EFFECT OF BACTERIAL ENDOTOXIN ON GASTRIC EVACUATION AND PASSIVE ABSORPTION OF SALICYLATE IN THE SMALL INTESTINE

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KEY WORDS: endotoxin; gastric evacuation; passive absorption; histamine; serotonin.

Bacterial endotoxins can pass through the intestinal barrier in various pathological processes of the intestine or under the influence of circulating vasoactive substances [1, 3, 5, 6, 11]. Meanwhile endotoxins themselves act on the absorptive power of the intestine by means of several mechanisms, including a change in the general and regional hemodynamics [7, 15], disturbance of enterocyte metabolism [4, 9], direct injury to the intestinal villi [12], etc. To assess the state of passive absorption in the intestine of animals various workers have used enteral administration of salicylate followed by determination of its blood level [2, 8, 12].

The aim of this investigation was to study the intensity of absorption of salicylate in experimental endotoxemia and to determine the effect of histamine and serotonin, factors regulating the permeability of biological membranes, on this process.

EXPERIMENTAL METHOD

Experiments were carried out on male albino mice weighing 18-22 g. The animals were deprived of food for 24 h before the experiment but were allowed water *ad lib*. During this period they were kept under conditions excluding the possibility of coprophagy. Endotoxin, obtained from *Shigella sonnei* cells at the I. I. Mechnikov Moscow Research-Institute of Vaccines and Sera by Westfall's method, was injected intraperitoneally in a dose of 2.5 mg/kg (0.67 LD_{50}). The dose of sodium salicylate injected was equivalent to 200 mg/kg of salicylic acid. Since the blood salicylate level after intragastric administration may depend not only on the absorptive power of the intestine, but also on the rate of evacuation on the gastric contents, the animals were divided into three groups (with 10 to 13 mice in each group). Blood was taken from the animals of groups 1 and 2 1 h (S-1) and 2 h (S-2) respectively after injection of the compound into the stomach, and blood from the animals of group 3 was taken 1 h after injection of salicylate into the small intestine (I-1). An aqueous solution of sodium salicylate in a volume of 0.2 ml was injected into the stomach through a tube, and into the initial part of the jejunum through an injection needle after midline laparotomy under superficial ether anesthesia. Blood was collected from the decapitated animals into test tubes containing heparin. The salicylate level in the blood plasma was determined by a colorimetric method [13]. In the process of selection of the dose of endotoxin, segments of intestine were subjected to morphological investigation and histological sections were stained with hemaotoxylin and eosin.

EXPERIMENTAL RESULTS

Distinct morphological changes in the intestinal wall were observed in the animals 2-6 h after intraperitoneal injection of endotoxin in a dose of 2.5 mg/kg: congestion of the blood vessels, edema of the submucosa, focal desquamation of the epithelium, and round-cell infiltration of the mucosa. After injection of endotoxin in doses of 1.25 and 0.6

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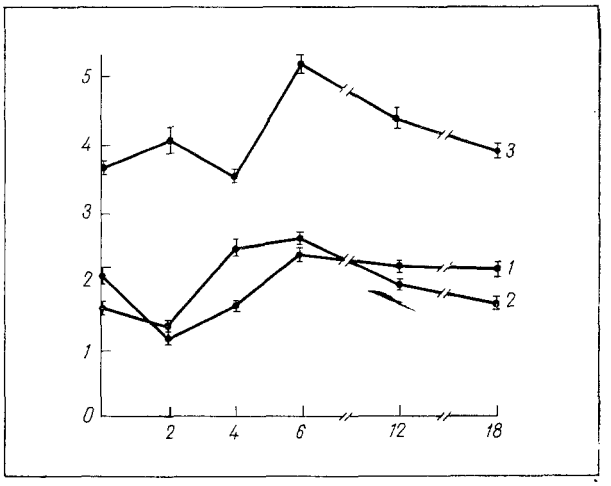

Fig. 1. Effect of endotoxin on blood plasma salicylate level 1 h (1) and 2 h (2) after injection of salicylate into stomach and 1 h after injection into small intestine (3). Abscissa, time after injection of endotoxin (in h); ordinate, here and in Figs. 2 and 3, blood plasma salicylate level (in M).

mg/kg the changes described above were less marked. These data provided the basis for the subsequent biochemical tests.

It was shown to begin with that the plasma salicylate concentration of healthy mice 1 and 2 h after injection of the compound into the stomach was 2.08 ± 0.17 and 1.63 ± 0.09 M respectively, and 1 h after injection into the small intestine it was 3.67 ± 0.22 M. The salicylate level was lowered in blood samples taken 2 h after the beginning of poisoning from the animals of group 1 (Fig. 1). Meanwhile the blood salicylate concentration in groups 2 and 3 showed no significant change at this time. The results are evidence that in the early stage of endotoxemia gastric evacuation is delayed. Similar results have been described by other workers [8, 10, 12, 14]. The blood salicylate level in the mice of group 1, determined 4 h after the beginning of poisoning, was a little higher than in the previous series, and in the mice of group 2 it actually exceeded the control level, evidence of the commencing normalization of gastric evacuation. Salicylate transport through the intestinal wall remained unchanged at this stage. A parallel rise of the blood salicylate level, after injection of the compounds both into the stomach and into the small intestine, was observed 6 h after injection of the endotoxin. Consequently, in the later stages of poisoning the permeability of the intestinal barrier was increased. This phenomenon was not found by the writers cited above, who used relatively small doses of endotoxin.

Normalization of the absorptive function of the intestine took place after poisoning lasting 12 and 18 h.

Since histamine and serotonin, on the one hand, are among the main mediators of the pathogenic action of endotoxins and, on the other hand, regulate the permeability of biological membranes, it was interesting to study their effect on the processes now being investigated. The first question to be answered is: do the biogenic amines affect the delay of gastric evacuation observed during poisoning for 2 h. It will be clear from Fig. 2 that injection of histamine into healthy and poisoned animals led to a dose-dependent fall in the blood salicylate level after intragastric administration. After injection of serotonin, however, only a small decrease was found in the blood salicylate concentration of healthy mice, and no change in this parameter in the experimental group. Parallel with this result, after injection of salicylate into the intestine, the biogenic amines caused no significant changes in passive absorption either in the control or in animals with endotoxemia (Fig. 3).

The effect of histamine on the blood level of salicylate given by intragastric injection was thus due to its action on gastric evacuation and not to its action on the absorptive function of the intestine. This conclusion is confirmed by the fact that H_1-receptor

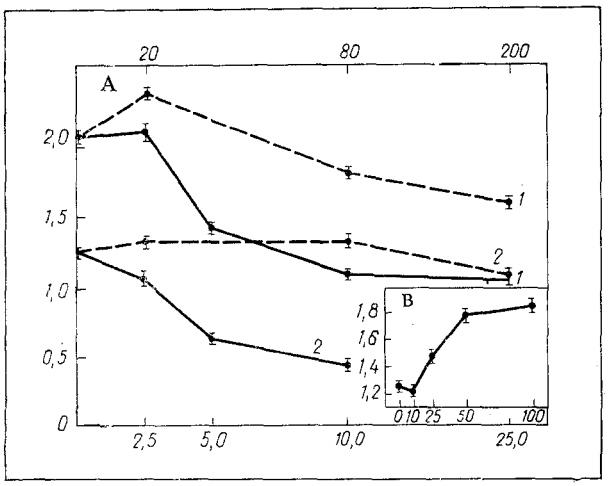

Fig. 2. Effect of biogenic amines (A) and of pyrilamine (B) on blood plasma salicylate level of healthy mice (1) and mice poisoned with endotoxin (2). Salicylate given by intragastric injection 2 h after endotoxin; biogenic amines injected intraperotoneally simultaneously with salicylate, pyrilamine injected intraperitoneally 30 min before salicylate. Blood samples taken 1 h after salicylate. Abscissa: below — histamine (continuous lines), above — serotonin (broken lines). Dose of pyrilamine in mg/kg.

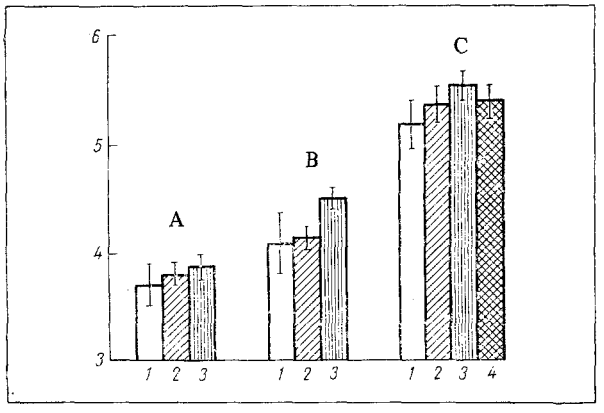

Fig. 3. Effect of histamine and serotonin on absorption of salicylate in small intestine. A) Healthy mice, B) endotoxin 2 h, C) endotoxin 6 h. Biogenic amines injected intraperitoneally simultaneously with salicylate, ciproheptadine 30 min before salicylate. Blood samples taken 1 h after injection of salicylate. Abscissa: 1) control (physiological saline), 2) histamine (10 mg/kg), 3) serotonin (200 mg/kg), 4) ciproheptadine (1.0 mg/kg).

blockage by pyrilamine almost completely prevented the disturbance of gastric evacuation caused by endotoxin (Fig. 2B).

An attempt was next made to study the effect of the mediators on increased absorption of salicylate found in the intestine after endotoxemia for a period of 6 h. At this stage also, the biogenic amines were found not to change the blood level of salicylate injected into the intestine (Fig. 3). Preliminary injection of ciproheptadine, which blocks histamine and serotonin receptors, into the animals likewise had no effect on absorption of salicylate.

The role of biogenic amines in the changes in permeability of the vessel wall in inflammatory and allergic conditions is well known. It has been reported that endotoxins can pass through the intestinal wall after intravenous injection of histamine and serotonin [3]. An essential role of biogenic amines in increasing the permeability of the intestinal barrier in endotoxemia cannot be postulated on the basis of the results of the present experiments. Meanwhile delay of gastric evacuation in the early stage of endotoxin poisoning could be largely prevented by administration of antihistamines.

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