “metabolic” effect. 1) Papaverine, which has been widely used in humans for clinical purposes, has never been shown to behave like or generate “ischemic metabolites.” 2) No comparable effects were observed after vehicle injection (HCl solution). 3) Many of the responding fibers belonging to the group IV afferents were stimulated by venous obstruction. This is in accordance with the receptive properties of these endings and the anatomic description of their origin in the muscle, i.e., they respond to mechanical stimuli of light intensity and are located close to vascular structures.

The question that, therefore, remains to be clarified is the nature of the mechanical stimulus that could have been sensed by the population of fibers that responded to papaverine injection. Although some of the fibers responding to papaverine appeared to mimic the expected change in the peripheral vascular events (flow or conductance), most of the individual fibers did
not follow the flow changes. The activity was either immediate and of a short duration or occurred with a delay associated with a second increase in flow or in pulse pressure. Like any other mechanosensitive units, only the distortion of the receptive field of a given unit is encoded. The observation that venous obstruction stimulated 57% of the fibers that responded to papaverine suggests a possible mechanism for the response to this vasodilatory agent. Indeed, the fibers that were stimulated by the venous obstruction 1) must have their receptive field close to the venular side of the microcirculation, which is supported by recent histological studies (30), and 2) respond to the deformation of the venular end of the muscle vasculature. A thorough analysis of the different patterns of response to venous occlusion suggests that some endings were likely to respond to venous or venular volume changes (immediate and brief response), as in Fig. 4, and thus were probably located very close to the venules. Others responded with a delay, suggesting that they take their origin at some distance from the vascular structures or have a different response threshold. Consequently, for the fibers that responded to both papaverine and venous obstruction, the most likely explanation for the stimulation triggered by papaverine could be the transmission of the vascular distension to the venular end of the microcirculation (and its vicinity). Fronek and Zweifbach (5) have studied the effects of papaverine injection on the pressure and diameter changes of arterioles, capillaries, and venules of the cat skeletal muscle. In brief, they found that papaverine injection produces a decrease in arterial pressure that affects the entire vascular bed, down to arterioles of 20 µm but that there was a substantial elevation of the pressure downstream that was transmitted to the venular side. This pressurization of the venular side was larger the greater the drop in arterial pressure (the greater the decrease in peripheral resistance). In other words, a common effect of venous occlusion and papaverine injection is the pressurization of the venular end of the vascular bed despite the decrease in perfusion pressure in the latter.

We have, however, little to offer on the location of the few endings that did not respond to venous obstruction but did respond to papaverine. The lack of effect of venous occlusion does not necessarily argue against vascular deformation as a mechanism of stimulation, as some of these endings have been found close to the small arteries (and, therefore, will not be affected by the effects of venous impediment). They may also discharge at a higher degree of venular distension or volume than that evoked in our experiments. Indeed, only a narrow range of venous, and thus venular, distension was tested with our experimental approach, and it is difficult to predict the effects of papaverine-induced hyperemia on interstitial pressure or on tissue blood volume for any given fiber. For instance, group III afferents supplying the adventitia of large veins have been shown to be stimulated by a relatively large range of venous pressures (35–250 mmHg) (19). The heterogeneity in the responses is thus not unexpected and may reflect the anatomic distribution of the "origin" of these fibers, their different thresholds of response to a mechanical stimulus, and the time course of the deformation of vascular structure close to a given ending. In addition, the temporal profile of the neural response may vary depending on 1) the type of vascular structure that is distorted (small veins or small arteries), 2) the mechanical properties of the vessels affected by the vasoactive agent (compliance and viscoelasticity), and 3) the arrangement of the ending with, and the distance from, the surrounding tissues that will be distended. Only determination of the relation between the precise location of a given ending and its pattern of response would give us the clue for any individual response, which will be quite difficult to obtain. Nevertheless, sensing the distension of the venular structures in the muscle during a vasodilation through the group IV afferent fibers offers the possibility of sending to the central nervous system an image of the change in local vascular conductance and the extent of the vascular bed that is being perfused.

The possibility that the injection of this vasodilatory agent may have changed the chemical environment of some of these endings should be considered, because many of group IV endings have been shown to behave like metaboreceptors (14, 17, 24, 27). However, it remains unclear what chemical changes occurring in the vicinity of a mechanosensitive ending could result from the recruitment of previously un- or underperfused regions of the muscle. In all instances, the peripheral vasodilation was associated with a decrease in perfusion pressure (decrease in systolic BP), but it is unlikely that this can provide a satisfactory explanation for our findings. Indeed, the effects on group III and IV afferents of decreasing the perfusion pressure to a resting skeletal muscle have already been extensively studied by means of total arterial impediment (18). The...
results are unequivocal: reducing the perfusion pressure to a resting muscle has no or little effect on group III and IV muscle afferent activity. These results imply, therefore, that the decrease in perfusion pressure during the vasodilation is unlikely to stimulate any of the group III and IV afferents.

Finally, we are intrigued by our finding that few of the tested group III afferents, which are more sensitive to mechanical stimuli than are group IV afferents, were responsive to the administration of the vasodilators or to venous distension. This observation appears in contrast with that expected from the description of the afferent innervation of the saphenous vein, which is mainly innervated by group III afferents (3). In the skeletal muscle, however, it is the group IV endings that can be found primarily in the vicinity of the venous system (30), which is also the most compliant system and thus the most likely and easily to be deformed. In contrast, group III endings are found mostly in connective tissue and arteries (30).

Response to Isoproterenol

We found that all the fibers responding to isoproterenol also responded to papaverine, with a very good agreement between the two types of responses (kappa coefficient = 0.7). Some fibers, however, that responded to papaverine did not respond to isoproterenol, despite a similar increase in blood flow. Papaverine and isoproterenol do not have the same effect on the vascular bed and thus are unlikely to produce a similar stimulation of mechanosensitive units located in the vicinity of the small vessels. Indeed, in contrast to papaverine, isoproterenol seems to decrease pressures along the entire length of the peripheral vascular bed (5). This observation may be perfectly correct for a perfused portion of the capillary bed but may not be true for a region of the muscle that was not previously perfused (which is actually the case for a large part of the capillary bed in a resting muscle). The fact that the deformation of the venular side of the microcirculation after isoproterenol administration is not as dramatic as for papaverine may, therefore, explain that some fibers responding to papaverine do not respond to isoproterenol. In addition, the fibers that responded to isoproterenol increased their activity after a delay that was usually associated with a reincrease in peripheral vascular conductance and flow, which may reflect the retarded recruitment of different territories and, therefore, nerve endings within the muscle. Endings close to previously un- or underperfused regions, when suddenly exposed to the mechanical consequences of the vascular deformation, could, therefore, account for such a delayed response to isoproterenol. Finally, as for papaverine, some of the fibers responding to isoproterenol but not to venous occlusion may originate in the small arteries and respond to any increase in arteriolar diameter.

Response to Dynamic Contractions

The observation that some of the rather small number of group IV fibers that responded to dynamic contractions were also stimulated by papaverine injection (4 out of 6 fibers) or during obstruction of the venous return (2 out of 6 fibers) suggests that their receptive field was close to vascular structures and could be affected by the distension of these vessels. Whether a mechanical stimulus of vascular origin can contribute to the "normal" response of group IV afferents to the dynamic contractions, as was recently suggested (7, 15), remains, however, to be established. Nevertheless, our finding that the group IV afferents that responded to dynamic contraction discharged also during the relaxing phase, a time at which the postcapillary system is being pressurized by the effect of the muscle pump, is intriguing. The increased pressure in the perivascular space due both to muscle contraction and distension of the venous end of the vasculature during the relaxing phase could constitute a stimulus to some of these endings. Interestingly, Mense and Stahnke (18) also identified some muscle afferent fibers that did not change or even decrease their activity during dynamic muscle contraction with total arterial occlusion, whereas the activity increased again after occlusion release. The mechanism underlying this pattern of response was obviously not compatible with the "metaboreception" hypothesis. Instead, these data may be explained by a mechanical stimulus of circulatory origin.

In conclusion, the observation that peripheral nerves transmit circulatory-related information to the central nervous system through group III and IV afferent fibers offers the possibility of an integrated cardiovascular and ventilatory control, depending on the perfusion rate in peripheral tissues when peripheral resistance varies. Such information could play a key role in the regulation of the body gas exchange by coupling ventilation and cardiac output to the magnitude of the vascular recruitment in the muscles. The venular network may be an important site for such a mediation.

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Address for reprint requests and other correspondence: P. Haouzi, Laboratoire de Physiologie, Faculté de Médecine de Nancy, Ave. de la Forêt de Haye, B.P. 184, 54505 Vandoeuvre-lès-Nancy, Cedex France (E-mail: p.haouzi@chu-nancy.fr).

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