CHANGE WITH DOSE OF THE CARDIOVASCULAR AND RESPIRATORY RESPONSES TO CHEMICAL STIMULATION OF THE SMALL INTESTINE RECEPTORS

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Cardiovascular and respiratory unconditioned interoceptor reflexes can be divided into two groups which appear at first sight to be of opposite kinds. The first group includes reflexes occurring on stimulation of the mechanoceptors of the aortic and sinocarotid zones, as well as those induced by stimulation of cardiac and pulmonary receptors, and which together are known as constituting the "phenomenon of Betsol'd-Yarish". The afferent pathway of the reflexes just described is along the nerves running to the medulla. When eliciting these reflexes, most workers observed a reduction in cardiovascular and respiratory activity. The second group consists of the reflexes which have been studied in detail by V. N. Chernigovskii and his coworkers [5-7] and which are evoked by stimulating various interoceptors of the abdominal cavity; the afferent fibers concerned enter various segments of the spinal cord. In the great majority of cases, these reflexes increase respiration and circulation. However, the two groups of reflexes are not exact opposites, because in cats in which powerful stimulation is applied to the pericardium [2-4], or to the mediastinal pleura [1], from which afferent fibers run to the medulla, or in which electrical stimulation is applied to the central ends of the aortic, sinocarotid, or vagus nerves [8,9], it ispossible to evoke not only depressor but also pressor reflexes.

In the present work, an attempt has been made to induce both pressor and depressor reactions by varying the strength of chemical stimulation applied to the interoceptors of the abdominal cavity.

METHOD

The experiments were carried out on acute preparations of cats under 1 g/kg intravenous urethane anesthesia. For the selective stimulation of the intestinal receptors we used the method described by V. N. Chernigovskii [6], which consisted of perfusing the organ while it retained only nervous connection with the rest of the body. We tried to isolate and perfuse the whole of the small intestine from the duodenum to the caecum, because although well-developed reflexes may be obtained initially from small sections of the intestine, the excitability of such a preparation becomes rapidly reduced, whereas if larger portions are used they remain excitable for long periods while perfused with Ringer-Locke solution. The chemical stimuli used were nicotine and acetylcholine, and were used in concentrations from $1 : 10^{-9}$ to $1 : 10^{-1}$ in Ringer-Locke solution.

The time at which 1 ml of the stimulus was injected into the perfusing system was recorded by means of an electromagnetically operated marker. Intervals of 10 minutes were left between injections, and these were increased to 30-40 minutes when concentrated solutions were used. The blood pressure in the left carotid artery was recorded using mercury and membrane manometers, respiration was measured using a Marie's capsule and a tracheal cannula, and the drop rate of the perfusate from the vein was also recorded. From the curves, changes

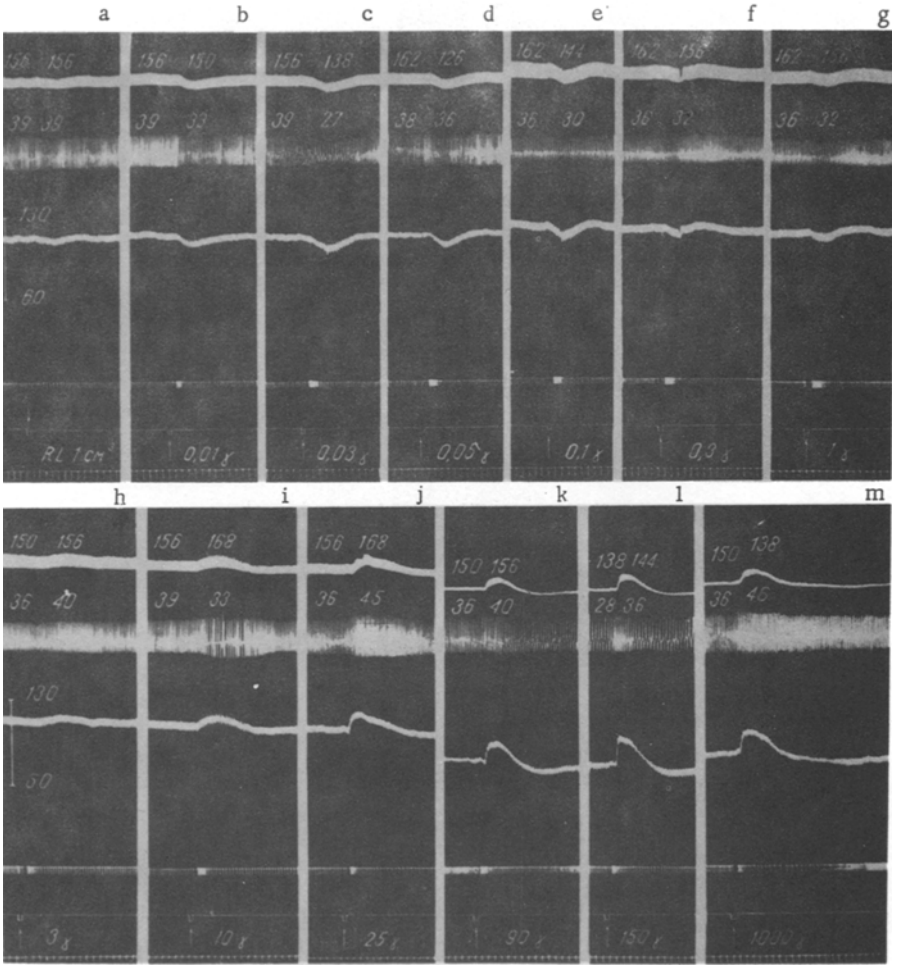

Fig. 1. Cardiovascular and respiratory responses to the injection of various concentrations of nicotine into the perfusate. Curves, from above downwards: arterial pressure (tonometer), respiration, arterial pressure (mercury manometer), drops of perfusate from vein, stimulus marker, time marker (5 seconds). Figures over the tonometer curve indicate number of heart beats per minute, numbers over the respiratory trace indicate rate of breathing (see explanation in text). ↓) injection of Ringer-Locke solution into the perfusate; ↑) injection of nicotine.

in the arterial blood pressure, heart beat, and respiration in response to any particular stimulus were read off and expressed as a percentage of the original level, and plotted as a graph; the percentage change in the quantity measured was plotted as ordinate, and the concentration of the stimulus as abscissa.

RESULTS

The cardiac and respiratory changes induced by nicotine and acetylcholine were closely similar.

Fig. 1 shows the traces obtained when the small intestine receptors were perfused with nicotine. The introduction of 1 ml of Ringer-Locke solution into the perfusate has practically no effect on any of the quantities recorded (Fig. 1, a).

Nicotine in doses from 0.01-1γ ($1 : 10^{-8} - 1 : 10^{-6}$) always caused a small but definite reduction in arterial pressure and a fall in heart and respiration rates (Fig. 1, b – g). Evidently, a "pure" depression developed only in response to 0.01 γ of nicotine (see Fig. 1, b) and the arterial pressure then returned gradually to its initial value. Large doses of the stimulus (see Fig. 1, c – e) first caused a greater fall in arterial pressure and a reduction in the heart beat; however, these reactions terminated abruptly as though under some counteracting influence.

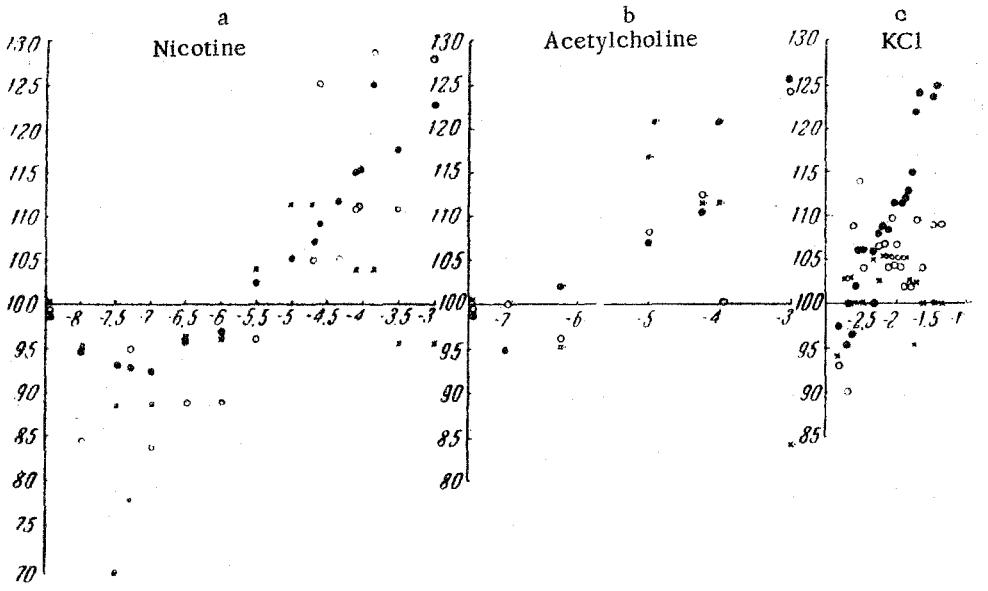

Fig. 2. Dependence of the nature and extent of the arterial pressure change (O), respiration (●) and heart rate (X) on the intensity of stimulation of the small intestine receptors by nicotine (a), acetylcholine (b), and potassium chloride (c).
Percentage change in the different quantities plotted as ordinate; minus one multiplied by negative logarithm of stimulus concentration plotted as abscissa.

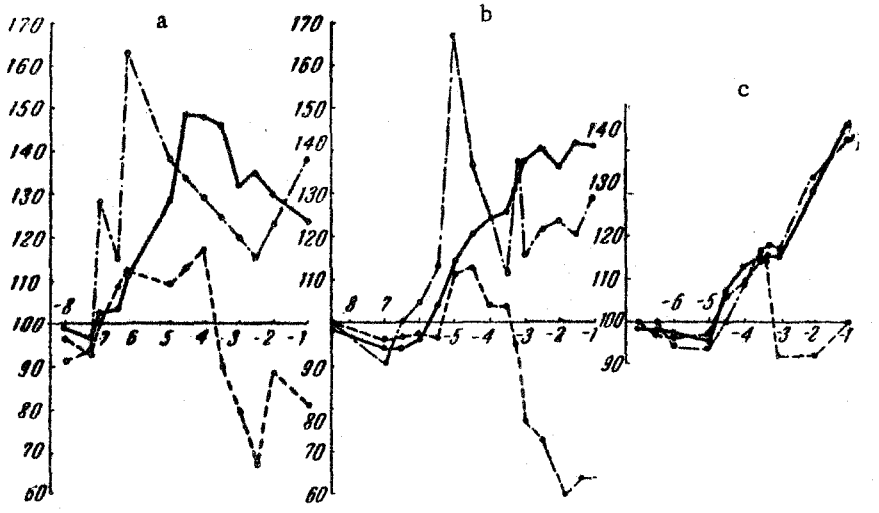

Fig. 3. Relationship between the nature and the intensity of the cardiovascular and respiratory responses to different intensities of small intestine receptor stimulation by acetylcholine, and the threshold at which transition from depressor to pressor response occurs. Symbols as in Fig. 2.
—)arterial pressure changes; – – –)changes in heart rate; – – –,)respiratory changes.

That there was such an influence was confirmed by the fact that still greater doses of nicotine caused a biphasic reaction in which the small initial reduction in the arterial pressure rapidly changed over to a brief pressor response, and it was only after this had occurred that the pressure once more returned to the original value (Fig. 1, f, g). Evidently, 3 γ of nicotine is a threshold dose for the pressor reaction (see Fig. 1, h), although this same dose causes induction of a biphasic respiratory response. Even when 10 γ of nicotine are injected (see Fig. 1, i), when there was a marked increase in arterial pressure and heart rate, the respiratory change consisted of an increase in amplitude of the movements and a disturbance of the rate, which was usually reduced; only when the amount was increased to 20-25 γ was there a definite increase in respiration (Fig. 1, k).

The different quantities recorded reached maximum values at different stimulus strengths: the greatest increase in the heart rate was caused by 10-20 γ of nicotine, the greatest arterial pressure increase by 150 γ, and the maximum respiration was caused by 1000 γ. Higher concentrations caused a reduction in the response, so that when 300-1000 γ of nicotine were injected, the heart was slowed, the pressor response was reduced, but respiration was maximally stimulated.

These changes are shown in Fig. 2, a, which represents the results of one of the experiments (Fig. 1). On comparing graph a with the two others (b, c) shown in the same figure, it can be seen that the nature and the extent of the cardiovascular and respiratory responses are the same for the three different stimulators nicotine (a), acetylcholine (b), and potassium chloride (c) *.

The differences between the different graphs are purely quantitative: each substance shows a particular value for the threshold of the primary response and for the reversal of the reaction, and a range of values for which the reaction takes place in a particular direction; each substance also has its own particular value at which the reaction reaches a maximum, and a particular ratio of this value to the threshold dose. There is very little difference between the actions of acetylcholine and nicotine; there is some difference in the values for the changeover from depressor to pressor reaction and in the range of concentration over which depressor reactions and increasing pressor responses occur. Depressor effects were over a greater range and were more marked with nicotine, while acetylcholine produced greater pressor effects. The pressor response to nicotine occurred not only at a higher threshold, but also reached its maximum value more rapidly.

There are very clear differences between nicotine and acetylcholine on the one hand, and potassium chloride on the other. For the latter the threshold value is 1000 γ. Increasing the dose 10-14 times produces a maximum effect. All the changes described for nicotine and acetylcholine occur over this range.

Differences between the ways in which the respiratory response changes with concentration (Fig. 2) evidently does not depend on the properties of the particular stimulating agent. The graphs of Fig. 3 have been constructed from the results of three different experiments in which 1 ml of solution containing from 0.01 to 100,000 γ were added to the perfusate. Increasing the concentration showed that not only the respiratory response but also that of the circulation varied from one experiment to another. In some experiments, both reactions were maximal at a certain stimulus strength and began to fall with higher acetylcholine concentrations (Fig. 3, a). This effect occurred very frequently in the case of respiration (Fig. 2, c; Fig. 3, a, b) but sometimes the pressor response was reduced (Fig. 2, a; Fig. 3, a). As a rule, the maxima of the two responses do not coincide, so that in different experiments (with lower stimulus values) each reaction will reach its limit at a different concentration.

However, the respiratory reaction usually reaches its maximum earliest, even when it is depressed by small doses of the chemical stimulus (Fig. 2, a, b; Fig. 3, a, b), and also when higher stimulus concentrations are used (Fig. 2, c; Fig. 3, a, b). This effect is associated with the steep increase in the respiratory response between threshold and maximum, and in many cases with its lower threshold value. Even in cases when the threshold of one or another respiratory reaction was above that of the reversal of the pressor reaction (Fig. 2, a, b; Fig. 3, c), the two attained their maximum values at almost identical stimulus values.

It can be seen from Fig. 3 that the maximum pressor response depends upon its threshold value. When the threshold was low (Fig. 3, a), injection of 30 γ of acetylcholine caused a maximum increase in arterial pressure, and larger doses evoked a smaller reaction. When the threshold was higher (Fig. 3, b) the maximum reaction occurred at a dose of 3000 γ of the same substance, but in an experiment when the threshold pressor response was very high, a considerable increase occurred even with a stimulus dose of 100,000 γ.

The results indicate convincingly that the reflexogenous zone of the small intestine is not purely "pressor" and that stimulation of its chemoreceptors may produce depressor responses, either inhibition or stimulation of respiration, and either a fall or an increase in heart rate. In this respect it resembles the thoracic cavity. However, there are considerable differences in the changeover of the different responses to their opposites. With chemical stimulation of the pericardial receptors, weak stimulation brings about an increase in arterial pressure and a tachycardia, while stronger stimulation results in a fall in pressure and a bradycardia [2, 3]. Such a stimulation applied to the small intestine receptors causes changes in the reverse order (there is first a depressor and

* The results for the construction of graph "2, c" have been borrowed by permission of L. A. Baraz from her studies. — B. K.

then a pressor response, first a suppression and then a stimulation); the cardiac response is more complex (first an inhibition, then stimulation, then again inhibition).

The results presented do not solve the problem as to whether the opposite effects on circulation and respiration resulting from stimulation of the small intestine are due to different elements of the nervous system being involved, or whether they result from different levels of activity of similar elements of the reflex arc, as we attempted to show in the case of pericardial stimulation [2,3].

It must be realized that the different results obtained with identical stimulation of the interoceptors of the thoracic and abdominal cavities may be due to the fact that the afferent nerves of the former run chiefly to the medulla, and impulses from them induce a distinct set of cardiovascular and respiratory reflexes [6,7], whereas impulses from the latter run chiefly to the spinal cord and induce the functional changes we have recorded. A further complication is that in addition to the afferent spinal nerves, vagal branches also run to the intestine, and these contain afferent fibers of bulbar origin. Possibly it is this circumstance which accounts for the complex reversal of the cardiac response to chemical stimulation of the small intestine receptors.

SUMMARY

In experiments on acute cat preparations in which nicotine and acetylcholine were injected into the fluid perfusing the intestine, which retained only nervous connection with the body, the reactions induced depended only on the dose of the chemical substances. Low doses (0.01-1.0 γ) caused a slight drop in arterial pressure, and a fall in heart and respiration rates. On the other hand, large doses of 5-100 γ of these substances caused an increase in arterial blood pressure and a rise in pulse and respiration rates. The intensity of the reaction increased with increasing dose only up to a certain limit, which was not the same for the different responses; after the maximum has been reached, the blood pressure and respiration responses fall and the cardiac reaction becomes reversed, so that the heart rate falls in response to the action of nicotine upon the intestinal receptors.

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