CENTRAL AND REFLEX VASOMOTOR EFFECTS OF ADRENALIN

(UDC 615.361.45-092.259:612.18)

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 58, No. 11,
pp. 19-22, November, 1964
Original article submitted June 18, 1963

The elucidation of the effect of the central action of adrenalin and the limitation of its reflex and direct influences to certain vascular fields are factors of considerable interest to the understanding of the mechanism of the vasomotor effects of this substance. The most suitable form of experiment for the study of the central action of drugs is that using an animal's head, humorally isolated and perfused with the blood of a donor, with its carotid sinuses denervated, and with the nervous connections of the head with the trunk intact. Injection of drugs into the vessels of the head can be used to determine the character of their direct action on the nervous structures of the brain by recording the vasomotor effects in the trunk.

By the use of an experiment of this type, Taylor and Page [5] showed that the injection of pressor substances (adrenalin, noradrenalin, barium chloride) into the vessels of the humorally isolated head brings about a depressor reaction in the vessels of the trunk. Conversely, the injection of depressor preparations into the vessels of the head causes a pressor reaction in the trunk. These authors concluded from their findings that a central buffer mechanism exists, regulating the general level of the blood pressure in the vessels of the trunk.

However, these results were not confirmed by the work of Schneider and co-workers [4], using a similar method. They found that of all the pressor substances tested, only adrenalin causes a depressor reaction in the vessels of the trunk when injected into the cerebral circulation. However, the injection of depressor drugs into the vessels of the head causes, as a rule, a depressor reaction in the trunk. Schneider therefore concludes that there are insufficient grounds for recognizing the presence of a centrally situated buffer system. So far as the vasodilator effect of the central action of adrenalin is concerned, in the opinion of these authors this also cannot be of physiological importance, for this effect arises only after injection of doses of adrenalin of the order to 10 times larger than the maximally possible physiological concentrations.

The possibility of obtaining a depressor effect in the trunk by injecting large doses of adrenalin into the vessels of the humorally isolated head was demonstrated in principle in our laboratory by S. I. Bakulev. Because of the considerable interest of this problem and the conflicting nature of the few results reported in the literature, we carried out experiments in order to verify the effect of the central action of adrenalin.

METHOD

Experiments were conducted on dogs anesthetized with urethane and chloralose. The head of the experimental dog was totally isolated in respect of its blood vessels and perfused with blood from a donor dog. The carotid sinuses were denervated. In this way the head of the experimental animal retained only its nervous connections with the trunk, by means of the spinal cord and the vago-sympathetic trunks. The blood pressure of the experimental animal and donor was recorded in the femoral artery.

RESULTS

The 9 experiments of series I showed that injection of large enough doses of adrenalin (not less than 100 μg/kg) into the vessels of the isolated head evokes a definite depressor reaction in the vessels of the trunk. This reaction

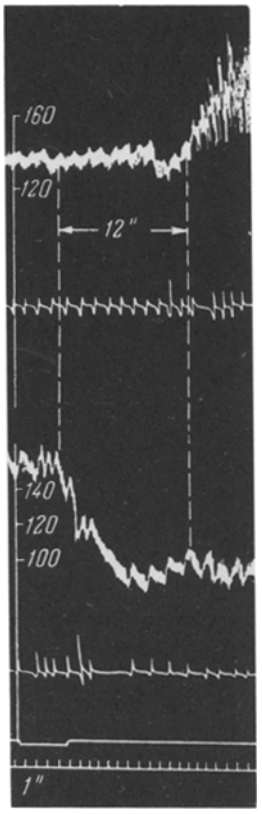

Fig. 1. Changes in blood pressure after injection of adrenalin into circulation of the humorally isolated head. Significance of curves (from top to bottom): blood pressure and respiration of donor, zero line of blood pressure, blood pressure in femoral artery and respiration of experimental dog, stimulation marker and zero line of arterial pressure, time marker (1 sec).

is independent of both the action of adrenalin on the carotid sinuses, since these were denervated and the results verified, and the variations in perfusion pressure in the vessels of the head. A kymogram of one of the experiments is shown in Fig. 1. Analysis of this kymogram shows that the depressor reaction of the vessels of the trunk of the experimental dog develops when the perfusion pressure in the vessels of the head is unchanged. The donor's blood pressure rose only when 12 sec had elapsed after the injection of adrenalin, when the venous blood removed from the head had passed through the extracorporeal system (pump, connecting tubes) and had entered the donor's circulation.

The depressor reaction arising in the vessels of the trunk as a result of the central action of adrenalin may evidently be regarded as the manifestation of a reflex from the chemoreceptors, stimulated by the adrenalin injected into the cerebral circulation. No results were obtained, however, which could be used to localize these vascular or tissue receptors more accurately and to define their characteristics.

It should be noted that the views of Taylor and Page, mentioned above, concerning the existence of a central buffer mechanism were not confirmed by our experiments, for injection of depressor substances (acetylcholine) into the cerebral circulation caused a lowering of the blood pressure in the trunk.

In the experiments of series II the regional vascular reactions arising after injection of moderate doses of adrenalin (5-20 μg/kg), adequate for obtaining a clear pressor reaction of the systemic blood pressure, were investigated. In this series (34 experiments) the method of resistography [1] was used, based on the autoperfusion of the region to be investigated with a constant minute volume of blood. These experiments were conducted on small dogs anesthetized with chloralose and urethane. Heparin was injected to prevent the blood from clotting.

The dynamics of the changes in the peripheral resistance of the blood flow were studied after injection of adrenalin into the vessels of the hind limb (perfusion through the femoral artery), the intestinal vessels (perfusion through the superior mesenteric artery) and the vessels of the brain (perfusion through the internal carotid and vertebral arteries. In the last case the central and peripheral ends of the common carotid arteries and one of the vertebral arteries were connected with the pump. The second vertebral artery and the external carotid arteries were ligated, and the carotid sinuses were denervated. Adrenalin was injected either into the femoral vein or into the vertebral artery.

In order to detect the reflex and direct actions of adrenalin on the vessels of the limb and intestine, the time taken for the blood to pass through the pump system, which was deliberately lengthened with coiled tubes [2, 3], was taken into account. The appearance of a reaction of the vessels of the region to be investigated during the time that the blood was passing through the extracorporeal system demonstrated its reflex origin. At the end of the time during which the blood passed through the artificial circulatory system, the second phase of the reaction of the vessels occurred, resulting from the direct action of adrenalin on the vessels of the perfused region. The reaction of the vessels of the brain and of the vessels of the hind limb to injection of adrenalin into the femoral vein (5 μg/kg) is shown in Fig. 2a.

With a very slight elevation of the general blood pressure level a definite increase was observed in the perfusion pressure in the carotid and vertebral arteries, indicating an increase in the resistance to the blood flow in the cerebral vessels and a decrease in the resistance to the blood flow in the vessels of the limb.

Injection of adrenalin (10 μg/kg) into the vertebral artery (Fig. 2b) caused an immediate and sharp constriction of the cerebral vessels and dilatation of the vessels of the perfused limb. This depressor reaction, reflex in nature,

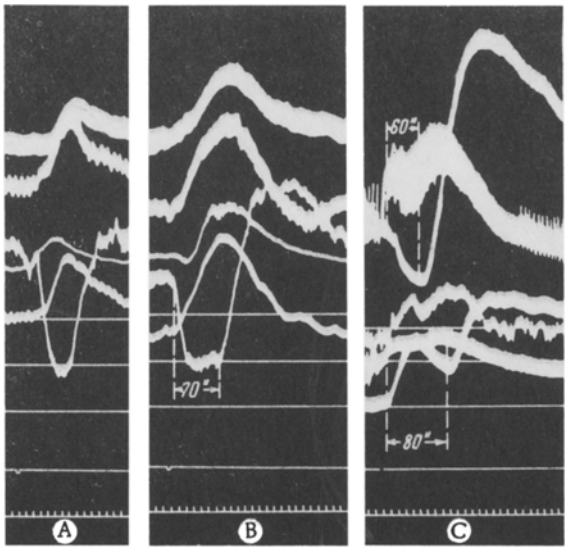

Fig. 2. Changes in the peripheral resistance of the circulation in the vessels of the brain, hind limb, and intestine after injection of adrenalin into the femoral vein in a dose of 5 μg/kg (a), into the vertebral artery in a dose of 10 μg/kg (b), and into the vertebral artery in a dose of 20 μg/kg (c). Significance of curves (from top to bottom): a) perfusion pressure in vertebral artery, right carotid artery, and femoral artery, systemic blood pressure, perfusion pressure in left carotid artery, zero lines of manometers, time marker (10 sec); b) perfusion pressure in vertebral artery, in right carotid artery, systemic blood pressure, perfusion pressure in femoral artery, in left carotid artery, zero lines of manometers, time marker (10 sec); c) systemic blood pressure, perfusion pressure in femoral artery, carotid artery, vertebral artery, and superior mesenteric artery, zero lines of manometers, time marker (10 sec).

lasted 70 sec, corresponding to the time taken by the blood to pass through the extracorporeal circulation. This was followed by a second pressor phase, caused by the direct action of adrenalin on the limb vessels.

The result of injection of adrenalin in a dose of 20 μg/kg into the vertebral artery is shown in Fig. 2c. The reactions of the cerebral vessels and of the vessels of the limb were of the type described above. A reflex and a direct action of adrenalin could also be detected in the intestinal vessels. The time taken for blood to pass through the extracorporeal circulation in the perfusion system of the superior mesenteric artery was 80 sec. During this period a first wave of elevation of the perfusion pressure (reflex effect) could be seen. After the adrenalin had passed directly into the vessels of the intestine, a second wave of increase of the resistance to the blood flow was found, caused by the direct action of adrenalin.

Hence, two phases were observed in the action of adrenalin on the vessels of the limb and intestine, the result of the reflex and direct action of adrenalin. Adrenalin caused a reflex dilatation of the limb vessels and constriction of the intestinal vessels. As a result of the direct action of adrenalin the vessels of the limb and intestine were constricted.

The view is firmly established that adrenalin dilates the cerebral vessels, on the basis of observations on the reactions of the superficial vessels of the brain. Meanwhile, in an experiment on the humorally isolated head, Kovacs has shown that following the central administration of adrenalin in a dose of 10-50 μg/kg, there is a reduction in the volume of blood flowing through the head.

As a result of our experiments it is possible to define the composite reaction of the cerebral vessels to injection of adrenalin, both intravenously and directly into the cerebral circulation. The results obtained demonstrate that injection of adrenalin increases the resistance to the blood flow in the cerebral vessels. This rule, observed in all our experiments without exception, indicates that the over-all reaction of the cerebral vessels to injection of adrenalin into the blood stream is vasoconstrictive.

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