SUMMARY

Initial muscular activity is associated with depression of the α-rhythm and appearance of high-frequency oscillations of the β-rhythm type in the electroencephalogram. On continuation of the work, short periods of α-rhythm begin to appear on this backgroun and gradually increase. If the work is continued further it is accompanied by an α-rhythm which is almost no different from the α-rhythm in the state of rest. The duration of the initial period of work depends on the character and power of the preparatory and the subsequent work.

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ELECTROPHYSIOLOGIC INVESTIGATION OF THE MECHANISM OF CHEMORECEPTION

COMMUNICATION III. THE EFFECT OF NICOTINE AND ACIDS ON THE INTESTINAL RECEPTORS IN MONOIODOACETIC-ACID-INDUCED DISTURBANCES OF METABOLISM

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Many authors are at present concerned with the problems of chemoreception [11]. There is still no single viewpoint, however, with respect to the mechanism of the action of various chemical stimuli. The majority of authors divide stimuli into 2 groups: the first includes hypercapnia and hypoxia as well as cyanide compounds, the second acetylcholine, nicotine and some others.

Many authors, in their attempts to approach the solution of the essential problem of chemoreception, chose the path of studying changes in metabolic processes which play an important part in the reception of the stimuli indicated [12, 9, 3].

It has been suggested [9] that the stimulus for chemoreceptors is a change of metabolism within the cells. The author supposed that there were two different mechanisms of chemical stimulus action on receptors. Substances belonging to the first group cause significant changes in cell metabolism which serve as chemoreceptor stimuli.

* In Russian.

Stimuli belonging to the second group act directly on receptors and possibly produce no marked changes in tissue cell metabolism. Such a concept is supported by experiments [9, 10, 8] in which it was shown that after chemoreceptors had been acted upon by certain substances (sodium fluoride, monoiodoacetic acid), carbon dioxide and a number of other substances produced none of the characteristic changes in blood pressure and respiration; at the same time, reflexes elicited by nicotine and acetylcholine were preserved. Moreover, following the action of monoiodoacetic acid, the reactions to carbon dioxide at first disappeared and then showed inversion from pressor to depressor, while the the reactions to nicotine were enhanced [5, 7].

In our experiments [2] we showed that when intestinal tissue metabolism was altered by the action of monoiodoacetic acid (4-5 ml 0.01 N solution), administration of nicotine produced a greater flow of impulses than in the normal and a higher rise of blood pressure. Carbonic acid caused a depressor blood pressure reaction and inhibition of initial impulse flow instead of its enhancement,as was observed before monoiodoacetic acid treatment. These data also supported the difference of monoiodoacetic acid (MIA) effect on nicotine and carbon dioxide reception.

However, according to M. L. Belen'kii's data [3], the reception of both groups of chemical stimuli is impaired after treatment of carotid body chemoreceptors with monoiodoacetic acid and other poisons which block various stages of carbohydrate metabolism. This author studied the effect of cyanides and lactic acid, as well as acetylcholine. He therefore considers that reception of various groups of chemical stimuli is connected with the same links in carbohydrate metabolism.

We have postulated the view that the different results obtained by the authors cited [9, 10, 8 and 3] depend to a considerable degree on the use of different doses of enzyme poisons in their experiments.

Moreover, in some experiments [3] the action of monoiodoacetic acid on the chemoreceptors was effected by means of prolonged perfusion whereas in others [8, 9, 10] the effect of a single administration of a relatively small amount of monoiodoacetic acid was studied.

The aim of the present investigation was the study of reception of various groups of chemical stimuli under conditions of impaired intestinal tissue metabolism effected by different doses of MIA. The receptor reaction under the influence of various doses of monoiodoacetic acid was judged on the basis of reflex changes in blood pressure arising from the action of chemical stimuli on intestinal receptors, and of changes in afferent impulse flow in intestinal nerves.

EXPERIMENTAL METHOD

Experiments were carried out with perfusion of an isolated portion of the intestine connected with the organism by nerves only. The chemical stimuli — nicotine and acids — were introduced into the perfusion fluid. Afferent impulses in the intestinal nerves were recorded simultaneously with blood pressure in the carotid artery (the method is described in detail in previous communications [1, 2]). The action of nicotine and various acids (carbonic, acetic and lactic) on intestinal receptors was studied afterthe use of different doses of monoiodoacetic acid. The influence of monoiodoacetic acid was studied both on single administration of its solutions by way of the perfusing fluid and on prolonged perfusion of fluid containing monoiodoacetic acid through the intestinal vessels. A total of 30 experiments was performed.

EXPERIMENTAL RESULTS

In the first experiments we introduced single relatively large doses of MIA which were larger than those used previously [8, 10, 9].

The data obtained are presented in Fig. 1 which shows that after introduction of 5 ml monoiodoacetic acid (0.01 N solution) there was increased intensity of impulses in response to administration of nicotine as compared with the effect obtained prior to the action of MIA (see Fig. 1, II and III). Subsequent administration of a relatively large amount of MIA (1 ml 0.1 N solution) resulted in the disappearance of impulses in response to subsequent administration of nicotine (Fig. 1, IV). Changes in blood pressure in response to nicotine were also absent under these conditions.

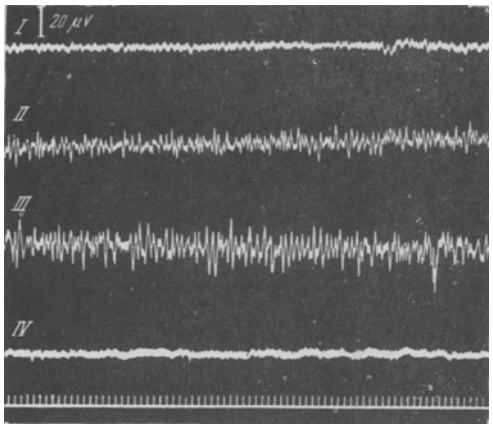

Fig. 1. Changes in intestinal receptor response to the action of nicotine after introduction of various doses of monoiodoacetic acid into the intestinal vessels. I) Initial electric activity in intestinal nerves; II) electric activity after introduction of 1 ml nicotine in 10^{-4} concentration into the intestinal vessels; III) the same with nicotine concentration 10^{-4} 10 min after introduction of 5 ml 0.01 N solution of monoiodoacetic acid into intestinal vessels; IV) the same with concentration of nicotine 10^{-4} after second introduction of monoiodoacetic acid (1 ml 0.1 N solution). Time marker 0.02 sec.

Thus in experiments with introduction of large amounts of monoiodoacetic acid, the effect of nicotine underwent changes similar to those in the experiments of M. L. Belen'kii [3]. However, the disappearance of the reaction to nicotine under the conditions indicated may not signify a specific interference of monoiodoacetic acid with metabolic processes participating in nicotine uptake, since introduction of a single large dose of this enzyme poison may produce irreversible "extinction" of receptors.

It was therefore essential to find the conditions under which it would be possible to trace the dynamics of changes in afferent impulse flow and reflex changes of blood pressure elicited by various stimuli acting on the intestinal receptors against a background of a gradually increasing influence of MIA. In connection with this, subsequent experiments were performed with the effect of nicotine studied against continuous perfusion of intestinal vessels with monoiodoacetic acid solution (0.002 N). In these experiments, changes of reaction to various stimuli appeared relatively rapidly. The experiments showed that reaction to all the acids studied was the same prior to the action of monoiodoacetic acid, during its action and after it had been washed away.

When a series of reflexes to chemical stimuli had been recorded, a solution of monoiodoacetic acid was passed through the vessels and against this background the reflexes and afferent impulses under the action of the indicated chemical stimuli were studied again. Following this perfusion with Ringer-Locke solution was resumed.

Figure 2 (1-3) shows pressor reactions of the blood pressure arising on introduction of 0.5 ml 2% lactic acid, 5 and 50 γ nicotine into the intestinal vessels. After this, perfusion with a solution of monoiodoacetic acid (0.002 N) was begun. At first there was a decrease and then disappearance of the reaction to nicotine in the dose 5γ (see Fig. 2: 4,5), then to lactic acid (Fig. 2: 6, 8), and finally to nicotine in the dose 50γ (Fig. 2: 9). Following the disappearance of the reaction to nicotine in the dose 50γ, perfusion with monoiodoacetic acid was terminated and perfusion with pure Ringer-Locke solution was resumed.

Figure 2 (10) shows that after this pressor reaction in response to nicotine in the dose 50γ are restored and then to nicotine in the dose 5γ [Fig. 2: 12], the latter reaction being even somewhat greater than that observed prior to the action of monoiodoacetic acid. The reaction to lactic acid, however, is first absent (Fig. 2: 11) although in the initial state it was considerably greater than the reaction to nicotine in the dose 5γ.

During perfusion with Ringer-Locke solution, the blood pressure reaction to administration of lactic acid becomes weakly depressor (Fig. 2: 13). On further perfusion with Ringer-Locke solution the depressor reaction to lactic acid action becomes more marked up to a certain moment, while the reaction to nicotine increases to a level exceeding the initial one.

Similar results were observed in all our experiments with the use of the monoiodoacetic acid concentration indicated.

Figure 3 (2, 3) shows the changes in afferent impulses under the influence of lactic acid and nicotine before perfusion with MIA; Fig. 3 (5, 6) shows corresponding changes in impulses against the background of MIA perfusion; Fig. 3 (8, 9) shows the impulses after washing with Ringer-Locke solution; Fig. 3 (1, 4, 7) shows the records of "background" impulses. It can be clearly seen from Fig. 3 (2, 3) that slow impulses arise in response to the action of both nicotine and lactic acid. The appearance of impulses coincides with the appearance of pressor reactions of the blood pressure as the result of the action of these stimuli. As can be seen from Fig. 3

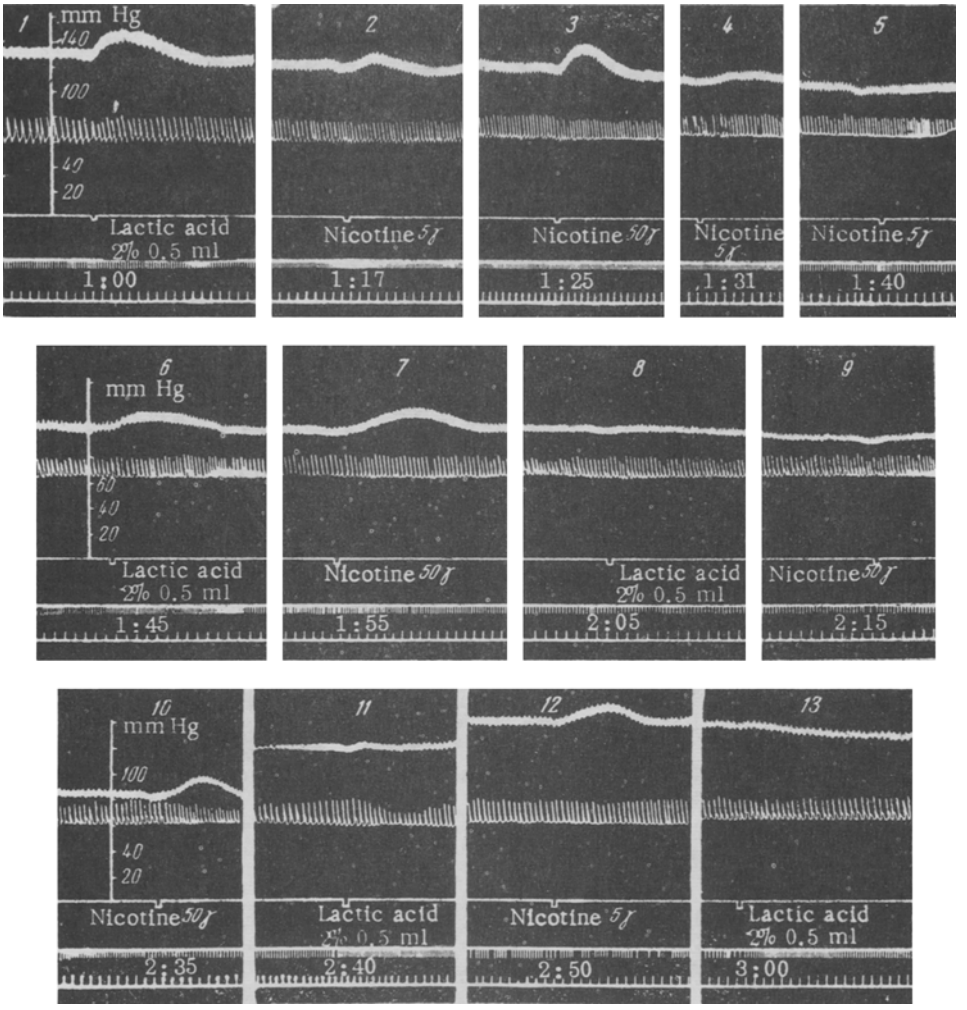

Fig. 2. Reflex changes in blood pressure under the action of nicotine and lactic acid on intestinal receptors before passage of monoiodoacetic acid (1-3) against background of perfusion with monoiodoacetic acid solution (4-9) and during washing with Ringer-Locke solution (10-13). Passage of monoiodoacetic acid was begun at 13 hrs 29 min and terminated at 14 hrs 17 min. Records (from above down): blood pressure in carotid artery, respiration, marker denoting administration of stimulus, record of the rate of perfusion, time marker (5 sec).

(5, 6) no impulses arise in response to the same stimuli, which coincides with complete absence of blood pressure reaction. Slow impulse activity again appears under the influence of nicotine as can be seen from Fig. 3 (8, 9). This coincides with the moment of restoration of pressor reactions to nicotine. In response to the action of lactic acid (Fig. 3: 8) there is, on the contrary, a small inhibition of "background" activity (Fig. 3: 7) which coincides with development of a depressor reaction of the blood pressure.

Deepening action of monoiodoacetic acid was associated with cessation of afferent-impulse enhancement and of reflex changes in blood pressure as the result of action of both groups of stimulating agents. However, when MIA perfusion of the intestine was terminated and washing with Ringer-Locke solution instituted instead, the reaction to nicotine was restored and this substance again elicited enhancement of impulse flow and reflex changes in blood pressure; the ability of acids to elicit impulse flow and pressor reactions of the blood pressure was, however, lost irreversibly. Several minutes after the beginning of Ringer-Locke solution perfusion, introduction of nicotine to the intestinal receptors caused increased blood pressure reaction, whereas the action of acid not only did not enhance the background afferent impulse flow, but inhibited it, and elicited depressor reactions of the blood pressure.

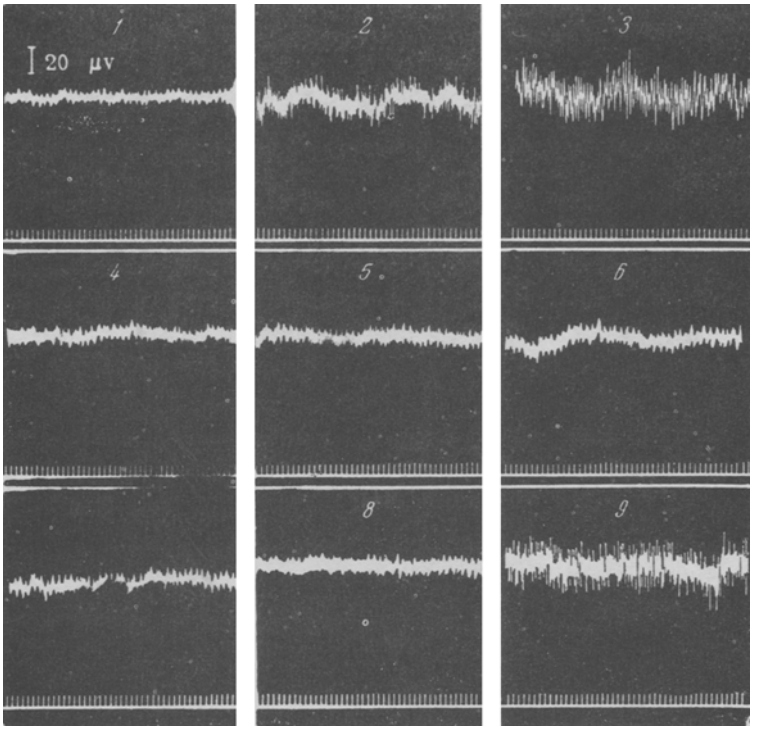

Fig. 3. Changes in afferent impulses in intestinal nerves under the action of nicotine and lactic acid on intestinal receptors before perfusion (2, 3) against the background of perfusion with monoiodoacetic acid (5, 6) and during washing with Ringer-Locke solution (8, 9). 1, 4, 7) Electric activity in intestinal nerves without stimulation; 2, 5, 8) changes in impulses under the influence of 0.5 ml 2% solution of lactic acid; 3, 6, 9) the same under the influence of 50γ nicotine. Time marker 0.02 sec.

Disappearance of the reaction to nicotine under the influence of large doses of MIA is, in our opinion, not the result of a specific blocking action of this substance on definite enzymatic processes connected with the mechanism of action of this stimulus, since these processes are disrupted irreversibly by MIA but the reactions to nicotine are restored.

How then can the transient disappearance of the reactions to nicotine be explained?

Experiments (6, 4, 2) have shown that prolonged action of carbon dioxide is associated with disappearance of reaction to all stimuli but, following washing with Ringer-Locke solution, the reflex returns. We carried out special experiments with perfusion of the intestine with a solution of acetic acid (0.1%); reflexes to both groups of stimulating agents disappeared very rapidly (2-5 min). On restoration, the blood pressure reactions to acid and to nicotine again assumed a pressor character. MIA also, evidently, can elicit temporary disappearance of the reaction to nicotine since it possesses acid properties.

The irreversible loss of intestinal receptor excitation in response to acids observed under the influence of MIA and expressed in the absence of a burst of impulses appearing in response to the action of the acids indicates that with respect to acids, monoiodoacetic acid behaves as an enzyme poison which blocks the metabolic processes participating in the reception of this group of stimuli.

Our experiments have thus confirmed our suggestion that the differences between the results obtained by V. N. Chernigovskii and M. L. Belen'kii are due to differences in the action of different doses of monoiodoacetic acid on receptors. By using doses of monoiodoacetic acid larger than those employed in V. N. Chernigovskii's experiments, we obtained, on the background of perfusion, results similar to those reported by M. L. Belen'kii.

However, the difference in intestinal receptor reaction to the 2 groups of stimuli found by us during the period of washing after MIA application, as well as the data previously obtained by V. N. Chernigovskii and V. A. Lebedeva [5-10], favor the concept of the existence of different mechanisms of action on receptors by different groups of chemical stimuli. It would appear that reception of nicotine and substances similar to it in their action does not include mechanisms which are blocked by monoiodoacetic acid whereas the uptake of acids by the receptors is impossible after specific blocking of these mechanisms.

The enhanced excitability of receptors with respect to nicotine and inhibition of these receptors with respect to acids observed during the period of washing after monoiodoacetic acid perfusion are evidently explained by the nonspecific influence of MIA on receptor excitability.

SUMMARY

The reception of various groups of chemical stimuli (nicotine and certain acids) was studied in conditions of deranged metabolism of intestinal tissue under the influence of various doses of monoiodoacetic acid. Experiments were performed with perfusion of an isolated portion of intestine connected to the organism by nerves alone. As the effect of monoiodoacetic acid becomes more pronounced the increase of the afferent impulse flow ceases and reflex changes of the blood pressure disappear.

Reactions of nicotine are re-established, the afferent flow increase and the reflex changes of the blood pressure recur after washing in Ringer-Locke's solution. At the same time, administration of acid depresses the impulse flow and causes depressive reactions of the blood pressure.

The conclusion was reached that the mechanisms blocked by monoiodoacetic acid evidently take no part in reception of nicotine and drugs with a similar effect. The reception of acids is impossible after specific block of these mechanisms.

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