THE EFFECT OF AMINO ACIDS ON UNCONDITIONED INTEROCEPTIVE REFLEXES

COMMUNICATION I. THE RELATIONSHIP OF CENTER TO PERIPHERY IN THE MECHANISM OF INTEROCEPTIVE REFLEXES

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The final form of a reflex is known to result from the interaction of three processes: the conditions of excitation of the receptors, the functional state of the central divisions of the reflex arc and the effective functional state of the organs responsible for performing the operation.

A considerable amount of material has now been collected which concerns this aspect of reflexes elicited by stimulation of the internal organs. Work by É. Sh. Airapet'yanets [1], I. A. Bulygin [3], M. L. Belen'kii [2] and V. N. Chernigovskii [12] has shown the importance of processes taking place in the receptor zone of the reflex and in the central nervous system.

N. A. Lapshin [7], investigating in 1948 reflexes caused by stimulation of the mechanoreceptors of the duodenum and rectum, found that they may appear in two forms: a fall or rise in the blood pressure. From analysis of this feature he established that this depended on whether the experiment was carried out on a starving or fed animal. After investigating the causes of this phenomenon, N. A. Lapshin [8] came to the conclusion that the changes in the reflexes could be explained by the difference in the pattern of impulses coming from the receptors in the alimentary tract of a fed or starving animal and also by the effect of certain chemical substances, circulating in the blood, on the functional state of the centers.

It was shown in work by V. V. Portugalov [10] that there are obvious differences in the state of the receptors Vater-Pacini corpuscles) of starving and fed animals, which can be demonstrated by histochemical methods. Recently work has been published by V. E. Delov, N. A. Adamovich, P. A. Kiselev and O. N. Zamyatina [4] which showed that the intensity of afferent impulses recorded in the celiac nerve of a cat depends on the functional state of the digestive system of the animal (the presence or absence of food in the alimentary tract, distension of the walls of the stomach with a rubber balloon). Meanwhile P. A. Kiselev, N. A. Adamovich and O. N. Zamyatina [6] have shown that the flow of afferent impulses in the sympathetic trunk of a frog depends on the functional state of the digestive system. A special investigation by O. N. Zamyatina [5] showed that in fed and starving animals there is a considerable difference in the pattern of impulses from the receptors. O. N. Zamyatina also established that the introduction of amino acids (leucine, cystine, tyrosine and tryptophane) into the lumen of the intestine in a concentration of 10^{-3} to 10^{-2} M causes the appearance of or the strengthening of existing afferent impulsation in the intestinal nerves. The receptors of the small intestine and pancreas are particularly sensitive to excitation by these substances.

V. A. Lebedeva [9] had previously shown that one of the amino acids — cystein — plays an important role in the mechanism of stimulation of receptors by chemical agents.

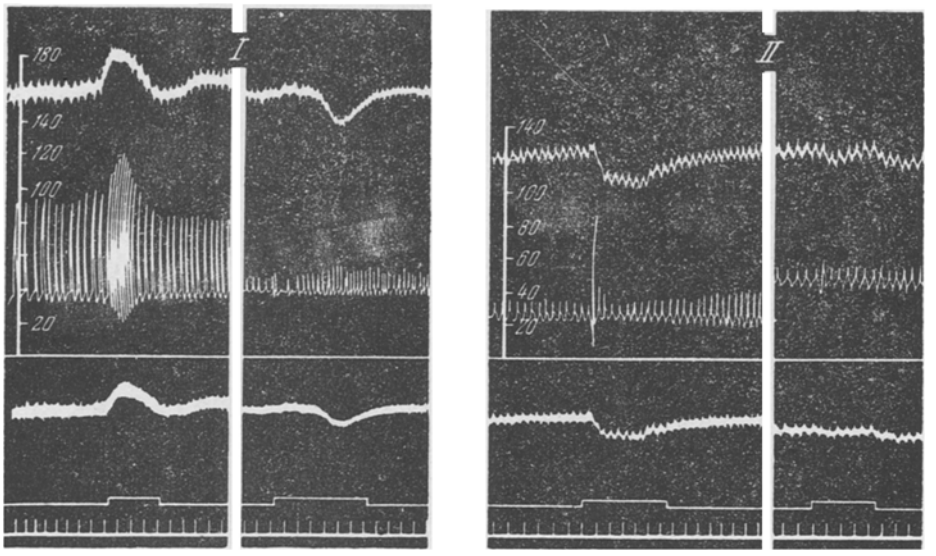

Fig. 1. Reflex changes in response to an increase of pressure in the duodenum. I) Transformation of the original pressor reaction (a) into depressor (b) after intravenous injection of glutaminic acid to a starving animal; II) transformation of the original depressor reaction (a) into pressor (b) after intravenous injection of glutaminic acid to a fed animal.
Significance of the curves (from above down): arterial pressure, respiration, zero line, pulse rate, stimulus marker (inflation of the duodenum), time marker (5 seconds).

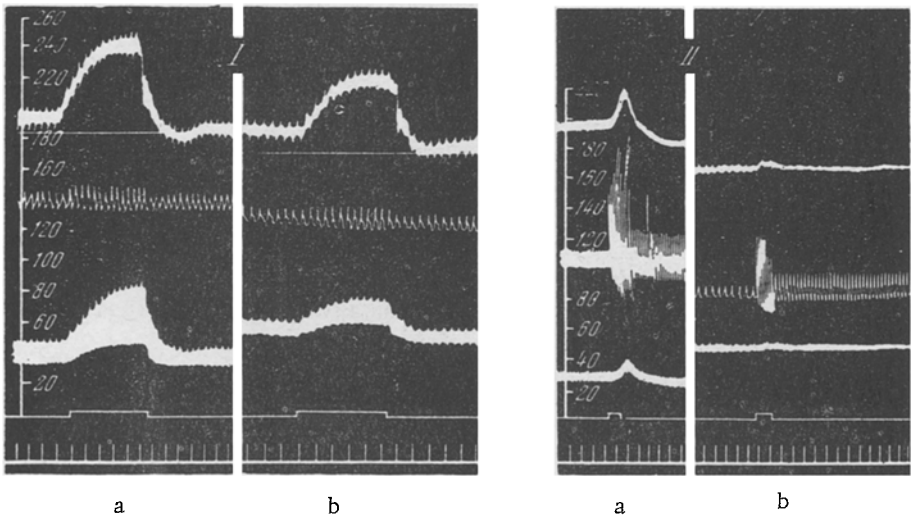

Fig. 2. Reflex changes during compression of the carotid artery.
I) Stimulation of the central end of the femoral nerve by an electric current; II) a) initial reactions; b) after intravenous injection of glutaminic acid.
Significance of the curves (from above down): arterial pressure, zero line of the reflex, respiration, pulse, stimulation marker which is also the zero line of the blood pressure, time marker (5 seconds).

In later work V. A. Tychinin [11] injected into the isolated carotid sinus of animals a mixture containing 10 amino acids (phenyl-α-alanine, glycocol, tryptophane, lysine, asparaginic acid, cysteine, glutaminic acid,

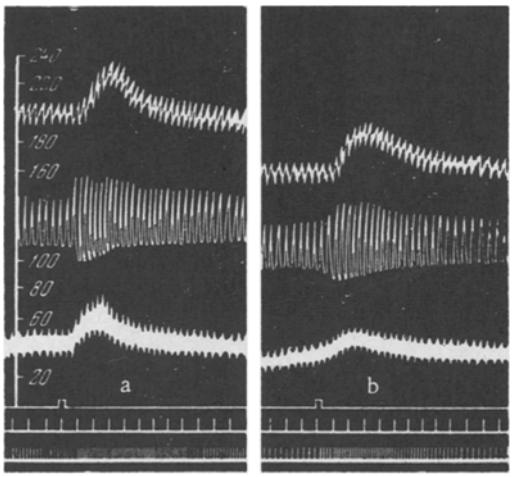

Fig. 3. Reflex changes during stimulation of the chemoreceptors of the small intestine. a) Initial reaction; b) after intravenous injection of glutaminic acid. Significance of the curves (from above down): blood pressure, respiration, pulse, stimulation marker (administration of acetylcholine 10^{-5}), time marker (5 seconds) which is also the zero line, number of drops perfused.

tyrosine, histidine and norleucine) and observed a fall in the amino acid content of the blood which, in his opinion, was reflex in origin, as a result of stimulation of the carotid sinus receptors by the injected mixture.

Hence it might be thought that the action of amino acids could conveniently be used to investigate the relationship of center to periphery in the mechanism of interoceptive reflexes.

In the present work our object was to investigate whether changes in the reflexes similar to those observed by N. A. Lapshin [8] can be obtained by the direct action of amino acids on the centers or on the receptors.

EXPERIMENTAL METHOD

The investigation was carried out on fed and starving cats. The starving animals received no food for 2-3 days before the experiment. The fed animals were given a plentiful diet for 3-4 days before the experiment. Intravenous urethane anesthesia was used (1.5 - 2 ml of a 25% solution per 1 kg body weight).

Indicators of the magnitude of the reflex reactions were : the blood pressure, respiration, the rate of the heart. The blood pressure was recorded by a mercury manometer connected to the carotid artery of the animal. The rate of the heart was indicated by a membrane manometer. The respiration was recorded by means of a Marey's capsule connected to the animal's trachea. The reflexes caused by stimulation of the mechano and chemoreceptors of the intestine, the reaction to clamping the carotid artery and the reflex caused by stimulation of the central end of the femoral nerve with an electric current were studied. Stimulation of the mechanoreceptors of the duodenum, with its nervous and humoral connections with the body intact,was carried out by inflating it with air to a pressure of 60 -80 mm of mercury.

The chemoreceptors of the perfused segment of the small intestine were stimulated by application of acetylcholine or nicotine in doses of 5 - 50 γ.

Compression of the carotid artery opposite to that in which the blood pressure was recorded was carried out by means of a special clamp for a period of 20 - 25 seconds. The central end of the femoral nerve was stimulated by an electric current from the secondary winding of an induction coil (4v, 50 impulses per sec, distance between coils 15 - 17 cm).

Solutions of neutralized L-stereoisomers (glutaminic acid, cysteine, alanine) in a concentration of 1: 10^{-3} were injected singly into the femoral vein. Altogether 87 experiments were performed.

EXPERIMENTAL RESULTS

The research of O. N. Zamyatina showed that introduction of amino acids into the lumen of the intestine causes a marked strengthening of impulsation. It might be considered that in N. A. Lapshin's experiments the changes in the reflexes were associated with a change in the functional state of the centers or the periphery following the appearance of amino acids in the blood of the fed animals.

It was therefore important in the first place to test the effect of intravenous injection of amino acids on the unconditioned interoceptive reflexes. It had to be ascertained whether amino acids had any effect on the blood pressure and respiration by direct action on the centers or periphery or both.

In the first series of experiments we studied the reflexes caused by stimulation of the mechanoreceptors of the duodenum in fed and starving animals after the intravenous injection of amino acids. The experiments

showed that the intravenous injection of amino acids to a starving animal (glutaminic acid, cysteine or alanine) leads to a replacement of the pressor reflex, previously observed in response to stimulation of the duodenum by a depressor reflex (Fig. 1, I, a, b). Injection of amino acids to a fed animal elicited a depressor reflex instead of a pressor (Fig. 1, II, a, b). In these experiments the amino acids could exert their effect either centrally or peripherally on the receptors of the duodenum which retained its nervous and humoral connections with the body.

In the second series of experiments we set out to study the possible action of injection of amino acids on the centers. We investigated the reflex to compression of the carotid artery. Fig. 2, I, a, b shows that in some cases the initial pressor reflex to compression of the carotid artery either diminishes slightly or increases and in other cases the pressor reactions are transformed into depressor. Thus in this series of experiments no conclusive results were obtained. It follows from these experiments that the central action of amino acids is not of decisive importance in influencing the direction of the reflexes.

In the third series of experiments (Fig. 2, II, a, b) the central end of the femoral nerve was stimulated with its contained somatic afferent fibers. After injection of amino acids the reflex action on the blood pressure was considerably depressed in both fed and starving animals. The results of this series of experiments showed that the peripheral elements of the reflex arc were concerned in the changes in the interoceptive reflexes after injection of amino acids. In order to settle once and for all the question of the degree of participation of the centers and periphery in influencing the direction of the reflexes, it was decided to examine changes in the reflexes from the chemoreceptors of the perfused segment of small intestine, retaining only its nervous connections with the body after the intravenous injection of one of the amino acids which we were using. Fig. 3 shows the kymogram of one of these experiments.

In these experiments the amino acid was not in contact with the receptors and the reflex action on the blood pressure and respiration was practically unchanged. These experiments demonstrate that central mechanisms are not the only ones in carrying out the interoceptive reflexes.

These results show that the injection of amino acids in very small amounts is capable of substantially influencing the interoceptive reflexes. As the investigations showed, the intravenous injection of amino acids alters the character of the reflexes, mainly by affecting the peripheral part of the reflex arc. This is shown by the experiments in which the reflexes from the duodenum and femoral nerve were altered after the intravenous injection of amino acids. The experimental results showing absence of changes during stimulation of the chemoreceptors of the perfused segment of the intestine after intravenous injection of amino acids do not support the view that the centers play a major role.

Decisive components of the mechanism of the interoceptive reflexes are evidently a change in the metabolic state of the receptive zone and the impulsation passing from that zone to the central nervous system.

SUMMARY

The aim of this work was the study of the effect of amino acids on the unconditioned interoceptive reflexes. The work was conducted on fasting cats and on those which were fed in condition of urethane anesthesia. Neutralized solutions of glutamic acid, cysteine and alanine were injected intravenously in the $1 : 10^{-3}$ concentration. The author studied the changes of the reflex reactions in response to the stimulation of duodenal mechanoreceptors, the chembreceptors of the perfused section of the small intestine, the baroreceptors of carotid sinus and in response to the electric stimulation of the central end of the femoral nerve. After the intravenous administration of amino acids to fasting animals a change of the blood pressure pressor reactions into depressor was noted, while in animals which were fed the depressor reactions changed into pressor. The pressor reflex to stimulation of the femoral nerve was depressed both in fasting cats and in those which were fed. In stimulation of the baroreceptors of carotid sinus in these conditions the reflexes did not follow any definite laws.

Reactions in response to the stimulation of the chemoreceptors of the perfused portion of intestine did not change. Thus, the intravenous administration of amino acids has a definite effect on the character of the reflexes, mainly by changing the condition of the peripheral part of the reflex arc.

Evidently, the change in the metabolic processes occurring in the receptive zones and the impulsation which is transmitted from the zone to the central nervous system are decisive in the mechanism of interoceptive reflexes.

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