PHYSIOLOGY

REFLEX CHANGES IN THE ACTIVITY OF THE CARDIOVASCULAR SYSTEM DUE TO CHEMICAL STIMULATION OF THE PERICARDIAL RECEPTORS

COMMUNICATION III. THE DEPENDENCE OF THESE CHANGES ON THE STATE OF THE VASOMOTOR CENTER

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In a survey of the finding on the nervous regulation of the tone of the blood vessels, Folkow[11]comes to the conclusion that an increase in the activity of the vasomotor center leads to an increase in the efferent impulses to the vessesl, as a result of which the tone of the vessels rises; inhibition of the vasomotor center is expressed as weakening of the efferent impulses, dilatation of the vessels and a fall in the blood pressure. Other things being equal, the state of a nervous center is a function of the number of afferent impulses reaching it. We have shown that chemical stimulation of the receptors of the pericardium of cats in the majority of cases causes in the same experiment both pressor and depressor reactions of the cardiovascular system, and that the former appear in response to stimuli of relatively low intensity whereas the latter are in response to more intensive stimuli; however, in some experiments pressor or depressor reactions only were observed (see Communication I). Exclusion of all the receptors or of the chemical receptors only in the pericardium always causes a rise in the blood pressure [7, 8].

Our findings compel us to disagree with the notion of the qualitative heterogeneity of afferent influences causing excitation or inhibition of the vasomotor center. These facts may explain, if they are accepted, how a different number of impulses could cause qualitatively opposite states at the place of their application [1, 5, 6].

For this explanation to be acceptable it is essential in the first place to prove that the character of the reaction of the cardiovascular system to stimulation of the receptors of the pericardium depends on the state of the vasomotor center and, secondly, that a change in the number of afferent impulses reaching the center may determine the state of this center and the character of the reflexes in which it takes part.

EXPERIMENTAL METHOD

In order to solve the first task we selected cats in which a chemical stimulation of the receptors of the pericardium of any intensity caused only pressor or depressor reactions. As an indicator of the state of the vasomotor center we used the reaction of the cardiovascular system to compression of the left common carotid artery (the right was ligated since the cannula for recording the blood pressure was inserted into it). For the second task we used 7 cats whose carotid sinus zones had been denervated 30-40 days before the acute experiment.

Denervation was carried out by means of bilateral extirpation of all the tissues situated at the bifurcation of the common carotid artery into the external and internal, the adventitia of the vessels was removed and the arteries painted with a 5% solution of phenol. The methods of chemical stimulation of the receptors of the pericardium and of recording the blood pressure and respiration were described in Communication I.

EXPERIMENTAL RESULTS

In the experiments in which stimulation of the pericardial receptors with nicotine in all the concentrations used caused an increase only in the blood pressure, transient compression of the common carotid artery raised the blood pressure very sharply (Fig. 1, a). This reaction was especially obvious if both pressor and depressor reflexes were observed. If in some experiments nicotine caused depressor reaction, the reflex to compression of the carotid artery was then markedly weakened or even distorted (Fig. 1, b).

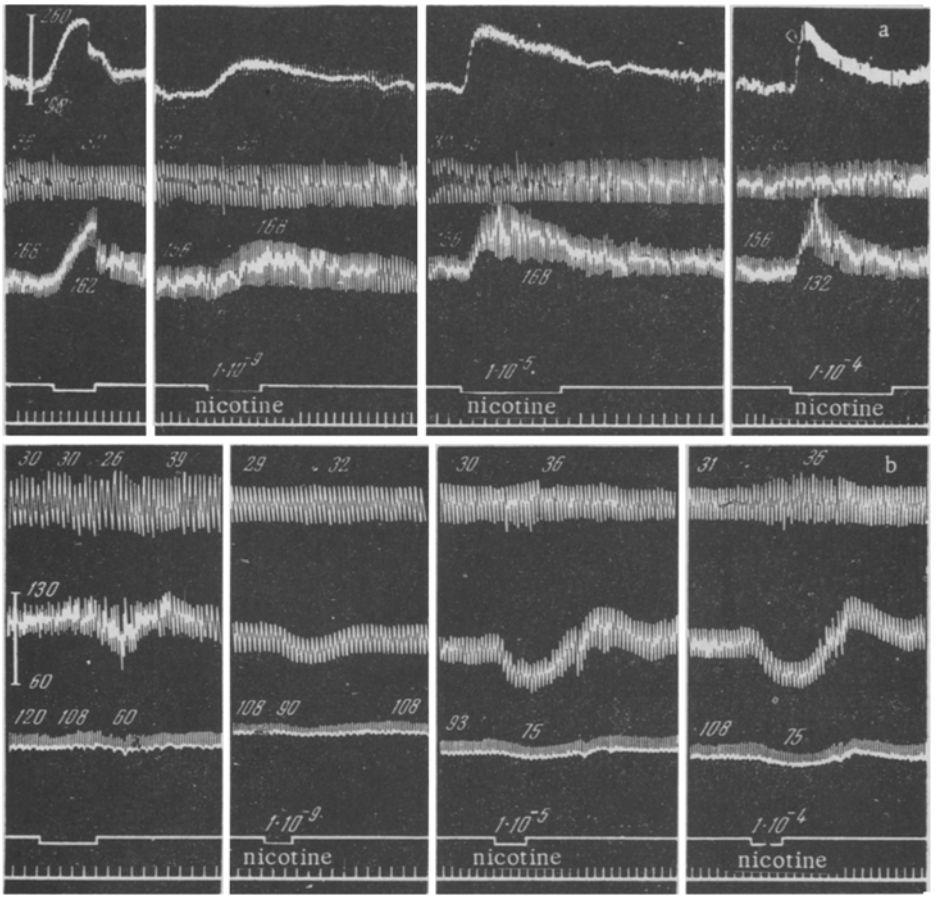

Fig. 1. Comparison of the reactions to compression of the left common carotid artery in cats reacting to stimulation of the pericardial receptors with nicotine in any concentration by either pressor (a) or depressor (b) changes in the blood pressure only (experiment on cats under urethane anesthesia).
Significance of the curves (from above downwards): on the series a kymograms: blood pressure (mercury manometer), respiration, blood pressure (membrane manometer), stimulation marker, time marker (5 seconds); on the series b kymograms: respectively respiration, blood pressure (mercury manometer), remainder as in the series a kymograms. The figures along the respiration curve indicate the respiration rate at that particular moment, and the figures along the membrane manometer curve — the rate of the heart (both calculated per minute); compression of the carotid artery, see the stimulation marker in the first kymograms on the left.

From a comparison of these facts it can be concluded that in the first case (see Fig. 1, a) the state of the vasomotor center brought about predominance and intensification of the pressor reactions, whereas in the second case (see Fig. 1, b) the pressor reflexes in which the vasomotor center took part, irrespective of whether caused by

chemical stimulation of the pericardial receptors or by compression of the carotid artery, were effected with difficulty, i.e. inhibition was dominant in the vasomotor center.

The state of the vasomotor center thus affects equally the reflexes caused by stimulation of the carotid sinus and the pericardial reflexogenic zones.

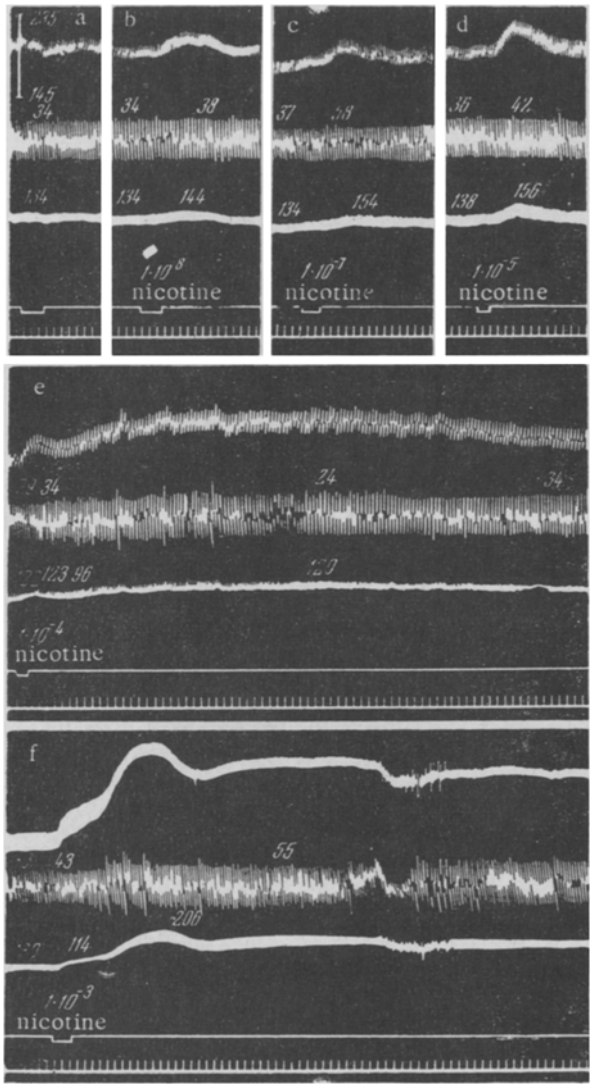

Fig. 2. The character of the reactions of the cardiovascular system and respiration to stimulation of the pericardium with nicotine in various concentrations (b-f) in cats whose carotid sinus zones had been denervated 40 days before the experiment.
On kymogram a – compression of the left carotid artery. The order of the tracins and the symbols are the same as in Fig. 1, a.

Exclusion of impulses from these zones causes similar changes in the blood pressure (see Communication II) and evidently identical changes in the center, brought about in both cases by a reduction in the number of afferent impulses reaching it. This provides good grounds for the attempt to influence the character of the reflexes caused by stimulation of the pericardial receptors by means of a reduction in the afferent impulses reaching the vasomotor center from the carotid sinus zones.

In all the experiments on cata with previous denervation of the carotid sinuses a chemical stimulus of any intensity applied to the pericardial receptors raised the blood pressure (Fig. 2). This indicates that the afferent impulses arising during stimulation do not themselves determine the character of the reflex reaction, but acquire some degree of importance which depends on the number of impulses reaching the vasomotor center not only from the stimulated reflexogenic zone but from others as well.

By artificially changing the number of impulses we make it possible to correct the vasomotor reactions. In this particular case, for instance, in animals whose vasomotor center received no impulses for a long time from the mechanoreceptors of the carotid sinuses, a raised blood pressure was observed in response to strong stimuli, which caused a fall in blood pressure in the majority of normal animals. In both the 25% of animals with intact carotid sinuses (see Communication I) in which only pressor reactions were observed to chemical stimulation of the pericardium, and in the animals undergoing the preliminary operation, the state of the vasomotor center favored predominance of the pressor reactions.

However, the magnitude of the pressor reactions of the blood pressure in the animals of these two groups were altered to a different extent as the strength of stimulation increased. This can be seen from a comparison of Figs. 1, a and 2. If in the cats with intact carotid sinuses the reactions to stimulation of the pericardial receptors increased in proportion to the intensity of stimulation and reached a maximum at only comparatively small concentrations of the stimulus (nicotine $1 \cdot 10^{-5}$), in the cats with denervation of the carotid sinus zones the reactions to weak and average concentrations of the stimulus ($1 \cdot 10^{-8}$ - $1 \cdot 10^{-4}$; Fig. 2, b-e) hardly differed at all from each other and were expressed as a small rise in the blood pressure. The reaction to the highest concentration of nicotine, however, was extremely intense, and was greater than the pressor reactions to the same stimulation of the pericardial receptors even in cats with intact buffer

nerves, in which pressor reactions only were observed.

Special experiments on animals of the latter group provide an explanation of these differences mentioned. If in these cats the reactions to compression of one of the carotid arteries ("carotid reflex") is recorded on a background of the pressor reactions caused by chemical stimulation of the pericardial receptors, then the change in the character of the carotid reflex will depend on the intensity of the pericardial reflex. In Fig. 3 it can be seen that at the peak of the small rise in blood pressure cuased by a chemical stimulus of average intensity (nicotine $-1 \cdot 10^{-5}$) applied to the pericardial receptors, the "carotid reflex" which is clearly marked anyhow in these animals increases still further; as a result the total effect of the two forms of stimulation exceeds the arithmetic sum of the reactions to each of them individually (see Fig. 3, a).

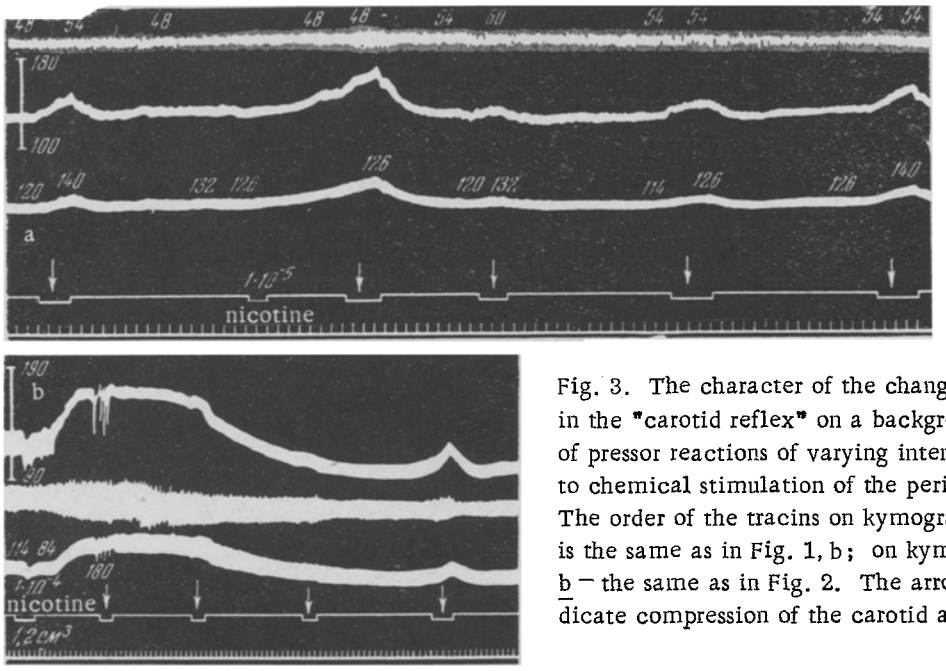

Fig. 3. The character of the changes in the "carotid reflex" on a background of pressor reactions of varying intensity to chemical stimulation of the pericardium. The order of the tracins on kymogram a is the same as in Fig. 1, b; on kymogram b – the same as in Fig. 2. The arrows indicate compression of the carotid artery.

At the peak of a great increase in the blood pressure, caused by strong stimulation of the same receptors (nicotine $-1 \cdot 10^{-3}$), the "carotid reflex" is distorted, lowering the level of the blood pressure which had been attained beforehand, which weakens the effect of stimulation of the pericardial receptors (see Fig. 3, b).

On the basis of these experiments it may evidently be postulated that in animals with normally functioning carotid sinus reflexogenic zones, these zones exert their buffering or compensatory function not only in the form of signals reporting severe changes in pressure in the carotid sinus, but also as a result of the constant influence of impulses flowing from the receptors of this zone on the state of the vasomotor center; the character of these influences is opposite, depending on the number of afferent impulses reaching the vasomotor center from the other reflexogenic zones. Summating with them, impulses from the carotid sinus zones intensify the excitation of the vasomotor center during reception of moderate impulses along other nerves, but partially inhibit it when impulses from other sources are strong. In cases when impulses from the carotid sinus receptors are absent, reactions to moderate stimulation of other zones are weakened but reactions to strong stimulation are abnormally intensified (see Fig. 2). The dual nature of the influence of the reflexogenic zones of the thorax on the blood pressure has been pointed out previously by Hering [12], V. V. Parin [3, 4] and Wang and Borison [13], who have shown that the depressor effect of electrical stimulation of the carotid sinus and aortic nerves, exactly like the analogous effect of adequate stimulation of the pressure receptors of the carotid sinus or the pulmonary vessels, is increased both after denervation of the other reflexogenic zones of the thorax and during simultaneous stimulation of these zones or of the nerves issuing from them.

It is impossible to account for this duality from the standpoint of a qualitative specificity of afferent impulses (in this case depressor); it becomes understandable if it is accepted that a different number of impulses,

identical as signals, may lead to qualitatively opposite states of the center. This conclusion can be reached essentially from the facts described by Douglas and his co-workers [9, 10].

This is also suggested by our own findings [2]. If this is so, then the increased blood pressure in response to compression of the carotid arteries must be regarded not as the consequence of weakening of the tonic inhibitory afferent influences on the vasomotor center but as the result of the action of this center of a different (smaller than normal) number of afferent impulses, causing excitation of the center and, it seems, having a different meaning as a signal.

In such a case the raised arterial pressure in response to exclusion of afferent impulses from any reflexogenic zone in the thorax must be regarded as the result of a diminution of the total sum of afferent impulses reaching the vasomotor center down to the number causing greater excitation of the center than at the level of reception of impulses which is normally observed. This is indirectly shown by the fact that in animals with denervation of the carotid sinuses the pressor effect of strong stimulation of the pericardial receptors is more pronounced than in normal animals. However, the individual component parts of the vasomotor center have their own special features, due to whatever reflexogenic zones supply the afferent fibers to the particular group of nerve cells; or more exactly, either constant impulses travel to these cells (as, for example, from the carotid sinues or the arch of the aorta) or they are episodic, arising in response to extraneous stimuli (for example from the epicardial receptors during chemical stimulation).

Under these circumstances a certain "normal" state of the vasomotor center is due to definite interaction of its component groups of nerve cells, in which excitation of the center as a whole, and consequently an increase in blood pressure, may rise only to a particular level; above this level, excitation is transformed into inhibition of the center as a result of further increase in afferent impulses, which leads to a compensatory fall in the blood pressure. However, in animals such as rabbits, in association with the peculiarities of their ecology, the normal state of their center is such that any additional stimulation inhibits it and causes a fall in the blood pressure [7, 8]. In these animals also, under suitable conditions of anesthesia, pressor reactions to weak stimulation of the pericardium can be observed [2].

It is characteristic that denervation of the carotid sinus, which alters the character of the vascular component of the reactions under study, hardly affects the character of the changes in the cardiac component. In Fig. 2, d, e, it can be seen that whereas strong stimulation of the pericardium leads to an increase in the blood pressure, the rate of the heart is at first not increased but decreased. This is understandable, since inhibition of the heart is not a feature of the medullary centers but of the structures of the heart itself [6], and so by altering the number of impulses to the medulla we destroy the conditions necessary for inhibition of the vasomotor center but not the conditions determining inhibition of the heart. It is true that during the strongest stimulation (see Fig. 2, e) inhibition of the heart is replaced, during growth of the vascular reaction, by a considerable increase in its rate, which may be regarded as the result of inhibition of the bulbar center of the vagus nerves; but this is presumably the consequence of wide irradiation of excitation in the medulla, manifestations of which may be seen also in the unusually prolonged vascular reaction, and in the appearance during its course of vomiting movements (see Fig. 2, e) and of periodic respiration (see Fig. 2, d, e) and even of inhibition of respiration (see Fig. 2, d). We never observed these latter phenomena in animals with intact carotid sinuses; in these animals stimulation of the pericardial receptors always led to stimulation of respiration, which we explained by the small number of connections between the pericardium and the respiratory center. However, P. A. Spiro [5] showed that as the afferent influences are strengthened, stimulation of respiration changes into inhibition, and with stimulation of intermediate strengths periodic respiration is observed. It may be postulated that in our experiments exclusion of the structures of the vasomotor center related to the carotid sinus reflex took place, as a result of which the conditions for the formation of the pericardial reflexes were destroyed. As a result the excitation irradiated to the adjacent areas of the vasomotor center and increased the duration of the vascular reaction.

SUMMARY

The stimulation of pericardial receptors by chemical substances in any concentration caused only pressor reactions in all cats with denervated carotid sinuses. However, these reactions could be observed only in 25% of the cats with the intact carotid sinuses. A cumulative effect of the separate action of these stimulants on the blood pressure was found in these 25% of the cases in clamping of the carotid artery on the background of a slight rise of the blood pressure caused by not very strong stimulation of the pericardial receptors. On the contrary, if the carotid

artery was clamped on the background of a considerable rise of the blood pressure caused by a strong stimulation of the pericardium these effects depressed each other reciprocally as a result of which a inversion in the carotid reflex was noted.

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