THE MECHANISM OF DYSENTERY INTOXICATION

COMMUNICATION III. SPECIFICITY OF ACTION OF THE ENTERIC GROUP OF TOXINS ON INTESTINAL CHEMORECEPTORS

I. P. Miyagkaya

Laboratory of Receptor Physiology (Director – Active Member AMN SSSR V. N. Chernigovsky), Laboratory of Pathologic Physiology (Director – the late Professor V. S. Galkin), The I. P. Pavlov Institute of Physiology, AN SSSR (Director – Academician K. M. Bykov) and Department of Internal Medicine (Director – Active Member AMN SSSR M. D. Tushinsky), The 1st I. P. Pavlov Leningrad Medical Institute

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The question of specificity of toxin action is a controversial one. A.D. Ado and collaborators and other [1,2] consider that toxins possess no specific properties in their action on the nervous system. A.D. Speransky and collaborators, H. Raskova and collaborators and others [9,10,14] maintain, on the other hand, that the relation of various toxins to nervous elements is specific.

As already reported [7,8], application of dysentery toxin to the mucosa of a perfused intestinal loop leads to changes in the intensity of arterial blood pressure reflexes to stimulation of receptors by nicotine.

METHODS

52 experiments were performed on cats. As in the previous experiments [7,8], chemoreceptor activity was studied on a portion of the intestine which had been isolated from the general circulation. The order of experimental procedure was the same as before. Exotoxins of Shiga bacilli and Staphylococcus aureus and endotoxins of Flexner bacilli C and E. coli was used.

RESULTS

In the first series of experiments (17 experiments) the E. coli toxin was studied. Being a constant inhabitant of the intestine E. coli may, under certain conditions, give rise to an illness resembling dysentery [5,12, 13]. According to observations by Vincent [15] intravenous injection of E. coli toxin into rabbits led to their death with manifestations of paralysis starting in the hind limbs. At autopsy severe myelitis with extensive cellular degeneration in the anterior and posterior horns was found together with signs of marked enteritis.

This gave rise to the question whether E. coli toxin resembled the Shiga bacillus toxin in its effect on receptors.

Twelve cats in this series were given E. coli toxin subcutaneously in amounts of 0.5-3 LD(mouse) per 1 kg body weight. Only two of these were very ill on the 3rd day of intoxication, and the animals died during preparation for the experiment. The remaining 10 cats did not differ in their behavior from healthy ones. These were subjected to experiments on the 1st and 2nd day of intoxication (8 experiments), 7th day (1 experiment) and 11th day (1 experiment). No autopsy was performed,but when the intestinal loop was being prepared it was seen that the small and large intestine mucosa was hyperemic and that there was enlargement of mesenteric lymph nodes; dehydration of tissues was noted in two cases.

Application of E. coli toxin to the mucosa of the perfused intestinal loop (2-4 mouse LD) led to reduction of intensity of reflex arterial blood pressure reactions to intravascular introduction of nicotine (7 experiments on the 1st, 2nd and 7th day of intoxication). Only in one out of seven experiments restoration of the intensity

of reflexes was observed after 8 minutes; enhanced reflexes were noted in two experiments performed by the end of the 1st day of intoxication. No changes in reflex were obtained on the 11th day of intoxication.

Figure 1 presents kymograms of one of such experiments. Introduction of E. coli toxin (↓) into the intestinal lumen reduced the intensity of reflex reactions to nicotine from 10 to 6 mm in 1 minute. After

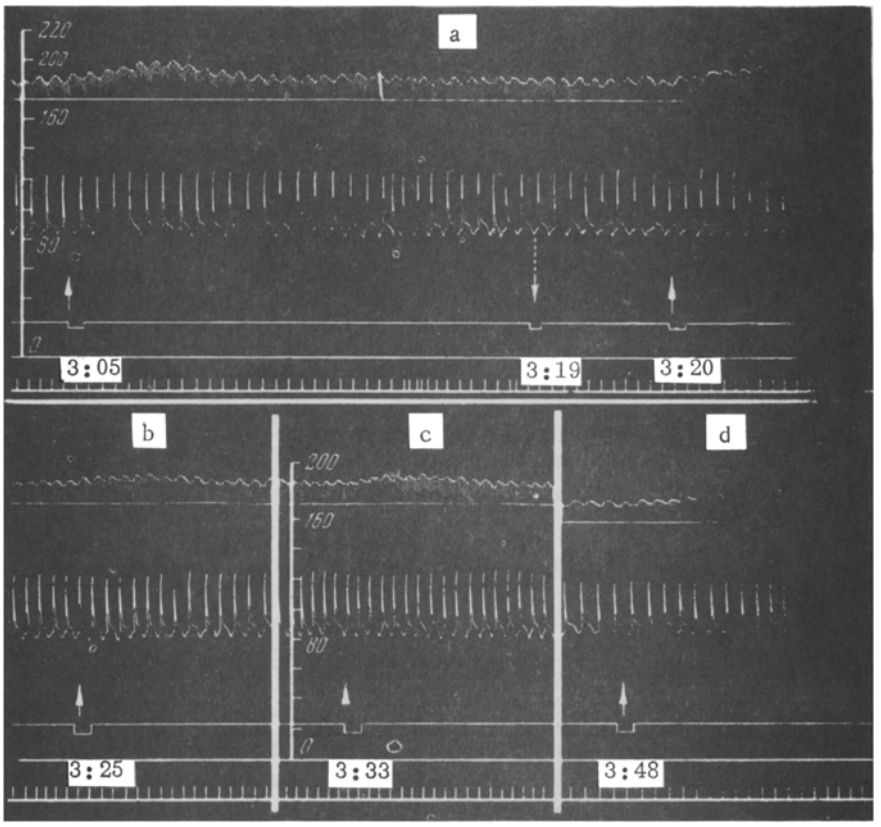

Fig. 1. Nature of reflex reaction to nicotine in cat upon introduction of E. coli toxin (0.6 LD per 1 kg body weight) (second day of intoxication).
Records from above down: arterial blood pressure, initial level of arterial blood pressure, respiration, stimulation mark (↓ – introduction of toxin, ↑ – introduction of 10 γ nicotine), manometer base line, time marker (2 seconds).

6 minutes the height to which arterial blood pressure rose following introduction of nicotine was only 4 mm (d). After 29 minutes the intensity of reflex reaction remained the same (f). The reflexes did not return to the initial level.

In control experiments introduction of E. coli toxin into the lumen of the perfused intestinal loop of seven healthy animals caused no change in the intensity of pressor reactions in response to nicotine stimulation of intestinal chemoreceptors.

This series of experiments thus indicates that E. coli toxin acting on an animal affected by the same toxin alters the chemoreceptor activity of the intestine similarly to Shiga bacillus toxin.

In the second series (14 experiments) a study was made of chemoreceptor activity of the intestine under the influence of Flexner bacillus C, a representative of the so-called weakly toxic group of dysentery pathogens.

The available toxin was weak (0.5-1 mouse LD per 1 ml solution), which could not but affect the extent of intoxication development, the morphologic picture and the influence of the toxin on interoceptive

reflexes. The general condition of these animals was considerably better than of those under the influence of Shiga bacillus toxin. In 5 out of the 14 experiments in this series no changes in the intensity of reflex reactions were obtained upon stimulation of the intestinal mucosa by the toxin. At autopsy only slight hyperemia of intestinal mucosa was found in all 5 animals.

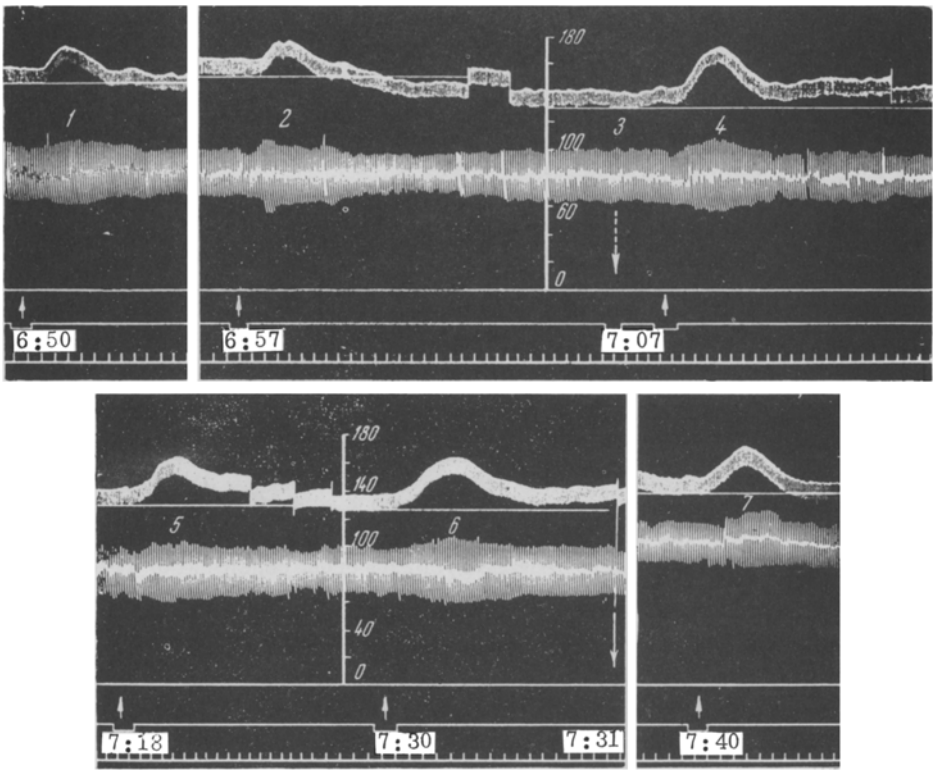

Fig. 2. Nature of reflex reactions to nicotine in cat upon introduction of Flexner toxin (0.85 LD per 1 kg body weight) 5 hours prior to experiment.
Records from above down: arterial blood pressure, initial level of arterial blood pressure, respiration, manometer base line, stimulation mark (↓ – introduction of toxin, ↑ – introduction 10 γ nicotine), time marker (5 seconds).

The experiments were performed 4-6 hours after subcutaneous administration of the toxin and on the 4th day of intoxication. In the first group of experiments in this series application of Flexner dysentery toxin (3-5 mouse LD in 1.5-2.5 ml solution) to the mucosa of the perfused intestinal loop led to enhancement of arterial blood pressure reflexes to nicotine stimulation in three experiments. In one case no change in the reflex was obtained.

At autopsy marked hyperemia of the intestinal mucosa especially of the small intestine, was observed. The results of the second series of experiments are presented in Fig. 2. Two and one-half hours after subcutaneous injection of the toxin (↓) the cat began to vomit repeatedly (5 times during 30 minutes). Motor restlessness appeared. Introduction of the toxin into the intestinal lumen was accompanied by a persistent enhancement of reflexes from 14 to 30 mm. After 10 minutes the reflex level dropped to 26 mm. Deepening the narcosis (↓) did not alter the intensity of the reflex reactions.

The second group of experiments in this series was performed on the 4th day of intoxication. In 5 out of 10 experiments introduction of Flexner bacillus toxin into the intestinal lumen elicited reduction of pressor reactions to nicotine with their restoration within 15-60 minutes. In 4 experiments no changes in reflexes were observed. In one experiment toxin stimulation of intestinal mucosa receptors increased the intensity of

reflexes to nicotine by 6 mm, compared with the initial level, in the course of 20 minutes. At autopsy the animals in which there was a lowering of reflex reaction showed macroscopic edema of the tissues of both the small and the large intestine with hyperemia and hemorrhages in the mucosa. A large amount of mucus was found in the intestine. No mucosal necrosis was found.

Comparsion of the experimental results obtained with Flexner bacillus endotoxin and Shiga bacillus exotoxin allows the conclusion that changes in intestinal chemoreceptor activity produced by these two toxins are analogous.

The third series of experiments (6) made use of Staphylococcus aureus toxin. It is well known that Staphylococcus aureus does not develop in the intestinal tract but when ingested with food may cause severe food poisoning with manifestations of gastritis and enteritis [3,4,6,11].

In this series the experiments were performed on animals previously poisoned by Staphylococcus aureus toxin. Stimulation of the mucosa of the perfused intestinal loop by Staphylococcus aureus toxin under conditions of intoxication did not affect the character of interoceptive reflexes in any of the 6 experiments (Fig. 3).

The experimental results in this series indicated that under conditions of staphylococcal intoxication application of Staphylococcus aureus toxin to the mucosa of the perfused part of the intestine left the intestinal chemoreceptor activity unchanged.

The results of the three series of experiments and those of our previous experiments with Shiga bacillus toxin [7] permit the conclusion that intestinal receptors possess particular sensitivity to pathogen toxins.

The fourth series (15 experiments) was concerned, on the one hand, with the effect of dysentery toxin on intestinal chemoreceptors under conditions of staphylococcal intoxication and, on the other hand, with the effect of staphylococcal toxin on intestinal interoceptive reflexes under conditions of dysentery intoxication produced by Shiga toxin.

1.2-1.5 ml Staphylococcus aureus toxin (16 thousand hemolytic units per 1 ml) was given to five animals 24 hours prior to the experiment. During the experiment dysentery toxin (60-120 LD) was applied to the mucosa of the perfused part of the intestine. In none of the 5 experiments was there any change in the nature of intestinal receptor reflexes to nicotine.

In the remaining 10 experiments intoxication was produced by subcutaneous injection of Shiga bacillus toxin (15-30 LD per 1 kg body weight).

Five experiments were performed on the 2nd day of intoxication. Introduction of Staphylococus aureus toxin into the intestinal lumen did not alter the intensity of reflexes to nicotine in any of the 5 experiments. The other 5 experiments were performed on the 4th day of intoxication. The animals were very ill; the arterial blood pressure and intensity of arterial blood pressure reflex reactions were diminished in the course of the experiment. No clearcut results could be obtained in these experiments.

The data of the last series of experiments convinces us that against the background of dysentery intoxication, the sensitivity of receptors is altered only with respect to dysentery toxin.

Staphylococcal intoxication, on the other hand, evidently does not enhance the intestinal receptor sensitivity to dysentery toxin.

The results of these experiments and those with the Shiga bacillus toxin [7] show that toxins of representatives of the enteric group of microbes, both pathogenic (Shiga and Flexner bacilli toxins) and conditionally pathogenic (E. coli toxin), exert an analogous influence on the intestinal chemoreceptors. Staphylococcus aureus toxin, a nonspecific intestinal stimulant, does not exhibit such influence either in dysentery or staphlococcal intoxication.

In acknowledging the existence of specific sensitivity of receptors to certain toxins we join the view held by O.Ya.Ostryi [9] who considers that in the process of phylo- and ontogenesis certain receptors which had been in predominant contact with certain stimuli have become the objects of one or other type of stimulation. Evidently that is the reason underlying the fact that toxins of various representatives of the enteric group possess common properties with respect to their action on intestinal receptors.

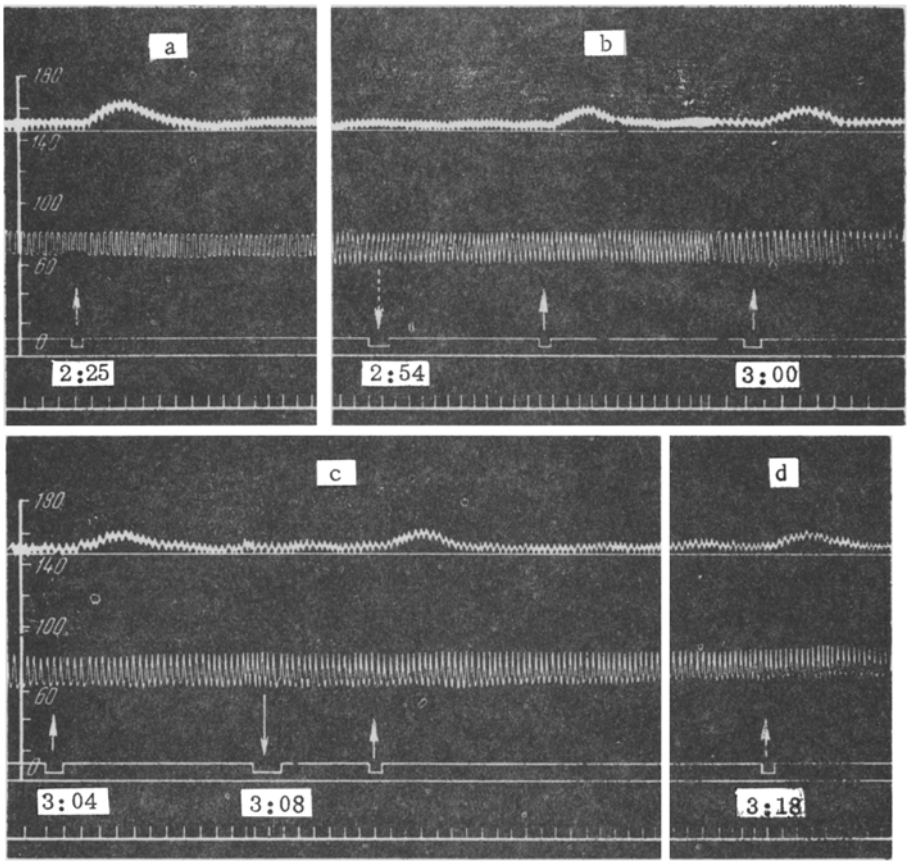

Fig. 3. Nature of reflex reactions to nicotine in cat in experiment with preliminary introduction of Staphylococcus aureus toxin (0.2* per 1 kg body weight). Records from above down: arterial blood pressure, initial level of arterial blood pressure, respiration, stimulus mark (| | – introduction of 0.5* staphylococcus, | – introduction 1γ nicotine), time marker (5 seconds).

SUMMARY

A comparison was made of the effect of exotoxins of the Shiga bacillus , endotoxins of Flexner bacilli and E. coli against the action of exotoxin of Staphylococcus aureus on the intestinal chemoceptors. The data which were received support the view of the presence of specific sensitivity of intestinal receptors to the toxins of pathogenic and conditionally pathogenic microbes of the intestinal group.

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