MODE OF ACTION OF REFLEXES DUE TO INTRAVASCULAR ADMINISTRATION OF CERTAIN SUBSTANCES ON RESPIRATION AND BLOOD CIRCULATION

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The introduction of therapeutic substances into the vascular bed occupies an important place in the system of therapeutic measures.

The medicines introduced into the blood stream can produce changes in the activity of the body systems, including the respiratory and cardiovascular systems, either by direct action on their peripheral elements, or by reflex processes, or by direct action on the nervous centers.

The question of the role of receptors of vessels, capillaries, and tissues in the reflex component of the effect of intravascular injections of medicines and chemical stimuli on the respiration and blood circulation has not been settled experimentally.

V. N. Chernigovskii [9, 10], L. M. Ishimova [6], and A. D. Ado [1] believe that the effects induced by intravascular injection of chemical stimuli are due to excitation of the tissue receptors. The difference in the reflex effects on respiration and circulation following the intra-arterial and intravenous injection of chemical stimuli is attributed to the excitation of local tissue receptors with intra-arterial injection of the substance and the absence of such excitation with intravenous injection.

T. A. Grigor'eva [4,5] and V. V. Kupriyanov [8] assign the chemoreceptive function of the organism to the vascular-tissue receptors providing innervation of the capillaries and the connective tissue surrounding them. Heger [11] and P. Yu. Kaufman [7] regard the capillary receptors as solely responsible for the response of organs to chemical influences.

Pagano [12], V. S. Galkin [3], and A. G. Bukhtiyarov [2] ascribe the reflex effects observed on intravascular injection of chemical stimuli primarily to the stimulation of the vessel receptors. The difference in reactions of of the respiratory and cardiovascular systems with intra-arterial and intravenous injection of chemical stimuli is regarded as the result of chemical stimulation of different kinds of vessel receptors. On intra-arterial injection of chemical stimuli, the arterial receptors are excited, and on intravenous injection the venous receptors are excited.

The contradictory opinions as to the role of vascular receptors in the mechanism of the respiration and circulation reactions induced by intravascular injection of chemical stimuli have led us to investigate this process experimentally.

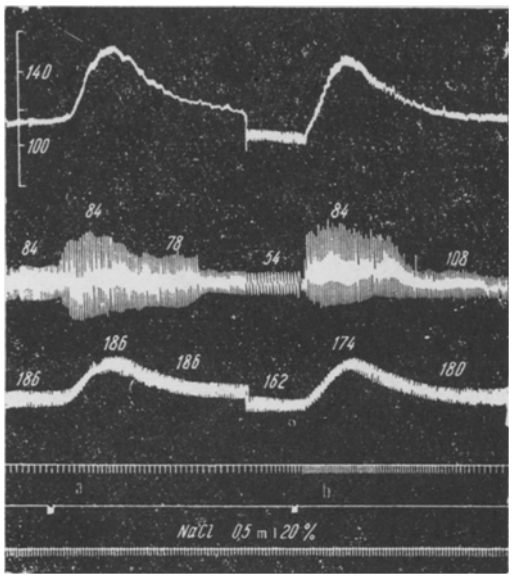

Fig. 1. Nature of reflex effects on respiration and circulation on delivery of chemical stimuli to the limb receptors by "direct" and "reverse" perfusion. Meaning of curves (top to bottom): arterial pressure, respiration, heartbeat; drop-recorder marks, stimulation marks, time marks (1 sec). Explanation in text.

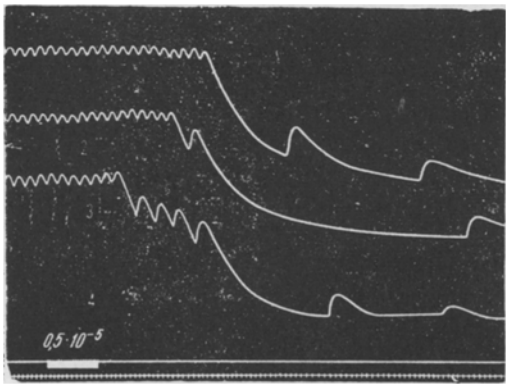

Fig. 2. Direct relationship between latent period of reactions of cardiovascular system and length of path of chemical stimulus introduced into different veins of greater circulation. Meaning of curves (top to bottom): depressor reaction on injection of chemical stimulus into subcutaneous vein at back of foot, into femoral vein, and into jugular vein; stimulation marks and time marks (0.45 sec). Explanation in text. 1) Subcutaneous vein; 2) femoral vein; 3) external jugular vein; 4) acetylcholine.

Method of Experiments

The experiments were performed on 62 cats under intravenous urethane narcosis. We recorded the respiration and arterial pressure. We used the method of perfusion of the vascularly isolated hind limb. The femoral and sciatic nerves were undamaged. The limbs were perfused with Ringer-Locke solution through cannulae inserted into the peripheral sections of the femoral vessels. The direction of flow of the perfusion liquid through the limb vessels was varied. For "direct" perfusion of the limb, the Ringer-Locke solution passed into the limb vessels through the cannula inserted into the artery and flowed out of the organ through the vein. On "reverse" perfusion of the limb, the perfusion liquid flowed into the vessels through the cannula inserted into the vein and flowed out through the arterial system. In "direct" perfusion of the limb, the chemical stimuli were introduced into the flow of Ringer-Locke solution through the cannula inserted into the artery, and in "reverse" perfusion they were introduced through the cannula inserted in the vein.

Experimental Results

The delivery of 0.5 ml of 20% sodium chloride solution to the receptors of the hind limb by "reverse" perfusion produced hypertension and dyspnea (Fig. 1a). The delivery of the chemical stimulus to the receptors of the limb by "direct" perfusion was accompanied by similar changes in respiration and circulation (Fig. 1b).

It should be noted that when the solution of substance was supplied to the hind limb receptors through the venous bed, the latent period of the reflex reactions of the respiration and circulation was longer than when this substance acted on the organ receptors through the arterial bed.

In addition to the above method, we inserted an injecting needle into the subcutaneous vein at the back of the foot. In "direct" perfusion of the organ, the chemical stimulus introduced into the subcutaneous vein through the needle passed through the veins of the limb and issued from the organ through the cannula inserted in the vein. The chemical stimulus acted on the vein receptors, but did not penetrate into the capillaries.

We found that flushing of the limb veins with a number of chemical stimuli was not accompanied by respiration and circulation reactions. However, on "reverse" perfusion of the limb, the introduction of chemical stimuli into the flow of Ringer-Locke solution by means of the cannula inserted into the vein produced hypertension, tachycardia, and dyspnea.

These results show that, in the case of intravenous injection of chemical stimuli the venous receptors are not responsible for the respiration and circulation reactions.

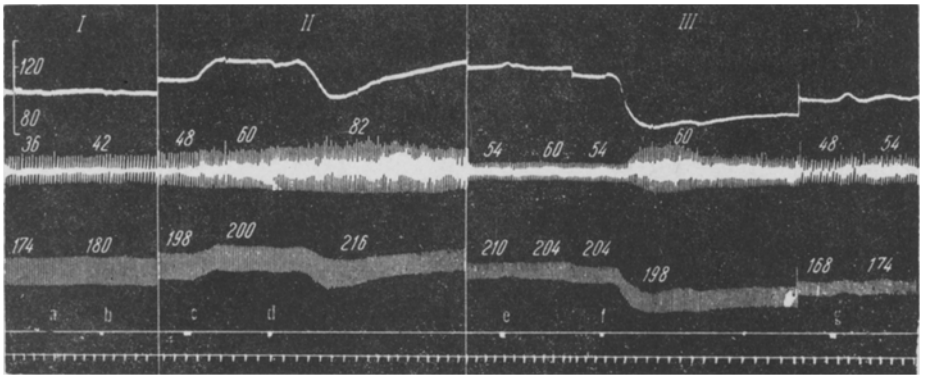

Fig. 3. Effects produced by acetylcholine introduced into vessels of limb connected with organism by femoral vessels and femoral and sciatic nerves. Meaning of curves (top to bottom): arterial pressure, respiration, heartbeat, stimulation marks, time marks (5 sec). Explanation in text.

In this connection, it was important to compare the latent period of reflex reactions of the respiratory and cardiovascular systems following the introduction of chemical stimuli into different veins of the greater circulation.

The corresponding experiments showed that the latent period of hypotensive reaction on injection of acetylcholine into the jugular vein was shorter than on injection into the femoral vein, and shorter again than on injection into the subcutaneous vein at the back of the foot of the hind limb (Fig. 2).

The role of the vascular receptors in the mechanism of the respiration and circulation reactions following intravascular injection of substances was also studied on animals with the limb amputated at the upper part of the femur, but still connected to the organism by the femoral artery, femoral vein, and femoral and sciatic nerves.

The introduction of 5 μg of acetylcholine in 0.5 ml of physiological saline into the femoral artery of this limb distal to a clamp placed on the femoral vessels produced no distinct changes in the respiration and circulation (Fig. 3a). Removal of the clamp from the vessels was not accompanied by reactions of these systems (Fig. 3b). On injection of 5 μg of the substance in 1 ml of physiological saline into the subcutaneous vein at the back of the foot after successive clamping of the vein and artery of the limb, hypertension set in and dyspnea appeared (Fig. 3c). Restoration of the blood flow in the femoral vessels produced a fall in the arterial pressure and an enhancement of the dyspnea (Fig. 3d). On introduction of 1 ml of physiological saline into the subcutaneous vein of the foot with the femoral vessels clamped again, no changes in respiration and circulation were observed (Fig. 3e). Hence, the reflex effect which occurred in the previous observation was due to the action of the chemical, and not the mechanical factor on the receptor. When this dose of the chemical stimulus was introduced into the subcutaneous vein of the limb, it produced a considerable drop in arterial pressure and an intensification of the respiratory movements (Fig. 3f). The introduction of acetylcholine into the subcutaneous vein in the case where only the femoral vein was clamped was not accompanied by any distinct changes in respiration and circulation (Fig. 3g). It follows from these results that excitation of the respiratory and vasomotor centers on introduction of acetylcholine into the subcutaneous vein of the limb after excluding its vascular system from the general circulation of the animal cannot be attributed to chemical stimulation of the venous receptors.

We know that injection of certain chemical stimuli into the femoral vein leads to depression of respiration and circulation, while on injection of stimuli into the femoral artery these systems are excited.

If the difference in the reactions of the respiration and circulation on intra-arterial and intravenous injection of a number of chemical stimuli depends on the stimulation of different vascular receptors, we would expect a rise in arterial pressure and dyspnea when chemical stimuli are delivered to the limb receptors by "direct" perfusion. When chemical stimuli are delivered to the limb receptors by "reverse" perfusion, there would be a different effect, i.e., a fall of arterial pressure and a depression of respiration.

However, in response to the introduction of chemical stimuli into the flow of perfusion solution entering the limb vessels through the arterial and venous bed, we noted the same reflex reactions of hyperpnea and

hypertension. The same reflex effect arose in spite of the fact that with "direct" perfusion the chemical stimulus acted first on the arterial system of the organ, while with "reverse" perfusion it acted first on the venous system.

A fact worth noting is that, with equal volume rates of flow of Ringer-Locke solution through the limb vessels in both kinds of perfusion, the latent period of the reflex reactions when the chemical stimulus acted on the receptors through the arterial bed was shorter than with action through the venous bed.

In view of the above, we infer that, in the vascular bed of organs, there are no special arterial or venous receptors, the chemical stimulation of which would be accompanied by opposite kinds of effects on the respiration and circulation.

The absence of reflex changes of the respiratory and cardiovascular systems following the action of a chemical stimulus on the limb arteries and veins and the direct relationship between the latent period of the respiration and circulation reactions and the length of the path of the substance through the veins of the greater circulation indicate that the receptors of the main vessels are not included among the receptors which, on chemical stimulation byintra-arterial or intravenous injection of pharmacological agents, lead to stimulation of the respiratory and vasomotor centers.

The receptors which are chemically stimulated by intravascular injection of chemical stimuli, and thus give rise to reflex effects, are obviously located outside the intimae of the large vessels of the organ. Since the sectional area of the venous vessels is greater than the sectional area of the arterial vessels, the chemical stimuli on "direct" flow of the perfusion liquid reach the reflexogenic zone of the organ earlier than in the case of "reverse" flow of the liquid.

We can postulate that the reflexogenic zone, which excited the reflex effects when the chemical stimuli are introduced into the blood stream, consists of the receptors of the capillaries and tissues.

When 5μg of acetylcholine in 1 ml of physiological saline was introduced into the subcutaneous vein at the back of the foot after clamping of the femoral vein, some of the chemical stimulus obviously passed back into the capillary and arterial system of the limb. The venous receptors and capillary receptors were subjected to the chemical action, but no reflex effect on respiration and circulation was noted. After clamping of the femoral vein and femoral artery, the introduction of the chemical stimulus into the subcutaneous vein of the limb was accompanied by hypertension and dyspnea.

When the clamp was placed on the two femoral vessels, the appearance of the reflex reactions of respiration and circulation following injection of acetylcholine into the subcutaneous vein of the limb was associated with an increase of pressure in the organ vessels, owing to the successive closing of the femoral vessels and the introduction of a certain volume of the solution into the closed vascular bed. The pressure in the capillaries was greater than in natural conditions of blood supply to the limb, and the chemical stimulus passed into the tissue in a dose sufficient to cause stimulation of the tissue receptors.

On intra-arterial injection of pharmacological agents, various receptor endings are probably stimulated, but stimulation of respiration and circulation is due mainly to stimulation of the tissue receptors.

In the case of intravenous injection of chemical stimuli, the reflexogenic zone which, under chemical stimulation causes depression of the respiratory and motor centers, is the lesser circulation.

SUMMARY

In experiments staged on cats, the author made use of the method of perfusion of the hind limb. In intravascular injection of chemical irritants, the vascular receptors play no essential role in the mechanism of respiratory and circulatory reflex reactions. A difference of reactions of respiration and circulation, observed in intra arterial and intravenous injection of certain chemical irritants, is called forth by irritation of receptors of various organs which are the source of counter-reflex influences on the respiration and circulation. Upon intra-arterial injection, excitation takes place in the receptors of the organ into the artery of which the chemical irritant was introduced, attended by stimulation of the respiratory and vasomotor centers. Intravenous injection of chemical irritants excites the receptors of organs of the lesser circulation, bringing about reflex inhibition of these centers.

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