CHANGES IN THE INTEROCEPTIVE REFLEXES AT AN INCREASED AMMONIA LEVEL IN THE BLOOD

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We studied the effect of increased blood ammonia level on the unconditioned interoceptive reflexes. As is known, an increased organic ammonia level of the blood (in common with carbamic acid) poisons the system and disrupts the activity of the nervous system[1, 2].

The investigation was carried out on cats under acute experimental conditions; a 10% solution of urethane, administered intravenously, was used as anesthesia. In various experiments the stimulants used were: dilation of an intestinal loop, dilation of the urinary bladder, administration of a 0.1% KCl solution or of acetylcholine in various concentrations into the artery of a section of the intestine which had been isolated from the general blood circulation and perfused. The dilation of both the intestine and the urinary bladder was carried out by means of a rubber balloon which was inserted through an incision in the wall of the organ and fastened with a purse-string suture. The balloon was connected by a rubber tube with a mercury manometer and a rubber bulb by means of a T-joint.

Three series of experiments were carried out – a total of 30 tests.

In the first series of tests, the effect of introducing ammonia into the blood stream of an animal on the course of unconditioned interoceptive reflexes was studied.

In these tests, dilation of an intestinal loop or of the urinary bladder was employed.

After the initial effect of dilating the organ at known pressure was determined, 1-5 ml of a 10% solution of ammonium citrate or chloride was administered into the femoral vein of a cat and then the organ was again dilated at varying intervals of time. The ammonia was introduced slowly, during 30-60 seconds.

The administration of ammonia salts decreased the manifestation of the unconditioned reflex considerably for some time, sometimes suppressing it completely.

Thus, in the experiment on 14 May, 1953 (Fig. 1,a), the effect of dilating the intestinal loop at a pressure of 8 cm of mercury, 3 minutes after administration of 3 ml of a 10% solution of ammonium chloride (NH_4Cl) into the general bloodstream, was decreased (b); 1-1/2 hours later it was almost completely re-established (c).

Similar results were obtained when the urinary bladder was dilated. For example, in the experiment of 23 April, 1953, its dilation at a pressure of 5 cm of mercury caused an increase in the blood pressure (Fig. 1,d); three minutes after introduction of 1 ml of a 10% solution of ammonium chloride, the effect was almost suppressed (e); 10 minutes later, it was completely re-established (f).

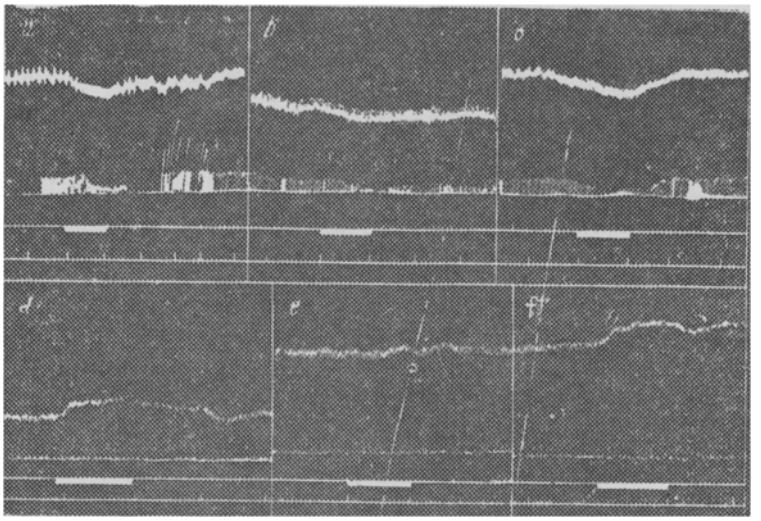

Fig. 1. Course of the unconditioned interoceptive reflex before and after administration of ammonia into the blood stream of an animal.
a) Change in blood pressure and respiration in response to dilation of an intestinal loop at a pressure of 8 cm of mercury; b) the same, 3 minutes after administration of 3 ml of a 10% solution of NH_4Cl into the blood; c) after 1-1/2 hours (experiment on 14 May, 1953); d) change in blood pressure and respiration in response to dilation of the urinary bladder at a pressure of 5 cm of mercury (experiment on 23 April, 1953); e) 3 minutes after administration of 1 ml of a 10% solution of NH_4Cl; f) the same after 10 minutes (experiment on 23 April, 1953).
Curves (top to bottom): blood pressure, respiration, application of stimulus, designation of time (30 seconds).

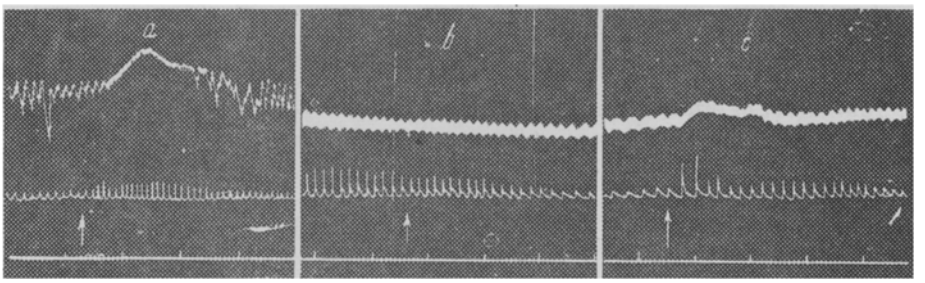

Fig. 2. Course of the unconditioned interoceptive reflex before administration of ammonia into the blood stream of the animal (a), 3(b) and 10 minutes (c) after administration of ammonia. Stimulus – 1 ml of acetylcholine (1×10^{-5}) perfused through an intestinal loop which was isolated from the general blood stream and was not subjected to the action of ammonia.
The moment of acetylcholine administration is designated by an arrow. The remaining symbols are the same as those in Fig. 1. Experiment on 20 May, 1953.

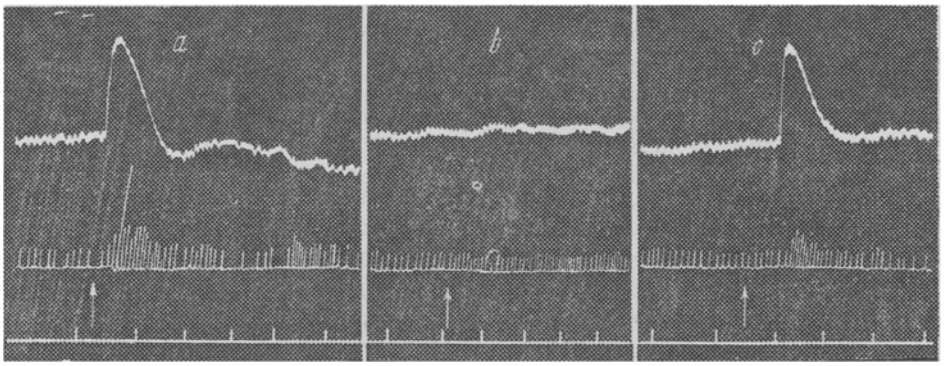

Fig. 3. Course of the unconditioned interoceptive reflex induced by the addition of 1 ml of 0.1% KCl solution to the perfused section of the intestines.
a) On the basis of perfusion with pure Tyrode solution; b) on perfusion with Tyrode solution with ammonia added; c) 15 minutes after renewal of perfusion with a pure solution of Tyrode. The arrow indicates the moment when the KCl was added to the perfusing fluid. The other symbols are the same as in Fig. 1.
Experiment on 26 May, 1953.

Ammonia was administered 2-3 times during an experiment; each time, the same relationship was observed*.

The larger the administered dose was, the longer the reflex was inhibited. The results were similar in all of the experiments.

In the second series of tests, ammonia was introduced into the blood stream of the cat in the same way, but the loop of the intestine which was subjected to stimulation was isolated completely and perfused with Tyrode solution; only a neural connection was left between the intestinal loop and the rest of the system. In this way, ammonia was prevented from entering this portion of the intestines.

1 ml of acetylcholine (in different experiments various concentrations of it were used: from 1×10^{-6} to 1×10^{-4}) or 1 ml of a 0.1% solution of potassium chloride (KCl), introduced into an artery of the perfused section, was used as the stimulus.

Under these conditions also, the introduction of ammonia salts into the cat's system temporarily decreased or completely suppressed the action of interoceptive stimulus.

Thus, in the experiment on 20 May, 1953 (Fig. 2), the introduction of 1 ml of acetylcholine (at a concentration of 1×10^{-5}) into the artery of the perfused section of the intestine caused a considerable rise in blood pressure and also an increase in the depth and frequency of respiration (a); 3 minutes after introduction of 1.5 ml of a 10% solution of ammonium citrate into the femoral artery of the cat, the effect of acetylcholine administration was absent (b); however, after only 10 minutes, acetylcholine administration again produced an effect, albeit a weaker one than initially (c).

When potassium chloride was used as a stimulant, the same results were obtained.

In the third series of experiments, we used ammonia only on that section of the intestine which had been isolated from the general blood stream and perfused, and which was being stimulated. Consequently, ammonia did not reach the general blood stream, and the cat's system (except for this section of the intestine) was not subjected to the action of ammonia. In order to achieve this, at the necessary moment, perfusion of the intestinal loop with Tyrode solution was replaced with perfusion with Tyrode solution containing 0.5% NH_4Cl. 1 ml of a 0.1% solution of KCl was used as the test stimulus.

* The short duration of the action of the ammonia can be explained, apparently, by its speedy neutralization in the system.

The experiments were carried out as follows. After perfusion and the establishment of a constant blood pressure, the initial effect was determined, then we changed the perfusion to Tyrode solution with ammonia chloride; after varying intervals of time , the action of KCl was tested with the action of ammonia in the background; after this, pure Tyrode solution was used for the perfusion again; this change of perfusion solution was carried out several times in the course of the experiment.

In these experiments, when the ammonia acted only on the receptors of the given section of intestine, the same relationship was preserved as in the first two series.

Thus, in the experiment of 26 May, 1953 (Fig. 3), the administration of potassium chloride into the artery of the perfused section caused a sharp rise in blood pressure and faster respiration (a). Only 15 minutes after the initiation of perfusion with Tyrode solution containing ammonia, the effect of potassium chloride administration disappeared completely (b). However, it was worth excluding the action of the ammonia since the effect was re-established after some time (c). Such "poisoning" can be produced several times in the course of the experiment, and the effect comes and goes correspondingly.

Thus, the experiments which we carried out show that an increase in the level of ammonia in an animal's blood produces a decrease or complete disappearance of unconditioned interoceptive reflexes. The isolation of the stimulated section of the intestine from the general blood stream does not remove this effect; the depressant action of ammonia is also evident when it acts only on the interoceptors of the section of the intestine from which the reflex is evoked.

These observations of ours agree with the data of investigators who have shown the sharp decrease in the reflex activity of animals in whom the symptoms of acute poisoning with protein metabolites – absence of sensitivity to pain, marked weakening of vision, ataxia, drowsiness – have developed as a result of excluding the barrier function of the liver.

LITERATURE CITED

[1] Pavlov, I. P. (with M. Gan, V. N. Massen and M. Nentskii) in the book: Complete Collected Works, (2nd edition, Moscow, 1951), Vol. II, Book I, pp. 210-238.

[2] Pavlov, I. P. (with I. Zalesskii and M. Nentskii), ibid. pp. 287-319.