Activation of Sympathetic Vasodilator and Vasoconstrictor Neurons by Electric Stimulation in the Medulla of the Dog and Cat

By Percy Lindgren and Börje Uvnäs

Electric stimulation in the ventrolateral area of the medulla elicited vasodilation in skeletal muscles, and vasoconstriction in the skin and intestines. The vasodilation was accredited to activity in the cholinergic sympathetic vasodilator outflow previously shown to originate in the motor cortex of the dog. The possible functional significance of the vasodilator fibers in regulating muscle blood flow during exercise is discussed.

In a recent article, we reported that vasodilation could be produced in the skeletal muscles of the dog by electric stimulation in two separate areas of the medulla.1 One responsive area was situated in the most distal part of the rhomboid fossa just below the dorsal surface. It included the region denoted in current textbooks by such names as the vasodilator center or the depressor area. The other "vasodilator" area—not previously described—was situated in the ventrolateral part of the medullary bulb. The vasodilation produced by stimulation in this region was considered to be due to the activation of cholinergic vasodilator nerves in the sympathetic outflow. The present paper reports further observations on sympathetic vasodilator and vasoconstrictor neurons in the lateral part of the medulla.

METHOD

The experiments were performed on cats and dogs anesthetized with chloralose (50-70 mg./Kg.) or dial (50-70 mg./Kg.). The weight of the dogs ranged between 5 and 8 Kg.

The occipital bone, the atlanto-occipital membrane and the dorsal surface of the first cervical vertebra were exposed by removing the overlying muscles. The occipital bone was removed and the atlanto-occipital membrane opened by a longitudinal incision. In order to make the rhomboid fossa accessible to inspection, the caudal part of the cerebellum was removed in most of the experiments.

Topical stimulation in the medulla was performed with a bipolar electrode oriented by means of a Horsley-Clarke instrument. The electric stimuli used were rectangular voltage pulses; their duration was two milliseconds; their voltage 1 to 3 volts; and their frequency 70 per second.

In most of the experiments, the blood flow was recorded with a method previously described by Eliasson and colleagues.2 In principle, the venous outflow was led to a photoelectric drop counter directing an ordinate writer, (see Clementz and Ryberg’s). Venous blood was returned to the animal by continuous intravenous infusion, usually into the external jugular vein. During the course of the investigations, a "closed" technique was substituted for the "open" method. The improved method will be reported elsewhere.

In most experiments, blood flow was recorded in one hind leg only, but in some, concurrently in both. In cats, the blood flow was usually measured in the femoral vein; in dogs, in the popliteal vein. In order to obtain, as far as possible, only muscle blood flow, the limb was skinned and the paw isolated by a tight ligature just above the ankle. Cooling and drying of the naked muscles were minimized by wrapping the loose skin around the extremity. In some experiments, blood flow was studied in regions considered to be chiefly cutaneous, such as in the saphenous vein from the paw and, in dogs, also in the marginal veins of the ear. Intestinal blood flow was recorded either in an arcade vein of the small intestines, or in the inferior mesenteric vein.

Coagulation was prevented by the intravenous administration of 0.1 mg. per kilogram of heparin. Carotid or femoral pressure was recorded with a mercury manometer.

In order to prevent changes in blood flow due to muscular activity caused by cerebral stimulation, the hind part of the animal’s body was denervated at the level of L-5 by tightening a ligature placed around the cord. This procedure spared the sym-
pathetic innervations to the hind legs, since the sympathetic outflow emerges only from the segments above L-5.

Fig. 1. Concomitant records of muscle blood flow in both hind legs during stimulation of lateral left half of the medulla.

Dog 4.0 Kg.; bilateral vagotomy. Both common carotids occluded. Spinal cord ligated at L-5. Artificial respiration. Voltage: 0.75. Duration of each stimulation (1, 2, 3) 15 seconds.

Note: Vasodilator responses confined to left leg and completely blocked by atropine, 0.1 mg. per kilogram (intravenous).

Both sinus nerves were exposed sufficiently to permit electric stimulation. The vagus nerves were dissected free from the sympathetic trunks and—in most experiments—ligated and cut. The baroceptor mechanisms in the carotid sinus were eliminated either by cutting the sinus nerves or by occluding both common carotids. Usually, the animals were given artificial respiration.

Fig. 2. Concomitant vasodilator responses in muscles of right hind leg, and vasoconstrictor responses in skin of right ear during stimulation of right half of medulla.

Dog 8.0 Kg.; spinal cord ligated at L-5. Voltage: 1.25. Duration of each stimulation 15 seconds.

Note: Vasodilator responses in right leg disappear but cutaneous vasoconstrictor responses in ear persist and cause pressor response after atropine.

In some experiments, one of the hind legs was cross-perfused using another animal as donor. The technic has been described previously by Eliasson and co-workers.
Whenever histologic examination was to be made, the brains were fixed in 10 per cent formaldehyde solution, frozen sections were cut 0.04 mm. thick and stained in Weil-hematoxylin. The sections were made in a frontal plane as nearly as possibly parallel to the punctures.

Blood pressure 140

Baroceptor mechanisms remained functionally intact, usually no significant changes occurred in the blood pressure or heart rate, despite a considerable increase in the blood flow. The increase must therefore be due to a vasodila-

RESULTS

Distribution of the Vasodilator Responses in the Muscles. In both cats and dogs, electric stimulation in the ventrolateral part of the medulla produced—after a latency of a few seconds—an abrupt increase in the venous outflow from the muscles of a hind leg. After the end of stimulation, the flow became normalized in about one minute. If any of the baroceptor mechanisms remained functionally intact, usually no significant changes occurred in the blood pressure or heart rate, despite a considerable increase in the blood flow. The increase must therefore be due to a vasodila-

Fig. 3. Concomitant vasodilator responses in hind leg and vasoconstrictor responses in intestinal vessels (jejunal arcade vein) during stimulation in lateral part of medulla.

Dog 7.0 Kg.; bilateral vagotomy. Spinal cord ligated at L-5. Artificial respiration. Voltage: 1.25. Duration of each stimulation (1, 2, 3) 15 seconds; at 4, 20 seconds.

Note: Vasodilator and vasoconstrictor responses seem to counterbalance each other and blood pressure is unchanged. After atropine, 0.2 mg. per kilogram intravenously, the vasodilator responses are accompanied by pressor effects.
In order to investigate the distribution of the vasodilator responses, blood flow was recorded simultaneously in the muscles of the two hind legs. It was then constantly found that no vasodilation occurred in the contralateral extremity (fig. 1).

The Vasodilator Mechanisms. Muscular activity often occurred concomitantly with the vasodilator responses, but it was usually slight. In order to exclude its influence on the muscle blood flow, either mechanically or via metabolites, the hind legs were denervated as described earlier. The vasodilator responses were uninfluenced by this procedure (fig. 1).

Ligation of the spinal cord also eliminated the possibility that vasodilator impulses travel over fibers in the dorsal roots. Thus, the vasomotor nerves must belong to the sympathetic outflow. The question remained, whether the vasodilation was due to an inhibition of vasoconstrictor tone, or to an activation of vasodilator nerves. Since atropine given intravenously, 0.1 to 0.5 mg. per kilogram, completely abolished the vasodilator, as well as the depressor, responses to medullary stimulation (see figs. 1 and 2) the vasodilation was due to activation of cholinergic vasodilator nerves. Eliasson and co-workers have shown that the blocking effect of atropine, in doses used, is in the periphery.

The Responses in Other Vascular Areas. In most experiments, the vasodilator responses were accompanied by only minor depressor or pressor effects. After atropinization, the pressor responses were increased. In order to investigate the cause of the pressor responses, blood
flow was recorded in several experiments concomitantly in one hind leg and in another vascular area. Figure 2 shows the changes in blood flow in the muscles of a hind leg, and in the skin of the ear. A vasodilator response in the muscles was constantly accompanied by vasoconstriction in the skin. Similar reciprocal reactions occurred in the intestinal blood flow. Thus, in figure 3, vasodilation in a hind leg occurs concurrently with constriction of the intestinal vessels.

Figures 2 and 3 also show the conversion of depressor to pressor effects in atropinized animals. In these experiments, the vasodilator responses in the muscles were abolished by atropine, but vasoconstrictor responses still occurred in the skin and the intestines.

Localization in the Medulla of the Sympathetic Vasodilator Outflow. The points at which the sympathetic vasodilator outflow could be activated were found to constitute a narrow longitudinal band, 1 to 2 mm. above the ventral surface of the medulla. It could be traced from the level of the restiform bodies down to 6 or 7 mm. caudal to the distal tip of the rhomboid fossa. Figure 4 shows vasodilations produced by stimulation at this distal level. In the dog, the vasodilator outflow ran about 4 to 6 mm. laterally to the midline; in the cat, the corresponding figure was 3 to 4 mm. Projected on the dorsal surface of the medulla, the "vasodilator" band fell outside the lateral border of the rhomboid fossa (fig. 5). The projection of the "vasodilator" band on a sagittal midline section is shown in figure 6. The maximal width of the band was found to be 1 to 2 mm. Stimulation at a point 1 mm. medially or laterally of a "vasodilator point" was very rarely successful. The dorsoventral extension of the "vasodilator" structures seemed to be even less; when the electrode was moved only 0.5 mm. up or down, they were outside the effective stimulation field.

Just above the "vasodilator" band, a somewhat wider vasoconstrictor layer was regularly observed. Stimulation in this area elicited vasoconstrictor responses accompanied by pressor reactions. The two responsive layers were, in fact, so close together that difficulties were encountered in selective activation of the vasodilator outflow. Accompanying vasoconstrictor responses occasionally made the interpretation of the stimulatory responses difficult. Figure 4 shows the vasomotor responses obtained on stimulation at adjacent points during one and the same puncture.
DISCUSSION

In studies of the cerebral distribution of the sympathetic vasodilator nerve outflow to the skeletal muscles, Eliasson and colleagues observed that sympathetic vasodilator discharges could be produced by electric stimulation in circumscribed areas in the hypothalamus, in the motor cortex and in the field between these areas. The observations were interpreted as indicating that the sympathetic vasodilator neurons originate in the motor cortex and pass caudally via the hypothalamus. Subsequent evidence suggested that the vasodilator impulses relay in the anterior part of the hypothalamus, and the neurons have been traced down to the cranial border of the medulla. Since the vasodilator responses were abolished by the peripheral action of small concentrations of atropine, the postganglionic sympathetic vasodilator fibers were considered to be cholinergic.

The present experiments have shown that electric stimulation within a longitudinal band passing through the ventrolateral part of the medulla can produce vasodilation in the skeletal muscle of an ipsilateral hind limb. The nature of the vasodilator responses, the fact that they were effected via the sympathetic outflow and abolished by atropine convinced us that the vasodilation was due to impulses in cholinergic vasodilator fibers in the sympathetic outflow. This outflow appears to form a direct extension of the cortico-hypothalamic-medullary pathway previously observed.

The vasodilator responses in the muscle previously reported to follow cortical or hypothalamic stimulation were bilateral. Those elicited by stimulation in the bulbar vasodilator band were exclusively ipsilateral, indicating that the vasodilator neurons cross at a supramedullary level.

It is impossible to determine from the present observations whether the bulbar “vasodilator” band constitutes a pure fiber tract, or whether it includes one or more relay stations. The former alternative appears the more plausible, but investigations in progress may provide the answer. The question is of certain interest, since it touches upon the problem of whether or not the bulbar portion of the sympathetic vasodilator outflow plays any part in the medullary vasomotor control mechanism.

The fact that the vasodilator responses in the muscles were regularly accompanied by vasoconstrictions in the skin and the intestines needs some comments. Eliasson and associates observed similar vasoconstrictions when sympathetic vasodilator discharges were elicited by hypothalamic stimulation. At least in the dog, these vasoconstrictions seemed to be due to the buffering action of the baroreceptor mechanisms. When these mechanisms were intact, the blood pressure usually showed no or only slight changes, despite pronounced vasodilations in the muscles. When the baroceptors were functionally eliminated, the vasodilator responses were accompanied by depressor reactions. When the vasodilator responses were blocked by atropinization of the animal, no vasoconstrictions supervened. The vasoconstrictor responses to bulbar stimulation behaved differently; they persisted in the atropinized animal and were therefore due, at least partly, to the direct activation of vasoconstrictor neurons.

In previous articles, the hypothesis was advanced that the sole function of the sympathetic vasodilator nerves is to participate in regulating the blood flow in the muscles during muscular activity. It is possible that the vasoconstrictor neurons which accompany the vasodilator fibers are also specially concerned with the redistribution of the circulating blood necessary during activity. The anatomic course of these vasodilator and vasoconstrictor fibers favors such an hypothesis. It is true that the responsive points have not yet been localized microscopically, but they seem to be situated adjacent to the pyramidal tract.

SUMMARY

Vasodilation was produced in the muscles of the ipsilateral hind leg by electric stimulation in the ventrolateral part of the medulla. The vasodilation was blocked by atropine and is assumed to be due to discharges in cholinergic sympathetic vasodilator nerves.

The “vasodilator” area was found to form a longitudinal band running 1 to 2 mm. above the ventral surface of the medulla. It was
traced from the level of the restiform bodies down to 6 to 7 mm. below the obex. This "vasodilator" band is assumed to form the bulbar extension of the cortico-hypothalamic-mesencephalic vasodilator pathway previously observed.

Vasoconstrictor fibers accompany the vasodilator outflow. The possibility that these vasomotor neurons take part in the regulation of the muscle blood flow during muscular activity is suggested.

REFERENCES


5 Lindgren, P., and Uvnäs, B.: Unpublished observations.

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