Rapid vasodilation in response to a brief tetanic muscle contraction. J. Appl. Physiol. 87(5): 1741–1746, 1999.—To test the hypothesis that vasodilation occurs because of the release of a vasoactive substance after a brief muscle contraction and to determine whether acetylcholine spillover from the motor nerve is involved in contraction-induced hyperemia, tetanic muscle contractions were produced by sciatic nerve stimulation in anesthetized dogs (n = 16), instrumented with flow probes on both external iliac arteries. A 1-s stimulation of the sciatic nerve at 1.5, 3, and 10 times motor threshold increased blood flow above baseline (P < 0.01) for 20, 25, and 30 s, respectively. Blood flow was significantly greater 1 s after the contraction ended for 3 and 10 X motor threshold (P < 0.01) and did not peak until 6–7 s after the contraction. The elevations in blood flow to a 1-s stimulation of the sciatic nerve and a 30-s train of stimulations were abolished by neuromuscular blockade (vecuronium b). The delayed peak blood flow response and the prolonged hyperemia suggest that a vasoactive substance is rapidly released from the contracting skeletal muscle and can affect blood flow with removal of the mechanical constraint imposed by the contraction. In addition, acetylcholine spillover from the motor nerve is not responsible for the increase in blood flow in response to muscle contraction.

Effect of Vecuronium on the Release of Acetylcholine After Nerve Stimulation

To the Editor: The recent article by Naik et al. (8) suggests that during a brief tetanic contraction of skeletal muscle, a vasoactive substance is released that results in vasodilation and thus contributes to the rapid increase in blood flow after the muscle contraction. The authors concluded that the acetylcholine released from the motor nerve ending in response to nerve stimulation is not this vasoactive substance, as muscle blood flow did not change in response to nerve stimulation during neuromuscular blockade. The neuromuscular blockade was produced by vecuronium bromide, which was assumed to have no effect on the release of acetylcholine in response to nerve stimulation.

However, in our opinion, this assumption may not be correct. In general, it is believed that a nondepolarizing muscle relaxant such as vecuronium bromide binds not only to the postjunctional sites at the muscle membrane but also to the presynaptic sites at the nerve ending (1, 2, 4, 6, 9, 10). By binding to presynaptic acetylcholine receptors, the muscle relaxant may diminish the release of acetylcholine from the motor nerve during tetanic stimulation (2). Therefore, the possible contribution of acetylcholine release to the increase in blood flow cannot be excluded on the basis of the described experiment. In general, the diminution in acetylcholine release is determined by the degree of presynaptic block, which may vary for each study performed. Thus the presynaptic block in the experiments performed by Naik et al. (8) may have been greater than that in the experiments performed by Welsh and Segal (11). Welsh and Segal showed vasodilation in the retractor muscle of anesthetized hamsters after nerve stimulation in the presence of tubocurarine chloride, another nondepolarizing muscle relaxant. The observed vasodilation was possibly the result of the action of the acetylcholine released from the nerve ending. Furthermore, the presynaptic block in the experiments performed by Dyke et al. (5) may have been great enough to prevent the possible action of acetylcholine on vessel diameter and blood flow. In these experiments, pipecuronium bromide was used, which is also a nondepolarizing muscle relaxant. Although pipecuronium bromide has a low affinity for presynaptic acetylcholine receptors, it may produce a presynaptic block, especially when muscles are profoundly paralyzed, as in the experiments described (3, 12).

To determine whether the release of acetylcholine from the motor nerve is involved in the increase in blood flow that follows muscle contraction, we suggest a study design using α-bungarotoxin instead of a nondepolarizing muscle relaxant such as vecuronium. α-Bungarotoxin prevents muscle contraction without affecting acetylcholine release from the nerve ending by binding selectively to the postjunctional acetylcholine receptors (7).

REFERENCES


http://www.jap.org

letters to the editor


G. van Santen
J. M. K. H. Wierda
University Hospital Groningen, 9700 RB Groningen, The Netherlands E-mail: j.m.k.h.wierda@med.rug.nl

REPLY

To the Editor: We thank Dr. van Santen and Dr. Wierda for the opportunity to provide further data to clarify the involvement of acetylcholine receptors in the vascular responses to skeletal muscle contraction.

A muscle contraction is initiated when acetylcholine is released from the motor nerve terminal and interacts with a neuromuscular nicotinic acetylcholine receptor on the motor end plate, causing depolarization that is propagated to the muscle fiber. The regulation of transmitter release at neuromuscular junctions is not fully understood and may vary depending on the type of muscle. Blockade of contraction is traditionally achieved by depolarizing blocking agents that may initiate transient muscle fasciculation or nondepolarizing agents, which are the standard clinical drugs employed for muscle relaxation. Vecuronium, a clinically used nondepolarizing agent, was chosen for our study (1) because of its limited cardiovascular side effects. As pointed out by van Santen and Wierda, nondepolarizing blockers do not interact exclusively with postjunctural receptors, and binding to prejunctural receptors could reduce the amount of acetylcholine released at the motor nerve terminals. We acknowledge that our conclusion from that “acetylcholine spillover from the motor nerve is not responsible for the increase in blood flow in response to muscle contraction” requires the neuromuscular blocker employed to have negligible prejunctural effects. Although we considered making the argument that vecuronium has a low affinity for prejunctural receptors, van Santen and Wierda kindly provided the optimal solution to the problem by suggesting further studies using α-bungarotoxin, which irreversibly binds postjunctural receptors with no detectable prejunctural effects (2). Because of the importance of this finding to an understanding of exercise hyperemia, we performed the proposed studies using the methods described in the original paper.

Tetanic muscle contractions were produced by sciatic nerve stimulation in three anesthetized dogs. The hindlimb blood flow responses to a 1-s stimulation of the cut sciatic nerve (30 Hz, 0.1 ms, 10× motor threshold) and a 30-s train of contractions (50% duty cycle) were determined in duplicate. As expected, the train of contractions used to mimic dynamic exercise produced a larger increment in hindlimb blood flow than a 1-sec tetanic contraction (Fig 1, left). Because of the gradual development of neuromuscular blockade after intravenous administration of α-bungarotoxin (0.2 mg/kg), a 1-h interval was allowed before the nerve stimulations were repeated. At that time, mean arterial pressure had increased by an average of 12 mmHg, and baseline blood flow was slightly reduced (Fig. 1). Sciatic nerve stimulation still produced barely visible contractions in one dog, but no contractions were apparent in the other two dogs. Nevertheless, as illustrated in Fig. 1 (right), the increases in blood flow to a 1-s tetanic contraction and a train of contractions were abolished in all three dogs.

The new data, presented in Fig. 1, are virtually identical to those presented in Fig. 5 of our original paper (1). The findings strengthen the conclusions from that paper and from Dyke et al. (3) that acetylcholine...

Fig. 1. Blood flow responses to sciatic nerve stimulation in 3 dogs before and after neuromuscular blockade with α-bungarotoxin (0.2 mg/kg body wt). Data for control conditions are the peak flows observed. Because no changes in blood flow were discernible after α-bungarotoxin, data were taken at the same time that the peak occurred under control conditions. Values are means ± SE. Single, 1-s stimulation (30 Hz, 0.1 ms, 10× motor threshold); train, 30-s stimulation train (30 Hz, 0.1 ms, 10× motor threshold, 50% duty cycle).
choline spillover is not the physiological mechanism underlying contraction-induced vasodilation. Furthermore, because the muscle pump cannot account for the magnitude of increase in blood flow or the time course of the blood flow response observed after a 1-s contraction, our findings suggest that there is rapid release of a vasoactive substance during muscle contraction. Despite more than a century of research and the identification of a plethora of candidates, the identity of this vasoactive substance remains an enigma.

REFERENCES


Philip S. Clifford
Zoran Valic
Jay S. Naik
John B. Buckwalter
Departments of Anesthesiology and Physiology
Medical College of Wisconsin and Veterans Affairs Medical Center Milwaukee, Wisconsin 53295