Cardiovascular and respiratory reflexes from muscles during dynamic and static exercise

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TALLARIDA, G., F. BALDONI, G. PERUZZI, G. RAIMONDI, M. MASSARO, AND M. SANGIORGI. Cardiovascular and respiratory reflexes from muscles during dynamic and static exercise. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 50(4): 784-791, 1981.—In anesthetized and deafferented rabbits, rhythmic and static contractions of the hindlimb muscles were elicited by stimulating the femoral nerve at 3 and 100 Hz with the intensity of 2.0-2.5 times threshold for the motor fibers. Rhythmic contractions caused a decrease in systemic blood pressure, heart rate, and vascular resistance of the resting hindlimb with hyperpnea. Tetanic contractions caused a rise in arterial pressure, in vascular resistance of the nonexercising hindlimb, and in pulmonary ventilation with small increases in heart rate. These responses were not obtained after sectioning the somatic nerves of the exercised limb or when the cut central end of the femoral nerve or the intact nerve in curarized animals was stimulated with the same intensity of 2.0-2.5 times the motor threshold. Both depressor and pressor responses were, therefore, reflexes initiated in the contracting limbs. Removal of the skin from the exercising limb did not change the typical patterns of response. The most likely source of the observed reflexes is that from receptors activated by metabolites released in the exercising muscles.

Cardiovascular reflexes from limbs; blood pressure; heart rate; vascular resistance; muscle receptors; metabolic receptors; rabbits

It is generally accepted that part of the circulatory and respiratory changes accompanying muscular work result from reflexes arising in the exercising limbs. Evidence has been also presented to show that these reflexes are elicited from receptors within the contracting muscle and that they are essentially of excitatory nature, being represented by increases in systemic blood pressure, heart rate, cardiac output, and breathing. (1, 2, 4, 9, 12, 15, 17, 18).

Most experiments aimed at demonstrating the existence in the somatic area of sensory receptors, responding to chemical or mechanical stimuli and producing excitatory cardiovascular responses during exercise, have been made on anesthetized animals in which a) various chemical substances were intra-arterially injected into the limbs, and b) active and passive movements of the limbs were electrically or mechanically induced. However, in previous research work on cardiovascular and respiratory chemoreflexes evoked by chemical stimulation of somatic receptors in rabbits, we observed that either inhibitory or excitatory reflex responses could be elicited from hindlimbs by intra-arterially injecting different types of chemical stimulants (21, 22). This finding provided a basis for assuming the existence in the skeletal muscles of two functionally distinct kinds of chemosensitive receptors producing pressor and depressor reflex responses and most probably serving different physiological purposes. This assumption was further substantiated by the observation that different kinds of muscular exercise could also induce in the anesthetized rabbit distinct types of cardiovascular responses: tetanic isometric contraction caused excitatory cardiovascular effects, while rhythmic contraction elicited inhibitory responses (23).

Our objectives in the current investigation therefore were 1) to study, in anesthetized rabbits, the comparative cardiovascular and respiratory responses originating in the exercising limbs during dynamic and static contractions and then to ascertain if there is any correlation among kinds of muscular activity and types of reflexes elicited; 2) to determine whether muscular exercise can produce cardiovascular and respiratory responses similar to those seen with chemical stimulation of muscle receptors; and 3) to examine whether activation of receptors in contracting muscles might be responsible for the responses observed during exercise.

MATERIALS AND METHODS

Experiments were performed on rabbits of both sexes (2.5-3.5 kg) anesthetized with intravenous pentobarbital sodium (30-40 mg/kg) and deafferented by bilaterally cutting the carotid sinus, aortic, and vagus nerves. The anesthesia level was continuously controlled by electrocorticogram and adequately maintained by additional doses of drug given intravenously as required. The electrocorticogram was amplified and displayed on a Hewlett-Packard oscilloscope (no. 1223A) together with the electrocardiogram (ECG) recorded using standard limb leads. To determine whether the responses might differ under different anesthetics, in some experiments anesthesia was induced with intravenous urethan (1 g/kg), or urethan and α-chloralose (500 and 50 mg/kg, respectively, iv), or ketamine hydrochloride (Ketalar, Parke, Davis; 25-30 mg/kg with supplemental doses of 10-20 mg every 15 min), or alfaxalone (CT-1341; Albhecin, Glaxo; 0.20-0.40 ml/kg supplemented by 0.10 ml every 5-10 min). The trachea was intubated; rectal temperature was
**CARDIOVASCULAR REFLEXES FROM EXERCISING MUSCLES**

maintained at 36-38°C with a steel hot plate on the operating table and heat lamps.

**Recorded variables.** All variables were recorded on a Hewlett-Packard multichannel polygraph (no. 7758A). Systemic blood pressure was recorded from the left common carotid artery via a saline-filled polyethylene cannula connected to a Hewlett-Packard 1280C pressure transducer. Heart rate was continuously recorded with a Hewlett-Packard 8812A tachograph triggered by the signal from the ECG (Hewlett-Packard 8811A) or pressure pulse. Respiratory movements were recorded via a tracheal cannula connected to a Hewlett-Packard 1280C pressure transducer; ventilation rate was measured from the respiratory tracings. Hindlimb vascular resistance was studied by perfusing the external iliac artery (contralateral to the exercised hindlimb) at constant flow with an occlusive pulsatile perfusion system using autologous blood drawn from the ipsilateral common iliac artery. A reservoir bottle was interposed in the perfusion line and the perfusate was maintained at 37°C by a heat exchanger. Haemaccel (Behringerwerke) or 6% dextran 70 (Macrodex, Baxter) warmed to body temperature was used as plasma expander. The adequacy of the isolation of the perfused vascular tree was tested in each instance by stopping the perfusion pump and observing a decrease in perfusion pressure to levels representing critical closing pressure. The absence of pulsations in the pressure tracing also indicated the absence of significant collateral circulation. With the pump operating, in our deafferented animals, evidence for isolation was reached by injecting intravenously a dose of norepinephrine or angiotensin sufficient to cause an evident rise in systemic blood pressure without a significant simultaneous increase in hindlimb perfusion pressure. The hindlimb perfusion pressure was recorded with a Hewlett-Packard 1280C transducer connected to a T junction placed just proximal to the point of insertion of the distal cannula into the external iliac artery. At the beginning of each experiment the perfusion system was adjusted to produce a pulsatile perfusion pressure similar to that observed in the external iliac artery during spontaneous flow.

All of the cannulas and the reservoir bottle were previously treated with silicon, and heparin (10 mg/kg, iv, with additional hourly doses) was given to prevent blood clotting.

**Simulated active muscular exercise.** Rhythmic or tetanic exercise of the hindlimb was induced by stimulation of the femoral nerve in the inguinal region at 3 or 100 Hz with square-wave impulses of 0.5-ms duration delivered from an isolated stimulator (Bio-Science CFP, model 8173). The hindlimb was tightly fixed at the knee and ankle. Periods of stimulation of 20 s were generally used. The exposed femoral nerve was kept moist in the intervals between periods of stimulation with warmed Ringer solution bubbled with 95% O_2-5% CO_2. At the beginning of each experiment the threshold voltage for muscle contraction was carefully determined. The intensity of stimulation was expressed in multiples of the threshold (xT) for the first signs of muscle contraction (activation of the α-efferents). Stimulus strengths of 2.0-2.5 times threshold (2.0-2.5 x T) for motor fibers were mostly used. Muscle tensions were not measured. The cardiovascular and respiratory responses were recorded, and then the femoral nerve was divided and the central end stimulated at 3 or 100 Hz with the same stimulus intensity previously applied to the intact nerve.

In 10 rabbits the reflex responses to rhythmic or tetanic stimulation of the femoral nerve were investigated before and after muscle paralysis induced by gallamine triethiodide (3-5 mg/kg, iv). The paralyzed animals were artificially ventilated at 60 cycles/min (inspiratory period at 30% of the total cycle) by means of a Palmer electronically controlled ventilator (model 5255). Arterial PO_2 was kept above 90 Torr, PCO_2 between 30 and 40 Torr, and pH between 7.35 and 7.40 (IL Micro 413 pH/blood gas analyzer).

The effects induced on the reflex responses to hindlimb contraction by performing pharmacologic blockades of autonomic system (atropine sulfate 2 mg/kg, iv, guanethidine sulfate 2.5 mg/kg, iv), or by removing the skin from the exercising limb or by sectioning the sciatic nerve in the upper thigh and the femoral nerve proximally to the point of stimulation were also investigated.

**Passive movements of the knee.** Passive movements of the hindlimb were performed to see whether joint receptors might play an important role in the cardiovascular and respiratory reflex responses to active physical exercise observed in the present experiments. The passive movements of the hindlimb were executed manually. The legs of the rabbits were held with one hand and the knee joints were flexed and extended for 20 s at a rate of 60 times/min through a range of about 90°.

The effects induced on the cardiovascular and respiratory responses to the passive movements of the knee by injecting the local anesthetic lidocaine (1 ml of a 2% solution) into and around the knee joint, or by administrating atropine (2 mg/kg) or guanethidine (2.5 mg/kg) iv, or by sectioning the ipsilateral femoral and sciatic nerves, or by inducing muscle paralysis with gallamine triethiodide were investigated.

**Mechanical stimulation of muscles.** Two kinds of mechanical stimuli, stretch and strong pressure, were applied to the triceps surae (gastrocnemius, soleus, and plantaris) and quadriceps muscles. Care was taken to remove the skin over the muscles to stimulate the muscles without skin stimulation. The muscles were squeezed between the finger and thumb either with constant or with rhythmic (60 times/min) pressure. Periods of squeezing of about 20 s were usually applied. The effects induced on the reflex responses to squeezing the hindlimb muscles by pharmacologically blocking the autonomic system or by curarizing the animal or by sectioning the ipsilateral femoral and sciatic nerves, or by inducing muscle paralysis with gallamine triethiodide were investigated.

**Analysis of data.** Mean values ± SE are shown (Tables 1 and 2). The maximum changes induced in each variable by exercise and other stimuli were averaged for each rabbit (from two to three trials). To standardize the results, the changes of variables, in addition to absolute units, were also calculated as percent of the control level.
TABLE 1. Reflex cardiocirculatory changes induced in anesthetized deafferented rabbits

<table>
<thead>
<tr>
<th>Group</th>
<th>n *</th>
<th>ASAP</th>
<th>% Change</th>
<th>ΔDAP</th>
<th>% Change</th>
<th>ΔHR</th>
<th>% Change</th>
<th>ΔVR</th>
<th>% Change</th>
<th>ΔHPF</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythmic</td>
<td>25</td>
<td>+32.9</td>
<td>22.7</td>
<td>+35.2</td>
<td>35.9</td>
<td>+21.6</td>
<td>9.1</td>
<td>+23.8</td>
<td>37.1</td>
<td>-26.0</td>
<td>-17.9</td>
</tr>
<tr>
<td>exercise</td>
<td></td>
<td>±2.7</td>
<td>±0.2</td>
<td>±2.8</td>
<td>±3.0</td>
<td>±2.2</td>
<td>±0.9</td>
<td>±2.6</td>
<td>±3.2</td>
<td>±5.6</td>
<td>±3.1</td>
</tr>
<tr>
<td>Tetanic</td>
<td>25</td>
<td>+13.0</td>
<td>±2.1</td>
<td>+12.3</td>
<td>±2.0</td>
<td>+4.6</td>
<td>±2.1</td>
<td>+12.7</td>
<td>±25.2</td>
<td>+6.5</td>
<td>±5.2</td>
</tr>
<tr>
<td>exercise</td>
<td></td>
<td>+11.0</td>
<td>±2.0</td>
<td>+14.6</td>
<td>±2.5</td>
<td>±1.1</td>
<td>±0.5</td>
<td>±1.6</td>
<td>±3.8</td>
<td>±1.0</td>
<td>±0.8</td>
</tr>
<tr>
<td>Passive</td>
<td>10</td>
<td>-17.5</td>
<td>±2.2</td>
<td>-19.0</td>
<td>±2.4</td>
<td>-10.5</td>
<td>-4.6</td>
<td>+8.0</td>
<td>+20.0</td>
<td>-7.0</td>
<td>-5.6</td>
</tr>
<tr>
<td>movement</td>
<td></td>
<td>-13.4</td>
<td>±1.5</td>
<td>-20.7</td>
<td>±2.3</td>
<td>+5.8</td>
<td>±1.1</td>
<td>±0.8</td>
<td>±2.0</td>
<td>±1.2</td>
<td>±0.8</td>
</tr>
<tr>
<td>Muscle</td>
<td>10</td>
<td>+24.5</td>
<td>±2.6</td>
<td>+25.0</td>
<td>±2.6</td>
<td>+7.5</td>
<td>±4.1</td>
<td>+18.0</td>
<td>±69.0</td>
<td>+17.1</td>
<td>+1.8</td>
</tr>
<tr>
<td>squeezing</td>
<td></td>
<td>+19.9</td>
<td>±3.0</td>
<td>+32.0</td>
<td>±3.4</td>
<td>+9.5</td>
<td>±1.6</td>
<td>+3.2</td>
<td>±12.2</td>
<td>±2.5</td>
<td>±1.5</td>
</tr>
</tbody>
</table>

Values are mean maximal changes ±SE; Δ, mean maximum change in the variable; ASAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; VR, ventilation rate; HPP, hindlimb perfusion pressure (in the nonexercised hindlimb). * No. of rabbits per group studied for ASAP, DAP, HR, and VR; † No. of rabbits per group studied for HPP.

TABLE 2. Effects of atropine and guanethidine on cardiovascular reflex responses in anesthetized and deafferented rabbits

<table>
<thead>
<tr>
<th>Group</th>
<th>Blocking Agents</th>
<th>n</th>
<th>ASAP</th>
<th>% Change</th>
<th>ΔDAP</th>
<th>% Change</th>
<th>ΔHR, beats/min</th>
<th>ΔVR</th>
<th>% Change</th>
<th>ΔHPF, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythmic</td>
<td>Atropine</td>
<td>6</td>
<td>38.2±5.5</td>
<td>41.4±2.2</td>
<td>40.4±5.8</td>
<td>-36.6±1.5</td>
<td>-17.2±2.6</td>
<td>-36.4±1.5</td>
<td>-20.8±6.6</td>
<td>-24.8±3.0</td>
</tr>
<tr>
<td>exercise</td>
<td>Guanethidine</td>
<td>6</td>
<td>-30.4±2.8</td>
<td>-28.8±1.8</td>
<td>-36.5±4.3</td>
<td>-3.2±2.3</td>
<td>-24.2±3.4</td>
<td>-16.4±2.2</td>
<td>-25.2±4.2</td>
<td>-6.2±0.6</td>
</tr>
<tr>
<td>Tetanic</td>
<td>Atropine</td>
<td>5</td>
<td>+13.2±1.8</td>
<td>+12.8±1.3</td>
<td>+13.2±1.3</td>
<td>+14.2±2.5</td>
<td>+4.8±1.5</td>
<td>+5.6±2.4</td>
<td>+5.6±2.2</td>
<td>+7.4±2.3</td>
</tr>
<tr>
<td>exercise</td>
<td>Guanethidine</td>
<td>5</td>
<td>+14.2±1.9</td>
<td>+12.0±0.9</td>
<td>+11.8±1.3</td>
<td>+0.8±0.8</td>
<td>+3.6±1.8</td>
<td>+0.4±0.4</td>
<td>+5.2±0.7</td>
<td>+0.6±0.6</td>
</tr>
<tr>
<td>Passive</td>
<td>Atropine</td>
<td>5</td>
<td>-17.8±4.2</td>
<td>-19.2±4.7</td>
<td>-20.4±5.5</td>
<td>-21.2±5.5</td>
<td>-11.6±3.1</td>
<td>-10.8±2.8</td>
<td>-13.2±2.8</td>
<td>-13.2±2.9</td>
</tr>
<tr>
<td>movement</td>
<td>Guanethidine</td>
<td>5</td>
<td>-18.8±4.4</td>
<td>-6.0±0.6</td>
<td>-9.1±5.9</td>
<td>-0.4±0.2</td>
<td>-12.8±3.3</td>
<td>-0.4±0.4</td>
<td>-16.4±3.0</td>
<td>-1.2±0.5</td>
</tr>
<tr>
<td>Muscle</td>
<td>Atropine</td>
<td>5</td>
<td>+22.4±3.7</td>
<td>+21.2±2.9</td>
<td>+23.4±2.6</td>
<td>+22.6±5.2</td>
<td>+5.6±0.9</td>
<td>+5.8±1.2</td>
<td>+15.4±1.2</td>
<td>+14.2±1.7</td>
</tr>
<tr>
<td>squeezing</td>
<td>Guanethidine</td>
<td>5</td>
<td>+24.2±4.6</td>
<td>+1.4±1.7</td>
<td>+24.8±3.0</td>
<td>+1.2±2.0</td>
<td>+7.6±0.5</td>
<td>+0.7±0.3</td>
<td>+16.4±1.5</td>
<td>+0.8±0.4</td>
</tr>
</tbody>
</table>

Values are mean maximal changes ±SE. Blocking agents were given intravenously (see Methods). Δ, Mean maximum change in the variable; ASAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate; HPP, hindlimb perfusion pressure (in the nonexercised hindlimb). n, No. of animals for each group; C, control (responses before blockade); B, blockade (responses after blockade).

RESULTS

Cardiovascular and respiratory reflex responses to induced rhythmic and tetanic contractions of the hindlimb muscles. In 25 anesthetized and deafferented rabbits, stimulation of the femoral nerve at 3 Hz, with the intensity 2.0—2.5 × T (times motor threshold) for 20 s, caused rhythmic muscular contractions of the hindlimb and a pronounced decrease in systemic blood pressure (larger for diastolic than for systolic values), in heart rate, and in vascular resistance of the contralateral hindlimb perfused at constant flow. Ventilation rate increased promptly by 20—30% of its resting level. Latency of response was about 1 s. A typical example of this reaction pattern is shown in Fig. 2. Mean data of the pressor response are given in Table 1. The time course of the average responses to induced rhythmic muscular work is plotted in Fig. 3 (left panel).

In the same rabbits, stimulation of the femoral nerve at 100 Hz with stimulus strengths of 2.0—2.5 × T for 30 s, caused tetanic contractions of the hindlimb muscles and a biphasic, depressor and pressor, cardiovascular response accompanied by hyperventilation. Usually, after an initial transient depressor effect, systemic and hindlimb perfusion pressures showed a slight increase over the resting values. Heart rate changes were small whereas ventilation rate increased promptly by 20—30% of its resting level. Latency of response was about 1 s. A typical example of this reaction pattern is shown in Fig. 2. Mean data of the pressor response are given in Table 1. The time course of the average responses to induced rhythmic muscular work is plotted in Fig. 3 (left panel).

The pattern of responses during the induced rhythmic and tetanic contraction was basically the same in animals anesthetized with pentobarbital sodium and in animals under urethane, chloralose-urethan, ketamine hydrochloride, or Althesin. Stimulation of the central end of the divided femoral nerve, at both 3 and 100 Hz, did not show any effect on circulatory and ventilatory parameters when the stimulus strength remained at 2.0—2.5 × T. If the intensity of stimulation was increased over four to seven times threshold for motor fibers, cardiocirculatory and respiratory reflex responses began reappearing. These results correlate well with those obtained in the experiments (10 rabbits) where muscle paralysis was induced with gallamine triethiodide. In fact, curarization completely prevented all the cardiocirculatory responses to both 3- and 100-Hz stimulation of the intact femoral nerve, when the intensity of the stimulus was kept at 2.0—2.5 times threshold for motor fibers. Both these findings were taken as evidence that the responses observed by stimulating the femoral nerve at 2.0—2.5 × T were not due to direct electrical stimulation of larger afferent fibers. In the paralyzed animals, as the intensity of 3-Hz stimulation of intact femoral nerve was increased over four to seven
CARDIOVASCULAR REFLEXES FROM EXERCISING MUSCLES

A? mmtig 150 WPP mmHg 100 FIG. 1. Anesthetized deafferented rabbit. Rhythmic hindlimb contractions (electrical stimulation of femoral nerve at 3 Hz with intensity twice motor threshold) cause an evident “depressor” response represented by a decrease in arterial pressure (AP), heart rate (HR), and vascular resistance of contralateral hindlimb perfused at constant flow (HPP: hindlimb perfusion pressure). This cardiocirculatory response is accompanied by hyperpnea (RESP). Bar between on and off indicates duration of stimulation. Time intervals in seconds.

times motor threshold, and smaller fibers were thus recruited, typical depressor responses (hypotension, bradycardia, hindlimb vasodilation) reappeared; this suggests that direct activation of somatic afferents endowed with inhibitory cardiovascular effects was reached; this suggests that direct activation of somatic afferents endowed with inhibitory cardiovascular effects was reached; this suggests that direct activation of somatic afferents endowed with inhibitory cardiovascular effects was reached. Stimulation strengths greater than 20–30 times the threshold for motor fibers were required to produce pressor effects with 100-Hz stimulation of intact femoral nerve in deeply anesthetized and paralyzed animals. The minimal intensity required to produce inhibitory or excitatory reflex responses by stimulating at 3 and 100 Hz, respectively, the intact nerve in paralyzed animals did not change when the nerve was sectioned and the central end was stimulated.

The stimulation of the peripheral end of the divided femoral nerve at 3 and 100 Hz, with intensity of 2.0–2.5 × T for 20 s, after the sciatic nerve was also sectioned in the upper thigh (10 rabbits), caused rhythmic and tetanic contractions but no evident changes in systemic blood pressure, vascular resistance of contralateral hindlimb, heart rate, and breathing.

Removal of the entire skin from the exercising limb did not change the typical depressor and pressor responses to induced rhythmic and tetanic contractions. The stimulation of the femoral nerve of the skinned hindlimb at 3 Hz, 2.0–2.5 × T for 20 s in three anesthetized and deafferented rabbits, produced a mean decrease in systolic blood pressure of 28.3 ± 1.7 mmHg, in diastolic blood pressure of 31.7 ± 1.7 mmHg, in heart rate of 18.3 ± 1.7 beats/min, and in hindlimb perfusion pressure of 25.0 ± 2.9 mmHg. The average increase in ventilation rate was 26.7 ± 4.4 breaths/min. Stimulation at 100 Hz and 2.0–2.5 × T induced a mean increase in systolic pressure of 11.7 ± 1.7 mmHg, in diastolic pressure of 13.3 ± 3.3 mmHg, in heart rate of 6.7 ± 1.7 beats/min, in hindlimb perfusion pressure of 6.7 ± 1.7 mmHg, and in ventilation rate of 11.7 ± 1.7 breaths/min.

The fundamental pattern of circulatory response to 3- and 100-Hz stimulation of the femoral nerve at the intensity of 2.0–2.5 × T was not significantly changed by atropine sulfate (up to 2 mg/kg, iv). Detailed results are given in Table 2. On the contrary, all cardiocirculatory reflex responses to both rhythmic and tetanic stimulation of the femoral nerve at 2.0–2.5 × T were virtually abolished by guanethidine sulfate (2.5 mg/kg, iv).

Effects of passive movements of the knee joints. In 10 anesthetized and deafferented rabbits, passive movement of one leg carried out by flexing and extending the knee joint at a rate of 60 times/min, caused a reflex depressor response qualitatively similar, but of smaller magnitude, than that elicited by rhythmic active hindlimb exercise: arterial pressure fall, vasodilation in the contralateral hindlimb, cardiac slowing, and hyperpnea. The latent

FIG. 1. Anesthetized deafferented rabbit. Rhythmic hindlimb contractions (electrical stimulation of femoral nerve at 3 Hz with intensity twice motor threshold) cause a decrease in arterial pressure (AP), heart rate (HR), and vascular resistance of contralateral hindlimb perfused at constant flow (HPP: hindlimb perfusion pressure). This cardiocirculatory response is accompanied by hyperpnea (RESP). Bar between on and off indicates duration of stimulation. Time intervals in seconds.

FIG. 2. Anesthetized deafferented rabbit. Tetanic hindlimb contractions (femoral nerve stimulated at 100 Hz and twice motor threshold) cause a pressor response represented by an increase in arterial pressure (AP), in vascular resistance of the nonexercising hindlimb (HPP), and in pulmonary ventilation (RESP). Heart rate (HR) changes are small. This response is preceded by a transient depressor effect. Bar between on and off indicates duration of induced tetanic contraction. Time intervals in seconds.
period was about 1 s. An example of this response is shown in Fig. 4. Results are summarized in Table 1.

This pattern of response was not fundamentally changed by injecting the local anesthetic lidocaine into and around the knee joint. In five animals passive movements of the knee joint injected with lidocaine caused a mean decrease in systolic blood pressure of 14.0 ± 2.4 mmHg, in diastolic pressure of 16.0 ± 2.4 mmHg, and in heart rate of 19.0 ± 5.8 beats/min. The mean increase in ventilation rate was 17.2 ± 0.9 breaths/min.

All responses caused by passive movement of the hindlimb were abolished by sectioning the ipsilateral femoral and sciatic nerves in the upper thigh (4 animals). The cardiocirculatory reflex changes were also suppressed when muscle paralysis with gallamine triethiodide was induced (5 animals).

The cardiovascular responses to passive movement of the hindlimb were not prevented by atropine sulfate (up to 2 mg/kg, iv), but they were abolished by guanethidine (Table 2).

Effects of squeezing the muscles. Static or rhythmic squeezing of the quadriceps and triceps surae muscles was performed in 10 anesthetized and deafferented rabbits. In response to this stimulus there was unvariably a rise in systemic blood pressure, heart rate, perfusion pressure of the contralateral hindlimb, and ventilation rate. A typical example is shown in Fig. 5. Mean data are listed in Table 1. In some cases, the typical pressor response was preceded by a fleeting depressor effect. The latency of response was about 1 s.

Muscle paralysis (3 rabbits) did not consistently change the cardiovascular responses to squeezing the hindlimb muscles. All the responses to this stimulus were abolished following section of the ipsilateral femoral and sciatic nerves in the upper thigh (three rabbits). The reflex cardiocirculatory changes were not influenced by atropine administration (up to 2 mg/kg, iv) but they were suppressed after guanethidine administration (Table 2).

Effects of stretching the muscles. Stretch of the triceps surae and quadriceps muscles was carried out in six anesthetized and deafferented rabbits. In all six experiments stretching these muscles up to a tension of 500 g had no significant effect on systemic and hindlimb perfusion pressures, heart rate, and breathing. Results typical of all experiments are shown in Fig. 6. Also when the triceps surae or quadriceps of both hindlimbs were simultaneously stretched with tension of 500 g, no appreciable cardiovascular and respiratory responses were elicited. In the same animals, all the other stimuli, active rhythmic and tetanic contractions, passive movement of the hindlimb, and muscle squeezing, produced typical cardiovascular and respiratory responses.

DISCUSSION

The present experimental results in rabbits agree in general with those of previous investigations in cats (4, 15, 17) and dogs (2, 16) and provide further evidence that physical exercise is accompanied by cardiovascular and respiratory changes that originate reflexly from activation of neural receptors within the exercising limbs. In fact, muscular contractions and concomitant responses were obtained by stimulating the femoral nerve with stimuli of so low intensity (2.0–2.5 times the motor threshold) as to be unable to directly activate the small-sized, high-threshold myelinated (group III) and unmyel-
CARDIOVASCULAR REFLEXES FROM EXERCISING MUSCLES

FIG. 4. Anesthetized deafferented rabbit. Passive movement of 1 leg, carried out by flexing and extending knee joint at a rate of 60 times/min for 20 s (between on and off) causes a reflex depressor response consisting of a decrease in arterial pressure (AP), heart rate (HR), and vascular resistance in resting hindlimb (HPP). This response, analogously with that induced by active rhythmic exercise, is accompanied by hyperpnea (RESP). Time intervals in seconds.

lated (group IV) afferent fibers that are known to cause consistent cardiovascular and respiratory effects (4, 7, 10, 11, 15, 16, 20).

That such an approach was appropriate was demonstrated by the evidence that, when the same stimuli were applied to the central end of the divided femoral nerve, no cardiocirculatory or respiratory changes were obtained. This evidence accords well with the other finding that the cardiocirculatory response to both rhythmic and tetanic stimulation at 2.0-2.5 X T of the intact femoral nerve was abolished after muscle paralysis. Both these findings clearly show that the cardiocirculatory and respiratory changes obtained by simulated exercise were not induced by direct electrical activation of somatic afferent fibers but that they were due to activation of nerve endings in the exercising limb by natural stimuli of a chemical or mechanical kind. In keeping with this, we observe that natural stimulations of somatic nerve endings by passive movements of the limbs or by pressure applied on the muscles could also produce similar, inhibitory, or excitatory reflex effects.

We conclude that cardiovascular and respiratory changes seen during muscular exercise in our experiments were not due to liberation, into the systemic circulation, of metabolic products which might act on the vasomotor and respiratory centers or other reflexogenic areas outside the leg. In fact, the changes a) came on almost immediately with the start of the muscle contraction, b) were maximal within 10-15 s from the beginning of exercise, c) were obtained in deafferented animals with carotid sinuses, aortic and vagus nerves cut, and d) were absent when exercise was induced by stimulating the peripheral end of the divided femoral nerve after the sciatic nerve was also sectioned in the upper thigh.

The present studies also demonstrate that different kinds of muscular exercise can induce different cardiocirculatory reflex responses initiated in the contracting limbs. In fact, rhythmic muscular contractions typically caused inhibitory reflex cardiovascular effects, while tetanic contraction provoked, after an initial transient depressor effect, excitatory reflex cardiovascular responses. Both these types of response were associated with hyperpnea. It is of interest also that in preliminary experiments we observed that depressor and pressor responses to induced rhythmic and tetanic contractions also occur in anesthetized rabbits with intact carotid sinuses and aortic and vagus nerves (23). The increases in systemic and hindlimb perfusion pressures during tetanic contraction in the rabbit were slightly lower than those observed in cats (4, 15) and dogs (2). The increase in heart rate was small, about in the same range of that obtained by other investigators in cats (4, 15, 17). In the present experiments, the rabbits were anesthetized deeply with pentobarbital sodium and this procedure may have re-

FIG. 5. Anesthetized deafferented rabbit. Squeezing quadriceps muscle of 1 hindlimb for 20 s (bar between on and off) causes a reflex pressor response consisting of an increase in arterial pressure (AP), vascular resistance in contralateral hindlimb (HPP), heart rate (HR), and breathing (RESP). Time intervals in seconds.
Depressor afferent fibers that are activated; during tetanic rhythmic exercise it is mainly receptors connected with 20). Our experimental results suggest that during myelinated type III fibers (pressor subgroup III) and unmyelinated (group IV) afferent fibers (7, 10, 16, 18), whereas the pressor responses are mediated by smaller activation of group III (Ay and AS) afferent fibers, nerves. The depressor effects are mainly provoked by carotid chemoreceptors in different types of afferent fibers in the somatic nerves. As is known, pressor and depressor responses are with depressor and pressor afferent fibers in the somatic nerves. This conforms with the previous finding that both depressor and pressor reflex responses, caused in anesthetized and deafferented rabbits by chemical stimulation of muscle afferents, are abolished by pharmacologic blockade of the sympathetic system (21).

The finding that two different patterns of cardiovascular reflexes can be elicited from the contracting hindlimb in response to different kinds of muscular exercise may be reasonably explained by activation of at least two functionally distinct types of sensory receptors associated with depressor and pressor afferent fibers in the somatic nerves. As is known, pressor and depressor responses are carried in different types of afferent fibers in the somatic nerves. The depressor effects are mainly provoked by activation of group III (Ay and AS) afferent fibers, whereas the pressor responses are mediated by smaller myelinated type III fibers (pressor subgroup III) and unmyelinated (group IV) afferent fibers (7, 10, 16, 18, 20). Our experimental results suggest that during rhythmic exercise it is mainly receptors connected with depressor afferent fibers that are activated; during tetanic exercise depressor, but mostly pressor afferent endings, are activated.

Certainly, cutaneous receptors are not significantly involved, since the inhibitory and excitatory responses were not changed by the complete removal of skin from the exercised limb.

It is also unlikely that receptors of the joints play an important role in initiating responses to exercise observed in the present experiments. Rhythmic passive movement of the knee joints led to a small depressor response with hyperpnea qualitatively similar to that obtained during rhythmic active exercise of the hindlimb. This response was reflexive and was abolished following section of the ipsilateral somatic nerves. However, the above effect was unimpaired by local anesthetic injected into the knee joint and articular tissues, while it was prevented by neuromuscular paralysis. This suggests that an afferent input from muscle, rather than from joint, receptors can be responsible for this reflex response.

The most probable source of afferent input for the reflex responses seen during rhythmic and tetanic exercise in this study is that from muscle receptors. It is unlikely that the most well-known mechanoreceptors, muscle spindles and Golgi tendon organs, are involved, because they do not seem to be effective in eliciting inhibitory or excitatory cardiovascular reflexes of much importance (4, 10, 11, 14, 15, 20). Evidence has been also presented that these receptors are not responsible for the increase in pulmonary ventilation during exercise (4, 6, 14, 15). On the other hand, the femoral nerve stimulation we used is subthreshold for the y-efferent fibers and should not cause muscle spindle activation (5, 15). The input from the Golgi tendon organs is carried out in group I fibers, but the data presented above indicate that stimulation of the largest myelinated afferents in the rabbit, as in the cat and dog, produces no significant cardiovascular or respiratory response. Moreover, the present experiments show that the passive stretch of muscles in the anesthetized rabbit is not an effective stimulus for eliciting cardiocirculatory and respiratory responses. This and similar findings of other authors (3, 6, 8, 9, 14) in decerebrate or anesthetized cats and dogs support the view that mechanoreceptors in muscle do not play any important role in causing cardiovascular and respiratory changes during muscular exercise.

Previous investigators have produced evidence that the muscular reflex component of the stimulus to the pressor responses during tetanic exercise is mainly due to “chemosensitive receptors” stimulated by metabolites from the contracting muscles (4, 9, 12, 15, 25). Our results are consistent with this view and, moreover, they suggest that chemosensitive receptors in muscles may also be concerned with the depressor responses evoked during rhythmic muscular work and at the beginning of the tetanic exercise.

In previous studies it has been shown that in the skeletal muscle of the rabbit there are receptors that respond to chemical agents by inducing either inhibitory or excitatory cardiovascular reflex responses (19, 21, 22). In this investigation it was found that bradykinin, potassium ions, and acid solutions, injected into the muscular arteries of anesthetized rabbits produce a “depressor” reflex response; by contrast, hypertonic solutions of NaCl...
or glucose generally cause a “pressor” reflex response. Both responses are associated with hyperpnea. The depressor reflexes and related muscular receptors, connected to the depressor subgroup III somatic afferent fibers and typically activated in the rabbit by minimal amounts of bradykinin, have been indicated as K-chemoreflexes and K-chemosensitive receptors (from kinin); the pressor reflexes and related receptors, connected to the pressor subgroup III and group IV afferent fibers and typically activated by classical pain stimulants and hypertonic solutions, have been indicated as P-chemoreflexes and P-chemosensitive receptors (from pressor and pain) (21).

The excitatory responses seen in the present work during tetanic contraction appear in all respects quite similar to those elicited in anesthetized rabbits by inducing in muscle a condition of hyperosmolarity (21). Also bearing in mind that a pronounced regional hyperosmolarity is known to develop during static contraction (13), P-receptors in skeletal muscle, especially susceptible to hyperosmolarity, may be rightly regarded to play a role in initiating in the rabbit the excitatory reflex responses to static muscular work.

The cardiovascular and respiratory responses seen during rhythmic contraction and at the beginning of the static exercise in the anesthetized rabbit closely resemble the depressor chemoreflexes obtained by injecting chemical stimulants into the muscular arteries. This suggests that activation of K-receptors can occur, by changes in their chemical environment, in the contracting muscles. The fact that activation of depressor receptors in muscle produces reflex vasodilation in the muscular circulation would imply that this receptor system may represent a peripheral mechanism for providing the supply of blood to the skeletal muscles, at least at the beginning of physical exercise.

Obviously, the findings described in this report are pertinent to the rabbit. Whether they also apply to other species is currently under investigation.

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REFERENCES