# RELATIONSHIP BETWEEN DEPRESSOR AND PRESSOR REACTIONS TO ACETYLCHOLINE

B. I. Tkachenko

K. M. Bykov Division of General Physiology (Head, Professor A. V. Rikkl'), Institute of Experimental Medicine (Director, Active Member AMN SSSR Professor D. A. Biryukov) of the AMN SSSR, Leningrad
(Presented by Active Member AMN SSSR D. A. Biryukov)
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The effect of intravenous injections of certain stimulants is not limited to their action on receptors in local vascular regions (except when this is determined by special experimental conditions), but changes take place in the vascular system as a whole. If the effect produced by the stimulus is similar in character in different parts of the vascular system, the general reaction of the arterial pressure is given by the sum of the regional changes and the variations in cardiac activity. Certain stimulants, for example acetylocholine, nicotine, and other solutions, produce a depressor reaction when their effect is general (when injected intravenously), but when parts of the body whose blood vessels are isolated from the rest of the vascular system (i.e., limbs) and which retain only their nervous connection with the body are perfused with these same solutions, a pressor results [6,8,9]. Consequently, injection of acetylcholine solutions into the general blood stream causes excitation of vascular receptors, the reflex effects from which may produce changes of opposite character in the blood pressure.

There are few reports in the literature of studies of the reactions of the cardiovascular system to the simultaneous action of different stimuli on different receptor fields [1,5,7,10,11]. The object of the present investigation was to study the character of the changes in the arterial pressure and in the strength and frequency of the cardiac contractions in response to the simultaneous injection of acetylocholine solutions into the vessels of the isolated limb and intravenously.

## EXPERIMENTAL METHOD

Experiments were conducted on cats anesthetized with urethane (1 g/kg body weight). So that the drug could be made to stimulate the receptors of an isolated vascular region, the animal's hindlimb was separated from the trunk, retaining only its nerve connections. The vessels of this limb were perfused with oxygenated Tyrode solution at 37-38° under constant pressure. The number of drops of perfusion fluid flowing from the vein was recorded on the kymograph paper by an electric drop counter. The chemoreceptors of the limb vessels were stimulated by injection of acetylcholine solutions of different concentration ($10^{-6}$-$10^{-3}$) into the tube of the perfusion system by a syringe.

The strength of the cardiac contractions was determined by a Petrov's cannula [4], introduced into the pericardial cavity and fixed hermetically to the pericardium. The cannula was connected to a Marey's tambour, the pen of which recorded the changes in the volume of the pericardial cavity on the kymograph paper. The injection of acetylcholine solutions into the general blood stream was effected by means of a syringe into the femoral vein. The pressure in the common carotid artery was recorded by a mercury manometer.

## EXPERIMENTAL RESULTS

In all the experiments stimulation of the chemoreceptors of the limb vessels by injection of acetylcholine solutions ($10^{-6}$-$10^{-5}$) caused an increase in arterial pressure without significant changes in the frequency and strength of the cardiac contractions (Fig. 1, A). After injection of acetylcholine solutions into the limb vessels in a higher concentration ($10^{-4}$-$10^{-3}$) the pressor reaction was increased in strength and was sometimes accompanied by an increase in the rate of the cardiac contractions and a decrease or, more often, no change in their strength.

The doses of acetylcholine solutions injected intravenously were so selected that they would not produce marked changes in the cardiovascular system. The concentrations of the solutions generally used were $10^{-20}$-$10^{-18}$. Injection

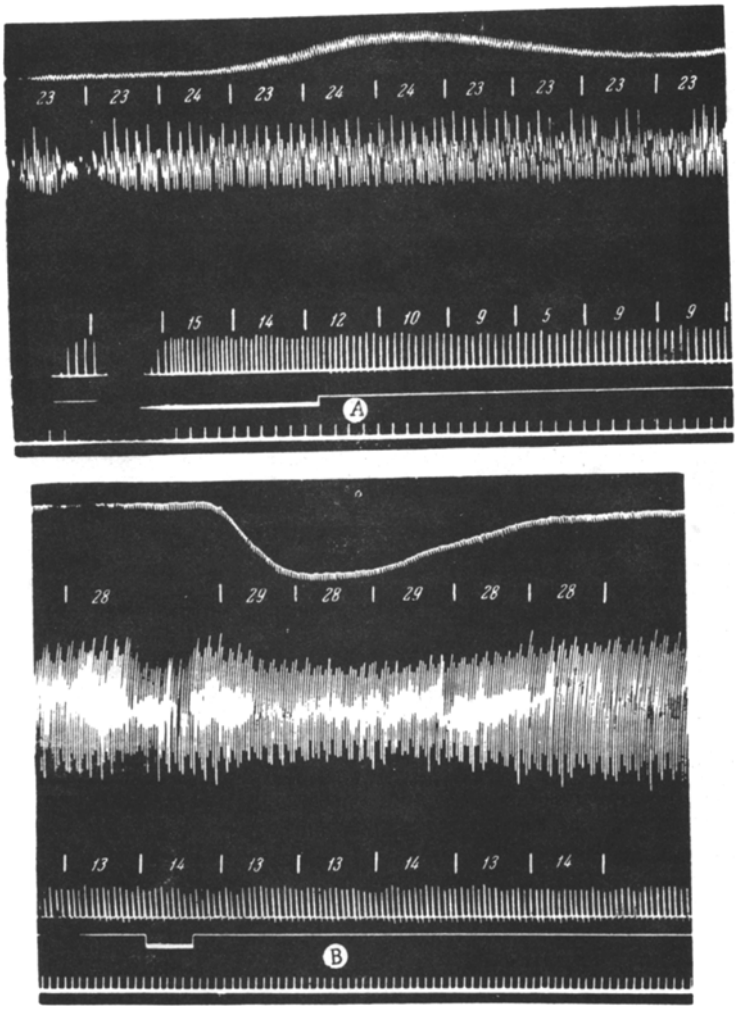


Fig. 1. Changes in arterial pressure and in the strength and frequency of the cardiac contractions after injection of 2 ml of acetylcholine solution ($10^{-5}$) into the perfusion fluid of the isolated limb (A) and after intravenous injection of 0.5 ml $10^{-20}$ acetylcholine solution (B). Significance of curves (from above down): arterial pressure; strength of cardiac contractions; outflow of drops of perfusion fluid from femoral vein; marker of beginning and end of injection of acetylcholine; time marker (2 sec). The numbers denote: above) number of cardiac contractions in 10 sec, below) number of drops of perfusion fluid flowing out in 10 sec.

of 0.5 ml of acetylcholine solution in these concentrations into the femoral vein led to a transient fall of arterial pressure, a decrease in the strength of the cardiac contractions and, in some experiments, a slowing of their rate (Fig. 1, B). The use of higher concentrations of acetylcholine ($10^{-15}$-$10^{-12}$) was accompanied by an increase in the intensity of these reactions, although their direction remained the same.

During stimulation of the limb chemoreceptors with acetylcholine solutions against the background of the action of the same stimulant injected into the general blood stream, the reaction of the cardiovascular system depended on the strength of the stimuli applied and on the interval between them. If weak acetylcholine solutions ($10^{-6}$-$10^{-5}$) were injected into the perfusion fluid 1.0-1.5 min after intravenous injection of acetylcholine ($10^{20}$), i.e., at the moment when the depressor reaction had already developed, no increase in arterial pressure in response to stimulation of the chemoreceptors of the limb vessels was observed against this background. With an increase in the concentration of the stimulus ($10^{-4}$-$10^{-3}$) injected after the same interval into the limb vessels, no pressor reaction still developed, but only a depressor reaction was observed in response to the intravenous injection of acetylcholine.

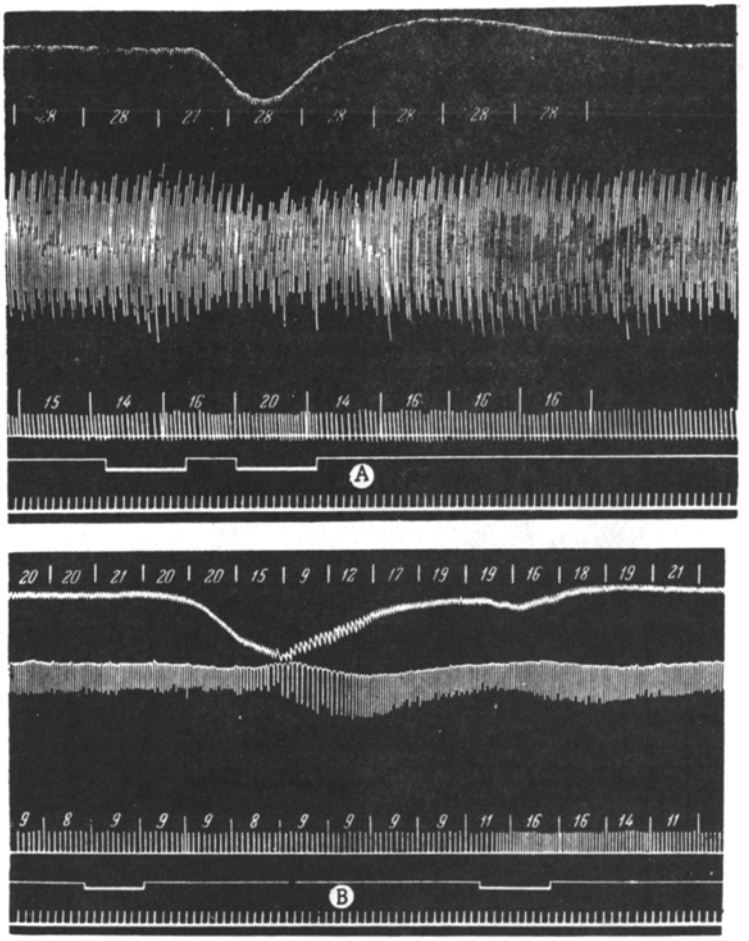


Fig. 2. Depressor-pressor reaction after injection of 0.5 ml of $10^{-20}$ acetylcholine solution intravenously followed by injection of 2 ml of $10^{-4}$ acetylcholine into the limb vessels (A). Change of the pressor phase of the reaction into depressor after injection of $10^{-12}$ acetylcholine solution intravenously and $10^{-3}$ acetylcholine solution into the limb vessels (B). Legend as in Fig. 1. Time marker for A) 1 sec, for B) 2 sec.

Shortening the interval between injection of the stimulant into the general blood stream and into the perfused limb to 5-10 sec, i.e., so that the chemoreceptors of the limb were stimulated before the depressor reaction to intravenous injection of acetylcholine had developed, gave rise to an initial fall of arterial pressure, followed by a rise (Fig. 2, A). The depressor reaction arising in these conditions was shorter in duration than the depressor reaction developing after injection of the stimulant into the general blood stream alone. The pressor phase of the general blood pressure reaction was especially well marked after injection of more concentrated acetylcholine solutions ($10^{-4}$-$10^{-3}$) into the limb vessels.

A change in the order of injection of the stimuli, i.e., injecting acetylcholine first into the limb vessels and later into the general blood stream, also caused a two-phase reaction, beginning with a pressor reaction which subsequently changed into a marked depressor reaction.

When, in order to obtain a depressor reaction, higher concentrations of acetylcholine solution ($10^{-5}$-$10^{-12}$) were injected into the general blood stream, the subsequent injection of acetylcholine solutions into the limb vessels produced a change in the character of the reaction of the arterial pressure in response to stimulation of the chemoreceptors of the limb vessels. In this case injection of acetylcholine into the blood vessels of the perfused limb 1.0-1.5 min after the intravenous injection of a comparatively large dose of acetylcholine ($10^{-12}$) led to the development of

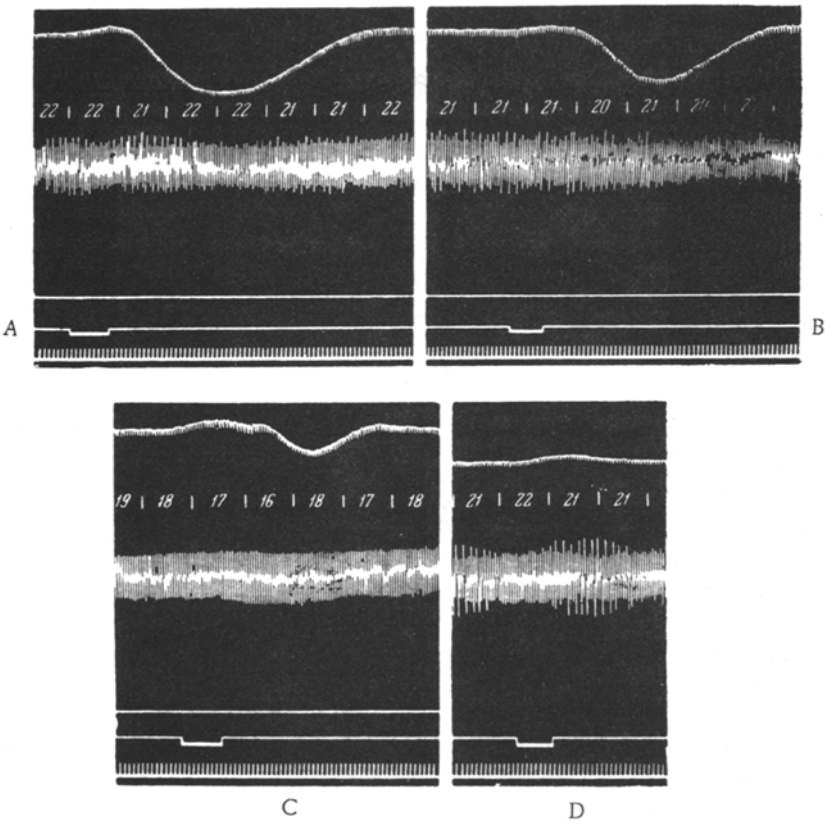


Fig. 3. Changes in arterial pressure in response to intravenous injection of 0.5 ml physiological saline 20 (A), 25 (B), 30 (C), and 35 (D) min after simultaneous injection of acetylcholine intravenously and into the vessels of the perfused limb. Legend as in Fig. 1. Time marker 1 sec.

a depressor reaction instead of a pressor, although less marked in degree (Fig. 2, B). It should be emphasized that in this case not only was the pressor reaction changed to depressor, but instead of the heart rate being increased after injection of acetylcholine into the limb vessels, it was slowed.

A shortening of the interval between the injection of these stimulants into the general blood stream and into the perfused limb to 5-10 sec was accompanied by the development of a more prolonged depressor reaction than was observed after injection of acetylcholine into the general blood stream alone.

It should be noted that after 3-4 intravenous injections of acetylcholine, followed by injection of the drug into the vessels of the isolated limb, intravenous injection of physiological saline now caused a marked depressor reaction. For example, in one experiment the injection of 0.5 ml of physiological saline into the femoral vein 20 min after the third combined injection of both stimuli caused a marked depressor reaction, and this could be reproduced for a further 15 min. This fall of arterial pressure with each seccessive injection of physiological saline gradually diminished and it disappeared at the end of 20 min (Fig. 3). In another experiment, after six clashes between the depressor and pressor reactions to intravenous and intra-perfusion injection of acetylcholine solutions, the depressor reaction in response to injection of 0.5 ml physiological saline into the general blood stream was observed for over 1 h. This reaction of the arterial pressure to injection of physiological saline appeared after injection of the drug not only into the femoral, but also into other veins.

The appearance of these reactions in the cardiovascular system after intravenous injection of acetylcholine followed by injection of the drug into the vessels of the isolated limb may be explained, we consider by A. A. Ukhtomskii's theory of the dominant. In the case of a dominant, ". . . the stable excitation present in the centers at a particular moment assumes the importance of a dominant factor in the working of other centers: it accumulates excitation from the most distant sources, but inhibits the power of other centers to react to impulses directly related to them.* "

* A. A. Ukhtomskii, Collected Works [in Russian], 1, 190 (1950).

Other authors have obtained results indicating the possibility that a dominant state may develop in the vasomotor center [2,3,7].

When other substances (histamine, nicotine) were used in the experiments, the depressor-pressor reaction as described above also occurred after injection of these drugs intravenously at the same time as the chemoreceptors of the limb vessels were stimulated by acetylcholine. Meanwhile, after the repeated injection of these drugs in different concentrations into the general blood stream, followed by injection of acetylcholine solutions into the perfusion system, no depressor reaction developed in response to intravenous injection of physiological saline. It is apparent that the excitation produced by intravenous injection of these drugs was inadequate to cause the development of a dominant state in the vasomotor center.

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## SUMMARY


Experiments were staged on urethane-anesthetized cats to investigate the correlation of depressor and pressor reactions to injection of acetylcholine intravenously and into the vessels of an isolated limb.


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