EFFECT OF *Shigella sonnei* ENDOTOXIN ON THE CHOLINERGIC CONTROL OF THE INTESTINAL CIRCULATION

Yu. P. Galaguza

UDC 616.34-005-022.7(Shigella)

The effect of *Shigella sonnei* endotoxin on the cholinergic control of the cardiovascular system was studied by an extracorporeal autoperfusion method with resistography of the intestinal vessels and synchronous multichannel recording of the parameters of the systemic circulation in experiments on *Macaca rhesus*. The development of toxemia was shown to be accompanied by changes in the cholinergic regulation and subsequent disturbance of the intestinal and systemic circulation. It is suggested that damage to cholinergic regulatory structures and disturbance of the circulation determine the development and course of the infectious process.

KEY WORDS: *cardiovascular system; cholinergic regulation; endotoxin of* Shigella sonnei.

The extensive clinical and pathomorphological material that has accumulated during the study of the pathogenesis of dysentery demonstrates the important role of the vascular component in the development of this disease [4, 5, 9]. However, the mechanisms of development of the infectious process have not yet received adequate study. Nevertheless, their study is assuming particular importance at the present time in connection with the need for developing a pathogenetic therapy of the infectious enterocolites. The most promising line of attack from this point of view, according to data in the literature [6, 10, 11], is to investigate the mechanisms of disturbance of the cardiovascular system in dysentery toxemia, for in this way it is possible to study the concrete ways by which bacterial endotoxins exert their effects on man.

It has been shown [1, 2, 6, 8, 10] that the development of the infectious process is accompanied by a marked disturbance of nervous regulatory mechanisms; it was accordingly decided to carry out investigations in this direction.

The object of this investigation was to study the mechanisms of disturbance of the circulation in the small and large intentines during dysentery toxemia in experiments on monkeys (*Macaca rhesus*).

EXPERIMENTAL METHOD

Experiments were carried out under superficial anesthesia with morphine and chloralose (2.5 and 35–100 mg/kg, respectively) anesthesia, ensuring a good anesthetic effect while leaving intact the mechanisms controlling the regional circulation.

Dysentery toxemia was produced by intravenous injection of breakdown products or complete antigen of *Shigella sonnei* cells at the rate of 20 lethal doses for newborn mice per kilogram body weight.

The state of the cholinergic regulatory system was assessed from responses of the blood vessels of the small and large intestines to acetylcholine and the character of the effector structure of changes in the systemic circulation in these reactions. Cholinergic reactions of the intestinal vessels were evoked by injection of 5 μg acetylcholine into the perfused

Laboratory of Pathophysiology, Kiev Scientific-Research Institute of Infectious Diseases.
(Presented by Academician of the Academy of Medical Sciences of the USSR, N. N. Sirotinin.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 83, No. 3, pp. 271–272, March, 1977. Original article submitted May 19, 1976.

intestinal blood vessels. Extracorporeal autoperfusion and resistography of the vessels of the small and large intestines were carried out, with simultaneous synchronous recording of the resistance of the intestinal vessels, the arterial and central venous pressures, the heart rate, and the rate and depth of respiration; in this way the character of the circulatory changes in the small and large intestines could be assessed in the course of dysentery toxemia.

EXPERIMENTAL RESULTS

In the control experiments, injection of acetylcholine into the perfused intestinal vessels of the monkeys caused a decrease in the resistance of these vessels by 10.8 ± 4.3 mm Hg in 9 of 12 experiments ($P < 0.01$), and in 3 experiments the resistance was increased by 17 ± 5.7 mm Hg ($P > 0.1$). The arterial pressure was lowered by 16 ± 6.2 mm Hg in 7 experiments ($P < 0.05$), in 3 it was raised by 13 ± 2.0 mm Hg ($P > 0.05$), and in 2 it was unchanged. In 5 experiments the heart rate was increased by 14 ± 5 beats/min ($P < 0.05$), and in 4 it was reduced by 38 ± 11.8 beats/min ($P > 0.05$). In 4 experiments acetylcholine caused no change in the heart rate. Changes in the central venous pressure were not significant and usually consisted of its elevation by 11 ± 12 mm water ($P > 0.1$). Respiration, recorded by means of a detector of the frequency and depth of respiration designed by the writer, was increased by 4 ± 3/min in 5 of the experiments ($P > 0.1$), in 5 it was reduced by 3 ± 3/min ($P > 0.1$), and in 2 experiments it was unchanged. The latent period of these reactions averaged 5.7 sec and their duration 2 min.

The development of toxemia was accompanied by a decrease in the resistance of the intestinal vessels and a fall of the blood pressure with marked changes in the effector structure of the cholinergic responses of the cardiovascular system; in one case this led to the development of severe cardiovascular failure and to death of the animal. In the other experiments, 10-15 min after the injection of the *Sh. sonnei* endotoxin, acetylcholine caused a decrease in the resistance of the vessels of the small and large intestines by 8.8 ± 2.9 mm Hg in 6 of the 11 experiments ($P < 0.05$). Poisoning thus had an inhibitory effect on the cholinergic responses of the intestinal vessels, which was also expressed as weakening of their pressor responses to acetylcholine to 6.3 ± 2.1 mm Hg ($P > 0.1$). In one experiment this response of the intestinal vessels disappeared during toxemia and was replaced by a decrease in the resistance of the intestinal vessels. In three experiments, the depressor responses were completely blocked, and only in one were they strengthened a little (by 4 mm Hg). A fall of 10.2 ± 2.9 mm Hg in the arterial pressure was found in 3 experiments ($P > 0.1$), an increase of 7 ± 3.1 mm Hg in 4 experiments ($P > 0.05$), and no change in 4 experiments. In one experiment the control pressor response to acetylcholine was replaced by a weak depressor response; and in another experiment, on the other hand, a marked depressor response was replaced by a small increase in the resistance of the intestinal vessels. In 2 experiments the depressor responses were completely blocked. It is interesting to note that in the same experiments the toxemia caused complete inhibition of the responses of the intestinal vessels also. The central venous pressure was raised by 3.2 ± 1 mm water ($P < 0.1$) in 5 of the 11 experiments, it fell but not significantly in 1, and in 5 experiments it remained unchanged. The heart rate in 6 experiments was reduced by 24.3 ± 8 ($P < 0.05$) beats/min and in 5 experiments it was unchanged. The general rule could be noted that the negative chronotropic effect of acetylcholine on the heart was depressed in experiments in which it was considerable, and it was manifested *de novo* in those experiments in which no such effect could be recorded in control investigations or there was a positive chronotropic effect on the heart. Under the conditions studied changes in respiration were negligible. The latent period of the responses of the cardiovascular system to acetylcholine was unchanged during toxemia, but in most cases (7 experiments) their duration was reduced to 1 min.

The results confirmed the view [6-8] that disturbances of the intestinal and systemic circulation may play an important pathogenetic role in the development of the infectious process in dysentery. Analysis of the changes in the intestinal and systemic circulation during dysentery toxemia shows that the changes in resistance of the intestinal vessels in cholinergic responses are not due to changes in the systemic circulation, for most frequently they did not correspond in magnitude and direction. It can rather be supposed that their effector structure is due to reflex influences from the receptive field of the intestine on the cardiovascular system and its regulatory apparatus.

Investigations by Ado [1-3] have shown that the endotoxin may have a reflex action on the cardiovascular system.

One possible pathway for the pathogenic action of the agents of infectious diseases of the intestine may thus be the toxic action of their products on the neurohumoral regulatory systems, caused by the penetration of bacterial toxins into the blood, as a result of which the cardiovascular system and the gastrointestinal tract, with their complex functional interrelations, are involved in the pathogenetic process; this leads to the development of an infectious disease and determines its course and outcome.

LITERATURE CITED

1. A. D. Ado, Antigens as Extraordinary Stimuli of the Nervous System [in Russian], Moscow (1952).
2. A. D. Ado (editor), On Mechanisms of Action of Microbes on the Nervous System [in Russian], Moscow (1957).
3. A. D. Ado, Usp. Sevrem. Biol., 55, No. 2, 239 (1963).
4. S. O. Badyl'kes and M. S. Stol'tser, Ter. Arkh., No. 3, 275 (1941).
5. V. A. Barbinov, Klin. Med., No. 5, 99 (1965).
6. A. F. Bilibin, Sov. Med., No. 3, 3 (1952).
7. Yu. P. Galaguza, in: Intestinal Infections [in Russian], No. 7, Kiev (1974), pp. 51-54.
8. N. N. Sirotinin, Abstracts of Proceedings of a Conference on Dysentery [in Russian], Kiev (1952), pp. 1-3.
9. A. V. Tsinzerling, Trudy Leningrad. Nauch. Obshch. Patologoanat., 13, 111 (1972).
10. P. S. Chulkov, Trudy Voenno-Med. Akad., 4, 279 (1935).
11. G. Kroneberg, Zbl. Bakt., 1 Abt., 158, 8326 (1952).

RHYTHM OF STRUCTURAL AND FUNCTIONAL CHANGES IN HEPATOCYTES AFTER EXPOSURE TO PESTICIDES

T. A. Popov and T. D. Zadorozhnaya

UDC 612.35.014.46:632.95

The biological transformation of Dursban was investigated during perfusion of the livers of rats exposed for 4, 8, and 15 days to poisoning by CCl_4 and Milbex (an inhibitor and inducer, respectively, of microsomal enzymes). The ultrastructure of the hepatocytes was studied in rats poisoned with these substances. Three stages of structural and functional changes were identified. After the eighth day, the pathways of transformation of Dursban were reorganized: dealkylation processes, leading to the formation of less toxic metabolites, were intensified.

KEY WORDS: *perfusion of the liver; microsomal oxidases of mixed function; pesticides; Dursban — biological transformation.*

The body can adapt itself to some extent to the action of harmful factors that differ in strength. Adaptive structural and functional changes reflects both the intensity and the rhythm of action of the pathogenic factor [9-11]. Sarkisov et al. [8] distinguished four types of structural and functional responses aimed at securing homeostasis. The first three responses they regard as nonspecific, while the fourth is to some extent specific for it is aimed "against" a particular toxic factor. According to the same [8] and other workers [1, 7], and also the present writers' observations [4], during daily exposure to poisons the structural and functional changes in the hepatocytes are more clearly expressed during the

Laboratory of General Toxicology, All-Union Scientific-Research Institute of Hygiene and Toxicology of Pesticides, Polymers, and Plastics, Kiev. Laboratory of Pathophysiology and Experimental Therapy, Kiev Scientific-Research Institute of Pediatrics, Obstetrics, and Gynecology. (Presented by Academician of the Academy of Medical Sciences of the USSR L. I. Medved'.)

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 83, No. 3, pp. 273-275, March, 1977. Original article submitted July 27, 1976.