INVESTIGATION OF THE MECHANISM OF CHEMORECEPTION

COMMUNICATION 4. THE ACTION OF NICOTINE AND OF ACIDS ON THE RECEPTORS OF THE INTESTINE DURING CHANGES IN THEIR EXCITABILITY UNDER THE INFLUENCE OF DIFFERENT CONCENTRATIONS OF MONOIODOACETIC ACID

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Chernigovskii [10] first discovered the fact that metabolic disturbances in the receptors caused by monoiodoacetic acid (MIA) differed in their effect on the perception of different groups of chemical stimuli. In these conditions carbon dioxide, when applied to the receptors, did not cause the changes in respiration and blood pressure which are characteristic of receptors in their normal state; at the same time reflexes caused by nicotine and acetylcholine remained intact.

Chernigovskii accordingly put forward the hypothesis that these two groups of chemical stimuli had different mechanisms of action. According to his view, acids (and also oxygen lack and cyanides) do not act directly on chemoreceptors, but cause some form of essential change in the cell metabolism, and this acts as the stimuli for the chemoreceptors. On the other hand, the chemical stimuli of the second group act directly on the receptors, and possibly do not cause significant changes in the metabolism of the tissue cells. Chernigovskii also showed that, under the influence of MIA, the reaction to carbon dioxide first disappears, and then is distorted, to become a depressor reaction. Subsequently Lebedeva [4, 5], on the basis of findings obtained without the use of electrophysiology, came to the conclusion that depressor reactions arise as a result of the exclusion of the receptors under the influence of carbon dioxide, and of the consequent cessation of the flow of pressor impulses into the centers, which we later confirmed by electrophysiological investigations [1].

Lebedeva [7] also showed that when the metabolism of the receptors was disturbed by the action of MIA, in addition to the disappearance and distortion of the reflexes to acids, an increase also took place in the excitability of the receptors by the chemical stimuli of the second group. On these grounds, Lebedeva developed the idea that the disturbance of metabolism was reflected in the general functional state of all the receptors, as shown by their increased excitability. The disappearance of the pressor reactions to carbon dioxide under these circumstances and the transformation of pressor reactions into depressor were regarded by her in the light of the views of Vvedenskii and Ukhtomskii, namely that an apparatus which is in a state of constant and fairly intensive activity must pass more easily into a state of inhibition than an apparatus which is in a resting, inactive state. Later, Lebedeva [8] examined these findings in the light of the possible depolarizing and hyperpolarizing action of carbon dioxide, depending on the initial level of the membrane potential, which may be changed under the influence of MIA.

Thus, Lebedeva, who was mainly concerned with the analysis of the depression in the response to acids, and with the associated increased excitability to nicotine, ceased to attach importance to the difference in the reactive systems receiving different groups of stimuli, and paid special attention to the change in the excitability of the receptors. From our point of view the idea that different reactive structures are present and that specific disturbances may take place in the metabolism of some of these structures by the action of MIA, is more correct.

In the present research we attempted to verify these points of view, i.e., to give an answer to the question whether the disappearance of the reflex reactions, arising in response to the action of carbon dioxide after changes in metabolism due to administration of MIA, is due to a change in the excitability or to the specific interference by MIA in the metabolism of the systems sensitive to the action of acid.

EXPERIMENTAL METHOD

The investigation took the form of acute experiments on cats under urethane anesthesia, in which an isolated segment of intestine, connected to the rest of the body only by its nerves, was perfused. Chemical stimuli – nicotine and acids – were introduced into the flow of perfusion fluid. The blood pressure in the carotid artery was recorded by means of a mercury manometer. In some experiments respiration was recorded by means of a Marey's capsule.

The influence of MIA on the reception of different groups of chemical stimuli was studied both after a single injection of solutions of the stimuli into the perfusion fluid and after prolonged passage of Ringer-Locke's solution containing MIA through the intestinal vessels. In Lebedeva's experiments MIA was usually allowed to act by giving a single injection of 5 ml of a 0.01 M solution. Under these circumstances an increase in excitability, as shown by an increase in the magnitude of the reflexes, was observed only in relation to the second group of substances, whereas the reactions to acid at once began to decrease. The absence of even an initial increase in the reflex reactions to acids may be explained by the immediate injection of too large a dose of MIA. In our experiments we therefore tested the influence of a small concentration of MIA (0.0005 M) during prolonged perfusion of the intestinal vessels with this solution. We studied the action of nicotine ($1:10^{-5}$ – $1:10^{-4}$) and acids (lactic acid, 0.5-2.0% solution, acetic acid, 0.5-1.0% solution and 0.03% hydrochloric acid). These solutions were injected in a volume of 0.5 ml. After a series of reflexes to chemical stimuli had been recorded, the MIA solution was passed through the vessels of the isolated segment of intestine, and the reflexes were again investigated during the action of the above-named chemical stimuli. In some cases perfusion of the vessels with Ringer-Locke's solution was then resumed.

EXPERIMENTAL RESULTS

The kymograms of one of the experiments are illustrated in Fig. 1. In kymograms 1-3 the reflex reactions of the blood pressure are shown during the action of 50 μg nicotine, 0.5 ml of a 0.5% solution of lactic acid and 0.5 ml of a 0.03% solution of hydrochloric acid on the receptors of the intestine by injection into the flow of Ringer-Locke's solution used for perfusion of the intestinal vessels.

Kymograms 4-6 show the reactions to the same chemical stimuli one hour after the beginning of perfusion with MIA(0.0005 M). It is clear that all the reactions are increased in magnitude. An even greater increase in the reactions to these chemical stimuli took place 1 hour 40 minutes after the beginning of perfusion with MIA (kymograms 7, 8 and 9). After further perfusion with MIA solution the reflex reactions in response to the action of nicotine began to fall (kymogram 10). At the same time the depressor reactions to lactic and hydrochloric acids either disappeared or were weakened (kymograms 11 and 12).

After rinsing with Ringer-Locke's solution the reactions to acids became obviously depressor, but those to nicotine were restored and exceeded the initial level (kymograms 13, 14, 15). All the experiments of this series followed a similar course with only slight variations. These variations primarily concerned differences in the degree of increase of excitability. The reflex reactions to nicotine in individual experiments reached 450% of the initial level. The increase in magnitude of the reflexes to acid reached 400%.

In some experiments the reflexes to nicotine increased more, in others those to acid. The subsequent decrease and disappearance of the reflexes to acid were usually accompanied by a weakening of the reflex to nicotine, although this weakening varied in degree. After rinsing with Ringer-Locke's solution the reflexes in

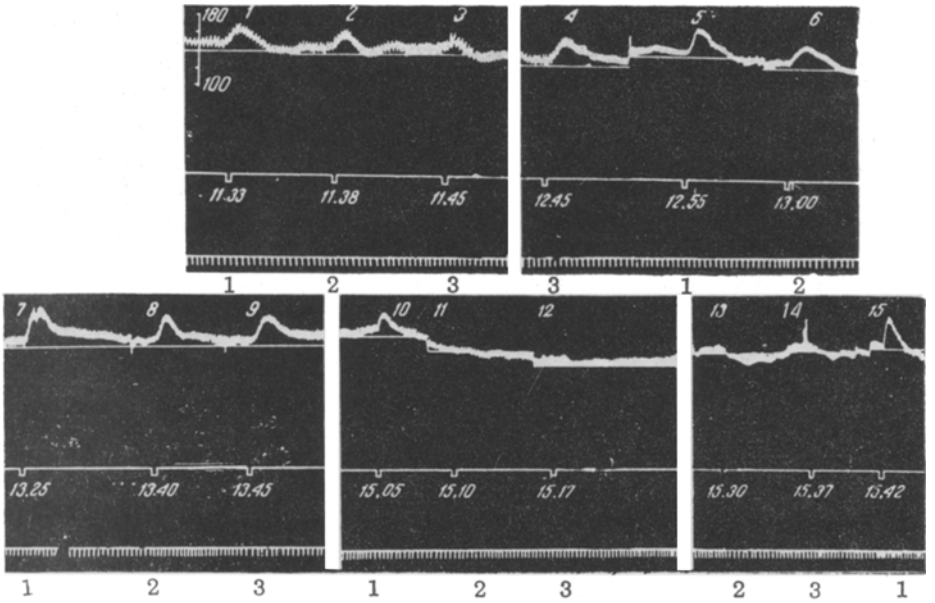

Fig. 1. Reflex changes in the blood pressure during the action of nicotine, and lactic and hydrochloric acids on the receptors of the intestine before perfusion with monoiodoacetic acid (MIA) (1-3), after perfusion with a 0.0005 M solution of MIA (4-12) and during rinsing with Ringer-Locke's solution (13-15). Perfusion with MIA began at 11 hr 47 min and ended at 15 hr 20 min. Significance of the curves (from above down): blood pressure in the carotid artery; marker of injection of stimulus; time marker (5 seconds). Key: 1) nicotine 50 μg; 2) lactic acid 0.5 ml 0.5%; 3) HCl 0.5 ml 0.03%.

response to the action of nicotine were restored and strengthened by comparison with their initial level, whereas the reflexes to acid were either completely absent or had become depressor in character.

We consider that the principal result of these experiments is the fact that, with a very considerable increase in the excitability of the intestinal receptors, which was shown by the increased magnitude of the reflexes to nicotine to 450% of their initial level, the reflex reactions to acid neither disappeared nor were distorted, but also increased. Decrease and disappearance of the reflexes to acid developed against a background of decrease of the reflexes to nicotine and not when these were increased. Distortion of the reflexes to acid developed only after their preliminary disappearance.

In order to solve this problem, it is equally important to present it in another way. Is it possible for the reflexes to acid to disappear or be distorted when the level of excitability remains unchanged? Is it possible for the pressor character of the reaction to acid to be restored after its disappearance or distortion under the influence of MIA when the level of excitability is lowered?

In Fig. 2 (1 and 2) we show the pressor reactions affecting the blood pressure and the slight increase in respiration arising in response to the injection of 5 μg nicotine and 0.5 ml of a 0.5% solution of acetic acid into the intestinal vessels. After injection of 5 ml of a 0.1 M solution of MIA (kymograms 3, 4, 5 and 6) a depressor reaction of the blood pressure develops in response to the same action of acid, whereas the reaction to nicotine maintains its original magnitude. Perfusion with MIA solution in a concentration of 0.002 M was then carried out, and this, as we have previously shown [2], quickly lowers the excitability of the receptors. Under these circumstances the reaction to nicotine was decreased (kymogram 7), although in this case too the reaction to acid continued to remain depressor (kymogram 8). Both reactions subsequently disappeared. After rinsing with Ringer-Locke's solution the reaction to nicotine was restored, whereas the reaction to acid remained feebly depressor. At the end of the experiment the reaction to nicotine was usually decreased and the reaction to acid absent (kymograms 13 and 14).

If we compare the results of these two series of experiments we see that, on the one hand, even a very large increase in the excitability and a sharp increase in the reflexes to nicotine did not lead to the disappearance and

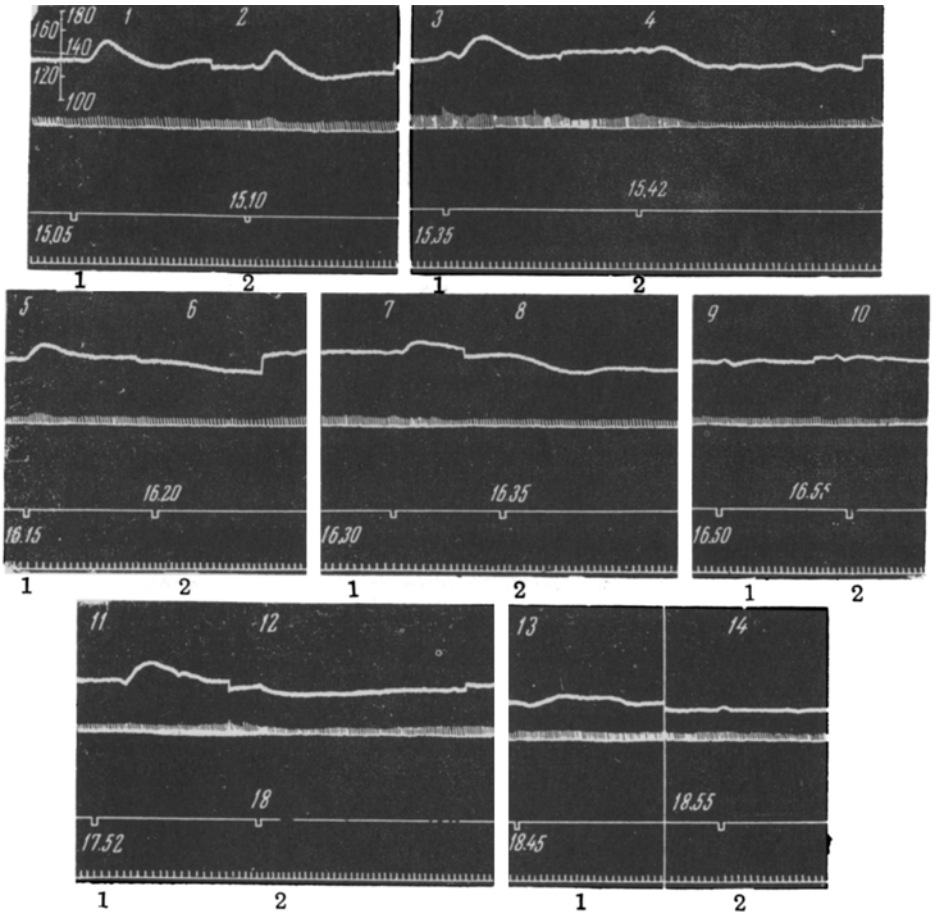

Fig. 2. Reflex changes in blood pressure and respiration during the action of nicotine and acetic acid on the receptors of the intestine before perfusion with MIA (1, 2), after injection of 5 ml of a 0.01 M solution of MIA (3-6), during perfusion with a 0.002 M solution of MIA (7-10) and after rinsing with Ringer-Locke's solution (11-14). The single injection of 5 ml of 0.01 M MIA solution was given at 15 hr 15 min. Perfusion with 0.002 M MIA solution began at 16 hr 27 min and ended at 17 hr 02 min. Significance of the curves (from above down): blood pressure in the carotid artery; respiration; marker of injection of stimulus; time marker (5 seconds). Key: 1) Nicotine 5 μg; 2) acetic acid 0.5% 0.5 ml.

distortion of the reflexes to acid, which also increased in magnitude. On the other hand, after poisoning of the receptors with MIA the pressor character of the reaction to acid was not restored when excitability was lowered, suggesting that the change in the level of excitability was not of decisive importance.

We cannot therefore agree with Lebedeva that the level of excitability is of paramount importance in the disappearance and distortion of the reflexes to acid. This phenomenon only develops during considerable degrees of poisoning of the tissue with MIA, and is due, in our opinion, to the irreversible inactivation of the reactive systems responsible for the perception of acids. We accordingly reverted to Chernigovskii's original view concerning the different points of application of the action of the two groups of chemical stimuli, which we designate as different reactive systems. It does not yet appear possible to answer the question whether these structures are morphological or biochemical.

Let us turn again to the action of MIA on the perception of nicotine which, according to the previous findings of Chernigovskii and Lebedeva, was not disturbed by the action of 5 ml of a 0.01 M solution of MIA. However, in both the present work and in our previous investigation [2] it was shown that the response to nicotine is also disturbed by a high concentration of MIA. The view was expressed above that this occurs as a result of the acid properties of MIA. However, the use of a neutralized solution of MIA in the present investigation gave the same result, the only difference being that the effect developed after longer intervals of time.

This action of MIA is similar to its influence on other excitable structures. It was demonstrated by several workers, for example, in nerves and muscles [3, 9, 11, 12, 13]. The fact that the reception of acids is comparatively quickly and irreversibly inhibited by the action of MIA indicates, in our opinion, the existence of special receptor systems, possessing a special type of metabolism which is readily disturbed by the action of MIA.

SUMMARY

The author investigated the effect of different concentrations of monoiodacetic acid (MIA) on the reception of nicotine and acids. It was shown that during the action of MIA in weak concentration (0.0005 M) the excitability in response to both stimuli augments at first and then becomes irreversibly disturbed; the action of nicotine changes but insignificantly. Higher MIA concentrations disturb the nicotine reception as well, however, this effect is reversible. A conclusion is drawn on the existence of separate reactive systems – for nicotine and for acids, with different metabolism.

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