Inhibition of the Vasomotor System of the Anesthetized Dog by Epinephrine and Norepinephrine

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Epinephrine, acting centrally, inhibits the vasomotor system to produce vasodilatation. This inhibition may be produced by a number of mechanisms, including stimulation of the sino-aortic baroreceptors, chemoreceptors, and thoracic mechanoreceptors, and by blocking transmission in the vasomotor pathway at the sympathetic ganglia.

The object of the following experiments was to determine the relative importance of these mechanisms in the anesthetized dog, to compare the actions of epinephrine and norepinephrine, and to find which blood vessels in the limb dilated and through which system of vasomotor nerves the dilatation was brought about.

Methods

Fifty-five dogs (7 to 16 Kg.) were anesthetized with sodium pentobarbital (Nembutal, 25 mg./Kg., injected intravenously), and the blood pressure was recorded from the femoral artery. One hind leg was separated from the body except for the sciatic nerve, the skin, muscle, and bone being divided. It was perfused through the femoral artery with oxygenated Krebs' solution contained in a reservoir at a height of 200 cm. and passed through a heating coil at 37 C. to the cannula. The perfusion pressure was measured with a water manometer attached to a side arm of the cannula, and before each experiment the pressure was adjusted to about 50 em. by means of a clip between the heating coil and the cannula. Subsequent changes in perfusion pressure were due to alterations in the peripheral resistance of the limb and were brought about entirely through vasomotor fibers in the sciatic nerve.

The solutions of synthetic (-) epinephrine (Burroughs Wellcome) and synthetic (-) norepinephrine (Levophed) were freshly prepared and diluted to 10 ml. with 0.9 per cent saline immediately before injection in a standard time of five seconds. To eliminate variations in the response of the preparation, all changes of peripheral resistance were expressed as a percentage of the change produced by the same dose of epinephrine (1 to 5 µg./Kg. of the base according to the sensitivity of the preparation) injected as soon as the basal conditions were restored.

Results

Epinephrine injected intravenously into the body of the dog produced a significantly greater vasodilatation in the leg, which had been skinned and its paw ligatured, than in the normal unskinned limb in 46 experiments on 11 dogs (P < 0.01), which shows that dilatation occurred predominantly in the blood vessels to the skeletal muscles. It has already been shown in the cat that dilatation produced by the central action of epinephrine was found in the skinned limb and therefore in the skeletal muscle blood vessels. The dilatation produced by the central action of epinephrine was unchanged after blocking the cholinergic vasodilator fibers to the leg with atropine (200 mg. atropine sulphate were injected through the perfusion cannula of four dogs) but was abolished or greatly reduced by adrenergic blockade with phenoxybenzamine (5 mg. Dibenzyline were injected into the perfusion cannula in four dogs), showing that the dilatation was mediated by a reduction of the vasoconstrictor tone rather than through increased activity in the cholinergic dilator system. The above experiments were made after baroreceptor inactivation so that the dilatation could not be attributed to the stimulation of the sino-aortic receptors.

The part played by the sino-aortic baroreceptors in the central dilator action was estimated by comparing the dilatation in the leg produced by intravenous injections of the catecholamines before and after the baroreceptors had been inactivated by ligaturing
The mean change of peripheral resistance in the perfused leg is expressed as a percentage of the change produced by the same dose of epinephrine (1 to 5 μg/Kg.) injected intravenously after inactivating the baroreceptors (--BARO.). The upper figure in the bar is the number of pairs of experiments yielding the mean, and the lower figure is the number of dogs used. The horizontal lines above and below the mean represent its 50 per cent confidence limits. Norepinephrine (N) and epinephrine (E) were injected intravenously (IV) into the vertebral arteries (VA) and into the lumbar arteries (LA).

The carotid arteries and their branches above and below the sinuses and by vagotomy at the same level. This procedure was found to be adequate since a rise of blood pressure in the aortic arch and carotid arteries produced by compression of the abdominal aorta no longer produced reflex vasodilatation in the perfused leg. Although this procedure could provide no direct evidence of baroreceptor stimulation by the catecholamines, there can be no doubt that such stimulation does occur,14,15 so that it seems reasonable to attribute any change in the response of the preparation, at least in part, to the loss of baroreceptor stimulation. Following baroreceptor inactivation, epinephrine retained 55 per cent of its previous central dilator action, whereas norepinephrine retained only 20 per cent of its previous activity (fig. 1). In the dog with normal baroreceptor activity, as in the cat,10 vasodilatation in the leg produced by intravenous injections of epinephrine and norepinephrine were equal (fig. 2), but after the baroreceptors had been inactivated, norepinephrine had 40 per cent of the activity of the same dose of epinephrine. These results suggest that norepinephrine exerted a stronger baroreceptor-stimulating effect, which is in keeping with its greater pressor activity, viz. twice that of epinephrine in 50 pairs of experiments on 18 dogs (P < 0.01).
FIGURE 3
Female animal, 10 Kg., pentobarbital anesthesia, baroreceptors inactivated. The records from above show the perfusion pressure to the leg in cm. of water, the arterial blood pressure in mm. Hg, and the time in 10-second intervals. At E and N, 25 µg. of epinephrine and norepinephrine, respectively, were injected into the lumbar arteries.

After inactivating the baroreceptors, the catecholamines were injected into various parts of the circulation of the body to localize the site responsible for their central vasodilator action. It was found that an injection of epinephrine into the lumbar arteries through a cannula in the abdominal aorta with its celiac, mesenteric, and iliac branches ligatured produced a dilatation in the leg which was 140 per cent greater than when the same dose was injected intravenously. This observation suggests that an important component of the central dilator action of epinephrine is through sympathetic ganglion blockade. When the same dose of norepinephrine was injected into the lumbar arteries, the vasodilatation was 50 per cent of that produced by epinephrine (fig. 3).

No evidence of the thoracic mechanoreceptor system was found, injections of the catecholamines into the abdominal aorta producing a far greater effect than when the same dose was injected intravenously. The action of the catecholamines was unchanged after ligaturing the celiac and mesenteric arteries, which would appear to exclude celiac chemoreceptor reflexes from playing an important part in their central vasodilator activity.

Although injections of the catecholamines into the vertebral artery, through a cannula passed along the subclavian artery, usually had no greater effect than when the same dose was injected intravenously, in two dogs vasodilatation occurred after a shorter latent period, and in one dog the dilatation was clearly greater than for the intravenous injection. These observations indicate that the cerebral chemoreceptor buffer mechanism may be partly responsible for their central dilator action. On the other hand, vertebroarterial injections of barium chloride (0.5 to 7 mg./Kg.) invariably produced vasoconstriction in the perfused limb in 15 experiments on five dogs. This result is in accord with the findings of Schneider and co-workers and is not compatible with the concept of a cerebral chemoreceptor buffer mechanism.

Discussion
Epinephrine and norepinephrine acting centrally, produced a dilatation of the blood vessels in the skeletal muscle of the leg which was mediated by an inhibition of the pre-existing constrictor tone rather than by cholinergic vasodilator activity. Whereas a large proportion (80 per cent) of the effect of norepinephrine was lost after baroreceptor inactivation, this was not the case for epinephrine (45 per cent).

After inactivating the baroreceptors, an attempt was made to localize the part of the vasomotor system inhibited by the catecholamines, and it was found that by far the greatest dilatation followed injections into the
lumbar arteries, which suggests that their main effect was to block transmission through the synapses in the vasoconstrictor pathway. The comparatively small action of norepinephrine on synaptic transmission accounts for its greatly reduced effect on the vasomotor system after baroreceptor inactivation, whereas the stronger action of epinephrine on the synapses permits a larger proportion of its activity to remain. Norepinephrine's greater pressor activity and consequent baroreceptor stimulation and its weaker effect on synaptic transmission readily account for the total central inhibitory action of norepinephrine being equal to that of epinephrine.

The question of a direct inhibition of the vasomotor center by the catecholamines cannot be regarded as settled. Recent work on this topic has been contradictory, Taylor and Page reporting that epinephrine had a pronounced depressor action through a cerebral chemoreceptor buffer mechanism, whereas Schneider and co-workers concluded that the action of epinephrine on the carotid sinus accounted for almost the whole of its depressor action when injected into the isolated head, the central action of epinephrine being negligible after carotid sinus deactivation. I am unable to account for this discrepancy but can only comment that my findings, with regard to vertebrarterial injections of the catecholamines after baroreceptor inactivation, are more consistent with the view that cerebral chemoreceptor stimulation is of relatively small importance in the central depressor action of the catecholamines.

Summary

The actions of epinephrine and norepinephrine on the vasomotor system of 55 dogs anesthetized with sodium pentobarbital were investigated with the innervated, perfused leg preparation attached to the body by the sciatic nerve alone. Injections of these catecholamines into the body of the dog produced a dilatation of the vessels in the skeletal muscle of the perfused limb which was unaltered by cholinergic blockade with atropine and no longer occurred after adrenergic blockade with phenoxybenzamine. Vasomotor inhibition by norepinephrine was greatly reduced after baroreceptor inactivation, whereas a much greater proportion of epinephrine's activity remained and is attributed to sympathetic ganglion blockade.

Acknowledgment

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Addendum

Since this paper went to print, Lloyd Beck has published a paper in which he describes an active vasodilation in the skeletal muscle blood vessels of the dog's innervated perfused hind leg produced by the central action of the catecholamines, which, he suggests is mediated through the release of histamine by sympathetic vasodilator nerve fibers. Beck, L.: Active reflex dilatation in the innervated perfused hind leg of the dog. Am. J. Physiol. 201: 123, 1961.

References

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