THE MECHANISM OF DYSENTERIC INTOXICATION

COMMUNICATION I INTEROCEPTIVE INTESTINAL REFLEXES IN THE PRESENCE OF EXPERIMENTAL DYSENTERIC INTOXICATION

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In the present study the chemoreceptors of the bowel were investigated as to the reflex effects produced on blood pressure and respiration under conditions of severe experimental poisoning with dysentery toxin.

The data in the literature [1, 2, 4, 7] concerning the effect various antigens produce upon the interoceptors seems inadequate to decide the question as to their participation in the pathogenesis of dysenteric intoxication.

EXPERIMENTAL METHODS

Fifty-two experiments were performed: 43 on cats being in a state of dysenteric intoxication and 9 on healthy animals.

The intoxication was produced by subcutaneous injection of Shiga dysenteric exotoxin (12-30 mouse LD per 1 kg weight). The chemoreceptors of the small intestine (45 experiments) and of the colon (7 experiments) were investigated with the use of the generally accepted technique. The experiments were conducted under urethane anesthesia given intravenously (4.1 cc of a 20% solution) some, 4-6 hours after injecting the exotoxin, some, 1,2, and 4 days later. The intestinal loop was extended from the general circulation and perfused with oxygenated Ringer-Locke solution at a temperature of 38-39°. The arterial pressure in the carotid artery and respirations were recorded.

The chemoreceptors were stimulated by a nicotine solution which was added to the perfusing fluid in a concentration of 1γ, 10γ, and 100γ per 1 cc of the solution. The toxin, sometimes 60-80 times the lethal dose, sometimes in individual instances 120 times the lethal dose, was placed upon the mucous membrane of the intestinal loop being perfused.

EXPERIMENTAL RESULTS

The first series of experiments were performed the 1st-2nd day after dysentery intoxication. Introducing the Shiga toxin into the lumen of the intestine had no effect on the arterial pressure, in 6 instances the pressure rose a minimal 2-3 mm mercury in the column and in only one instance was the rise equal to 10 mm mercury pressure.

After placing the poison upon the mucous membrane of the intestine, 7 out of 17 cases had increased reflex response to the nicotine, 6 – diminution or total suppression and in 4 – the reflexes were unaltered.

As an example of increased reflex response after placing the toxin, we can use the results obtained as represented in Fig. 1. As can be seen, introduction of the bouillon into the intestinal lumen ($\downarrow^1$) had almost no effect upon the arterial blood pressure (Fig. 1, a).

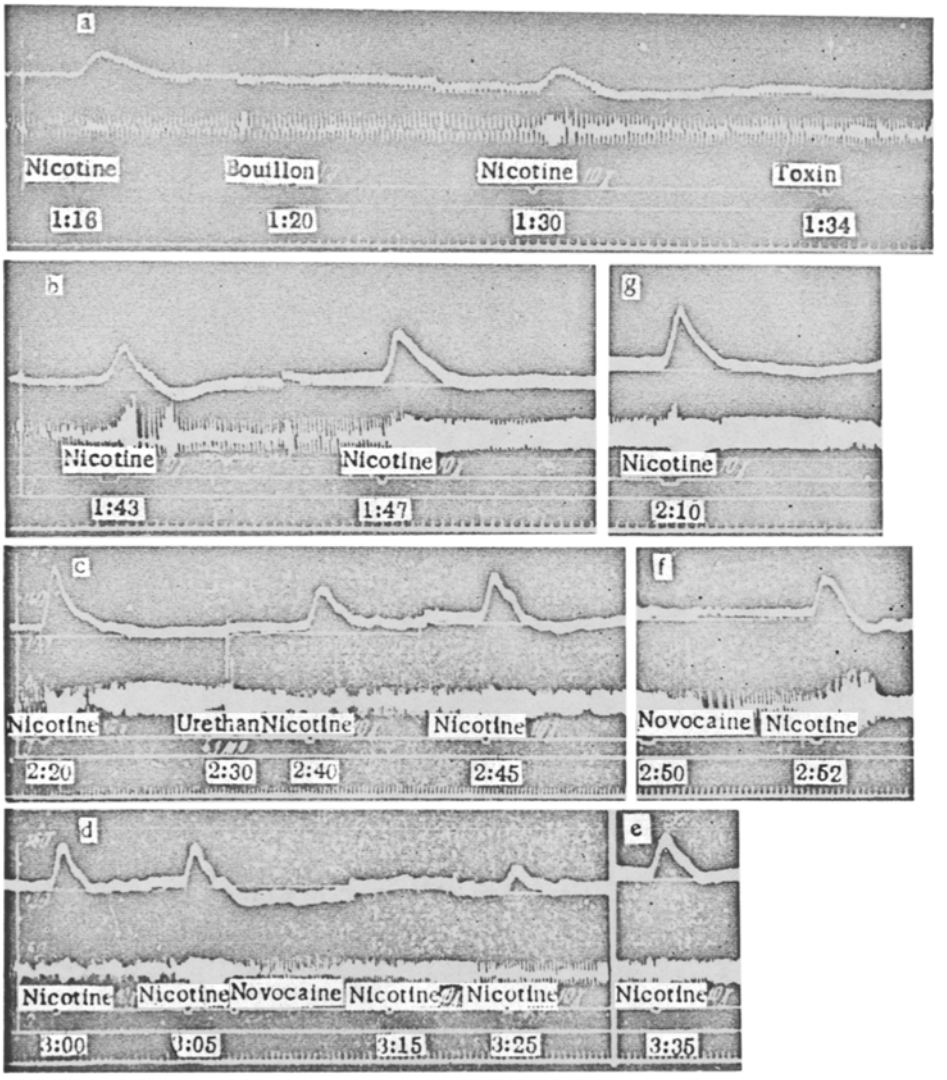

Fig. 1. Experiment of June 6, 1953. Cat, 3.2 kg. 2 days before the experiment 25 mouse LD of toxin per 1 kg weight were given subcutaneously (explanation in text).
Significance of the indicators (from above down): arterial pressure, base arterial pressure, respiration, marker of stimulator, zero line, time marker (5 seconds).

Nicotine did not alter the reflexes. After introducing the toxin into the lumen (1.0) of the intestine ($\downarrow^2$), the reflex responses were markedly reenforced (Fig. 1, b). Forty-six minutes after the introduction of the toxin, the same amount of nicotine (10γ) raised arterial pressure 54 mm of mercury, i.e., 38 mm more than before the toxin was introduced. After introducing the toxin, the amplitude of the respirations grew and the respiratory rate by 16-20 per minute, this being in contrast to the condition before the introduction of the toxin when 10γ of nicotine increased the respiratory rate only by 4-8 per minute. Deepening the narcosis somewhat decreased the reflex response to nicotine but they still conspicuously (by 14 mm mercury) exceeded the initial

responses. Introducing novocaine (2 cc 1% sol.) into the lumen of the cat's intestine did not alter much the reflex response of the arterial blood pressure. After the temporary abolition of chemoreceptor reflexes by injecting novocaine solution into the vessels of the isolated loop, the returning reflexes remained strong, considerably exceeding the initial response (by 18 mm mercury) even 2 hours after the toxin had been introduced into the intestinal lumen (Fig. 1,c).

Along with the increased reflex response to nicotine after the toxin had been placed on the mucous membrane of the poisoned cats, in 6 animals there was observed a depression or even a total abolition of reflexes. In 5 instances the reflexes were halved or even less as compared with base level; while in one the reflex response to nicotine was completely abolished.

In all 6 cases, within 15-60 minutes the reflex responses were fully restored. In the remaining 4 cases, there were noted no reflex alterations.

Analogous results were obtained in 7 experiments performed on the colon although the degree of reflex alterations was less. Apparently, this fact is associated with the lesser sensitivity of the colonic interoceptors to chemical stimulators [5, 9].

In this experimental series placing the toxin upon the mucosa within the first couple of days after dysenteric intoxication produced both a rise and a fall in the intensity of the reflex response to nicotine.

V. L. Troitsky and M. A. Tumanyan [8] report that, when dysentery toxin having a labeled phosphorus atom is given subcutaneously, the maximal urinary secretion of the toxin occurs after 4 hours. Using as a basis this statement, we conducted a series of studies on 10 animals 4-6 hours after poisoning them with the toxin.

In this series, 7 showed an increased reflex response to nicotine after the introduction of the toxin, while in 3 instances the reflexes remained unchanged. In no instance were the reflexes diminished. All these animals looked well; when sacrificed, there were no macrosocpic changes in the internal organs.

In the third series we studied interoceptive reflexes 4 days after poisoning the animals. As a rule, these animals became quite ill, frequently developed a diarrhea and lost muscular coordination. When sacrificed, there could be seen edema, hyperemia of both the serosa and mucosa of the bowel, hemorrhages, ulcerations and, sometimes, mucosal necroses. Analogous changes were seen in the stomach pylorus.

Of 9 experiments performed on these animals, in six the reflexes were diminished on the average some 4-6 mm of mercury with a restoration to normal after 7-35 minutes; in 2 instances the depressed reflexes failed in restoration, while in 3 – the reflexes remained unchanged.

Figure 2 presents the kymograms of one such experiment. Introducing the toxin into the intestinal lumen caused a slight rise in the arterial pressure and on this background the reflex response to nicotine (10γ) 20 seconds after introducing the toxin showed only a negligible alteration (Fig. 2, b). After 5 minutes there was a definite reflex depression (first, 6 and, then, 8 mm mercury; Fig. 2, b and 2, d). Thirty-five minutes after introducing the toxin (Fig. 2, g) the reflex response to nicotine failed to become restored; there was no increased reflex response in these experiments.

In 8 out of 9 control experiments conducted on well animals introduction of dysentery toxin into the intestinal lumen did not affect the arterial pressure or the respiration. In only one case introduction of the toxin led to a short, insignificant (3 mm mercury) rise of the arterial pressure. The reflex responses to nicotine remained either unaltered or changed but slightly. Of the 9 experiments in this series in six the reflexes stayed unchanged (Fig. 3), in 2 there was a slight reenforcement of the reflexes (response to 1γ of nicotine was increased 8 and 6 mm mercury) with a rapid restoration to normal (within 7-8 minutes). In one experiment the reflex response diminished by 4 mm mercury 13 minutes after introducing the toxin, by the 18th minute 1γ of nicotine had fully lost the capacity to elicit any response. In this experiment the reflexes remained lost.

In all the experiments, besides the arterial pressure, we recorded also the respiration but the small concentrations of nicotine used by us did not always increase respiration. For this reason we did not use the respiratory responses when analyzing the reflexes.

Thus we have established that the character of the reflex alterations depends on the phase of the intoxication.

The threshold dose for stimulating the chemoreceptors of the intestine in healthy animals, in our experiments, is 1 cc of a 10^{-6} (1γ) nicotine solution, this being in agreement with the greater material used by V. A. Lebedev [6].

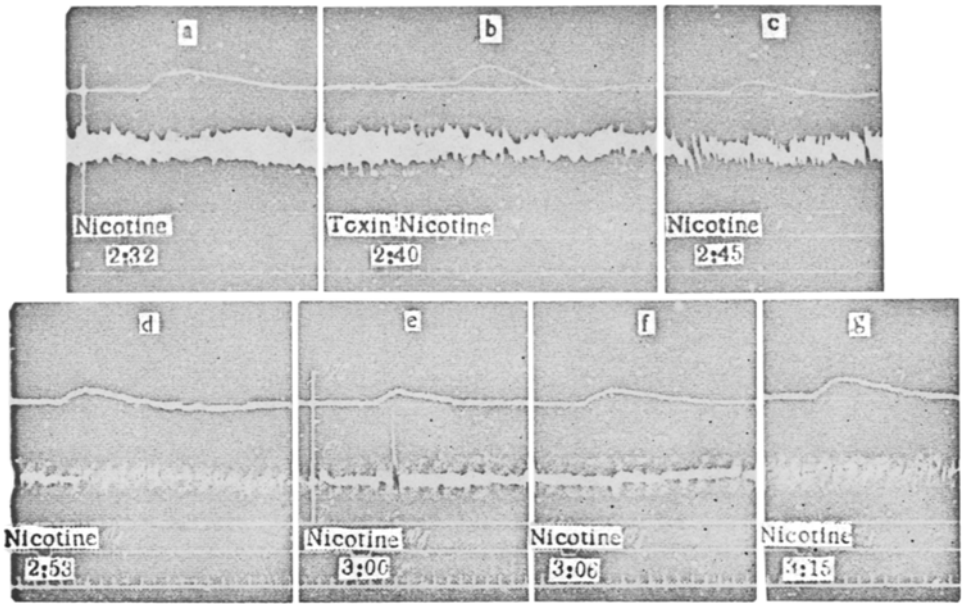

Fig. 2. Experiment of March 8, 1956. Cat weighing 2.9 kg. Toxin introduced 4 days previously (30 mouse LD per 1 kg). For clarification see text.
Significance of tracings (from above down): arterial pressure, initial level of arterial pressure, respiration, zero line, marker of stimulator, time interval (5 second marker).

Four to six hours after injecting subcutaneously the Shiga toxin, the threshold dose for nicotine stayed unaltered (1γ) remaining unchanged for 1-2 days. The intensity of the reflex response to 1γ of nicotine diminished over the first and second days for an average from 9.5 to 6 mm mercury. By the fourth day, a state of severe intoxication was apparent, the threshold rising to 10γ. There was no reflex response to 1γ.

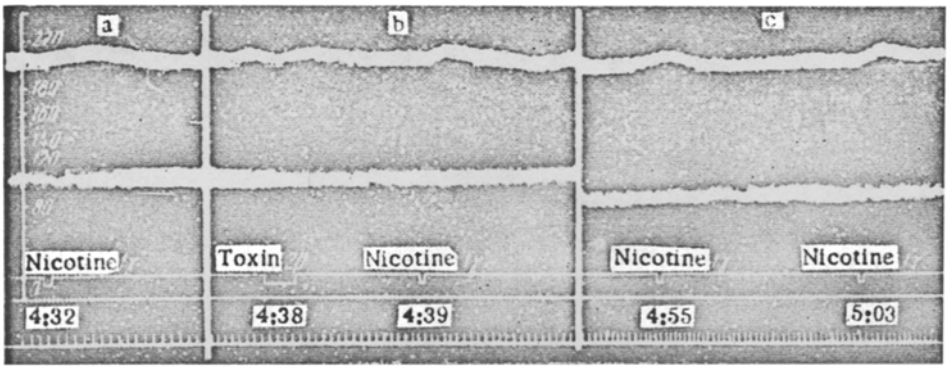

Fig. 3. Experiment of February 6, 1954. Cat weighing 4.150 kg, quite healthy. Explanation in text.
Significance of tracings as in Fig. 1. Time marker (2 seconds).

Our experiments suggest that even in the early phases of the intoxication offering the toxin to the intestinal receptors creates a greater sensitivity to the nonspecific chemical stimulator – nicotine.

When the dysenteric intoxication is fully developed, introduction of the toxin into the intestinal lumen provokes a temporary suppression of the reflex response to nicotine.

In healthy animals, analogous experiments produced no reflex alterations. Apparently, this indicates a greater sensitivity of the intestinal chemoreceptors to the dysentery toxin while the organism is suffering from dysenteric intoxication. A similar greater sensitivity of vascular receptors to antigens against a background of intoxication or sensitization to such agents was found by A. D. Ado and his associates [2].

There is also data indicating diminished sensitivity to acetylcholine after the dysentery toxin has acted upon the intestinal receptors [11].

The evidence presented seems to indicate that, during experimental dysenteric intoxication, the interoceptor chemical reflexes responding to chemical stimuli in the intestine become altered. It may be surmised that patients ill with dysentery have analogous changes which express themselves clinically [3].

Dysenteric toxins affect the interoceptive reflexes in a healthy organism very little if at all. For this reason, we agree with V. N. Chernova [10] who is of the opinion that irritation of the receptors in the intestine by dysentery toxins plays only a minor role in producing this disease.

SUMMARY

Reflexes obtained by perfusion of isolated intestinal loops with Shiga exotoxin and nicotine were used. Normal animals were tested first. Then, cats received large doses of Shiga dysenteric exotoxin subcutaneously and the isolated loop technique was followed within 4-6 hours in some animals; one, two and four days in others. Various concentrations of nicotine were used. Dysentery toxin was also placed on the mucosa of the loop as a definite maneuver.

The results were somewhat conflicting but there seemed to be an alteration of the reflexes in response to the stimuli. The time interval from the toxin injection is of great importance. Originally, there seems to be reenforcement of the reflexes; this being followed, later, by an inhibition.

The healthy animals were unaffected. These alterations are of such a nature that patients, already ill with dysentery, may have clinical manifestations analogous to those described here experimentally. It is doubtful if dysentery toxins play any role in the etiology of the disease.

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