THE EFFECT OF SEROTONIN (5-HYDROXYTRYPTAMINE) AND 5-HYDROXY-TRYPTOPHANE ON THE MORTALITY OF ANIMALS WITH EXPERIMENTAL PNEUMOCOCCAL INFECTION AND TYPHOID TOXEMIA

Z. A. Popenenkova and T. N. Zavenyagina

Division of Infectious Pathology and Experimental Therapy of Infections
(Head, Corresponding Member AMN SSSR Professor Kh. Kh. Planel'es),
N. F. Gamaleya Institute of Epidemiology and Microbiology
(Director, Corresponding Member AMN SSSR Professor O. V. Baroyan) of the AMN SSSR, Moscow
(Presented by Active Member AMN SSSR L. A. Zil'ber)
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We showed in our previous researches that serotonin undergoes essential quantitative changes in the blood and organs of animals with typhoid toxemia [2] and experimental pneumococcal infection [3].

Shimamoto and his co-workers [24, 25] suggest that endogenous serotonin, at the time of its release from the platelets, increases the toxicity of dysentery endotoxin. Observations by several writers [9, 11, 12, 13, 22] indirectly support the view that serotonin plays a part in the pathogenesis of endotoxin shock. Gordon and Linton [12] observed that serotonin and substance F were therapeutically effective in shock in mice caused by endotoxin from Escherichia coli. E. Ch. Pukhal'skaya and co-workers [4, 5] showed that endogenous and exogenous serotonin inhibit the growth of a transplantable tumor. 5-Hydroxytryptophane, the precursor of serotonin, which increases the concentration of the latter in the body [7, 8, 21], and serotonin itself possess a protective action against irradiation [1, 6, 16-18]. Meanwhile it has also been reported [10, 15, 20] that serotonin increases the susceptibility of mice to Haemophilus pentussis.

In view of the foregoing facts it was deemed interesting to study the effect of serotonin and 5-hydroxytryptophane on the course and outcome of bacterial infection and toxemia.

EXPERIMENTAL METHOD

Pneumococcal infection. Investigations were conducted on 120 male rats weighing 150-200 g, divided into 4 equal groups. The animals of all 4 groups were inoculated intradermally with 0.2 ml of an 18-hour culture of Pneumococcus type I, diluted 1:100, in the middle of the right side. The rats of the first group were treated with 5-hydroxytryptophane, the rats of the third group with serotonin, and the second and fourth groups acted as controls. Serotonin and 5-hydroxytryptophane were injected intramuscularly the former in a dose of 0.5 mg/kg body weight 3 times a day for 5 days, the latter in a dose of 20 mg/kg body weight once a day for 3 days. The first injection of the preparations was given 24 hours before inoculation of the pneumococci, and the second injection of 5-hydroxytryptophane and the fourth injection of serotonin were given simultaneously with inoculation of the pneumococci.

Typhoid toxemia. Investigations were conducted on 40 male rabbits weighing 2.5-3 kg, divided into 4 equal groups. The rabbits of all 4 groups received an intravenous injection of heat-killed typhoid vaccine from a laboratory strain of Eberthella typhosa 495 in a dose of 20×10^9 bacterial cells/kg body weight. The rabbits of the first group were treated with 5-hydroxytryptophane, the rabbits of the third group with serotonin, and the second and fourth groups acted as controls. Serotonin and 5-hydroxytryptophane were given to the rabbits in the same doses and in the same order as to the rats.

In vitro experiments. Tryptophane and 5-hydroxytryptophane were used in a dose of 530 μg/ml, and serotonin in a dose of 10μg/ml of nutrient medium. A volume of 0.1 ml of an 18-hour culture of Pneumococcus type I was seeded in 3 ml nutrient medium. The control medium contained only one of the three preparations or none of them and were inoculated with pneumococci. The 5-hydroxytryptophane used in the investigation was manufactured at the Ordzhonikidze All-Union Chemo-Pharmaceutical Institute, serotonin–creatine sulfate was obtained from the firm of L. Light and Co., Ltd. (England), and L-tryptophane from the British Drug Houses, Ltd. (England).

TABLE 1. The Effect of 5-Hydroxytryptophane and Serotonin on the Mortality of Rats with Experimental Pneumococcal Infection

Group	Compound	Mortality at different periods (days)								Survival rate
		2nd	3rd	4th	5th	6th	7th	9th	10th	
First	5-Hydroxytryptophane	4/30 (13.3%)	4/30(13.3%)	3/30 (10%)	1/30 (3.3%)	–	1/30 (3.3%)	–	–	17/30 (56.7%)
Second	–	10/30 (33.3%)	7/30 (23.3%)	3/30(10%)	2/30 (6.7%)	1/30 (3.3%)	–	–	–	7/30 (23.3%)
Third	5-Serotonin	4/30 (13.3%)	7/30 (23.3%)	3/30 (10%)	–	–	–	–	–	16/30 (53.3%)
Fourth	–	13/30 (43.3%)	5/50 (16.7%)	3/30 (10%)	–	–	–	1/30 (3.3%)	1/30 (3.3%)	7/30 (23.3%)

Note. The numerator gives the number of animals dying (or surviving); the denominator gives the total number of animals in the experiment; the figure in parentheses is the mortality (or survival) rate in per cent.

TABLE 2. The Effect of 5-Hydroxytryptophane and Serotonin on the Mortality of Rabbits with Typhoid Toxemia

Group	Compound	Mortality at different periods (hours)				
		0-$1\frac{1}{2}$	$1\frac{1}{2}$-3	3-6	6-11	at the end of the first day
First	5-Hydroxytryptophane	–	1/10 (10%)	5/10 (50%)	3/10 (30%)	1/10 (10%)
Second	–	–	–	1/10 (10%)	4/10 (40%)	5/10 (50%)
Third	5-Serotonin	4/10 (40%)	–	2/10 (20%)	4/10 (40%)	–
Fourth	–	–	–	3/10 (30%)	4/10 (40%)	3/10 (30%)

Legend as in Table 1.

EXPERIMENTAL RESULTS

It follows from Table 1 that 5-hydroxytryptophane and serotonin lowered the mortality of the animals from pneumococcal infection, 26.6% of the animals in the first group and 36.6% of those in the third group died, whereas the corresponding figures for the second and fourth (control) groups were 56.6 and 60%. More than twice as many animals treated with 5-hydroxytryptophane and serotonin as untreated animals survived. Observations on the development of the local inflammatory reaction showed that in the first 24 hours 5-hydroxytryptophane slightly stimulated, and serotonin inhibited the development of the inflammatory process around the site of injection of the pneumococci. After 48 hours the local inflammatory reaction in the majority of the animals treated with 5-hydroxytryptophane remained unchanged, and in some rats it actually showed signs of regression, whereas in the control animals it was intensified. In most animals receiving serotonin, the further development of the local inflammation followed the same course as in the animals of the control group, in which it was more intensive.

Since 5-hydroxytryptophane and serotonin had an obviously favorable effect on the course and outcome of pneumococcal infection in the rats, it was essential to discover whether this benefician action of serotonin and its precursor was associated with their antibacterial properties against the pneumococcus. It is reported in the literature [23] that L-tryptophane, the precursor of 5-hydroxytryptophane and serotonin, has a bactericidal and bacteriostatic action of Mycobacterium tuberculosis [14]. Accordingly, experiments were carried out to study the action of L-tryptophane 5-hydroxytryptophane, and serotonin on the proliferation of a pneumococcal culture in vitro. None of these preparations, in the dose used in the animal experiments, had an inhibitory action on the development of Pneumococcus type I in vitro. Three hours after incubation at 37° the growth of the pneumococcus was identical in the experimental tubes with that in the medium not containing the preparation.

It is clear from Table 2 that the treatment of rabbits with 5-hydroxytryptophane and serotonin had an adverse action and hastened death of the animals from typhoid toxemia. During the first 1½ hours after injection of the typhoid vaccine, 40% of the animals in the third group died, whereas all the rabbits in the fourth group were alive. After the first 6 hours, 6 times as many animals in the first group as in the second, and twice as many animals in the third as in the fourth group had died from typhoid toxemia. After 11 hours 90% of animals in the first group and 100% of those in the third group had died, compared with 50% and 70% of animals in the control groups.

Hence exogenous serotonin and 5-hydroxytryptophane, by increasing the serotonin level in the organs, had a favorable effect on the course and outcome of experimental pneumococcal infection in rats, more than halving the mortality among the infected animals. This effect of these compounds was evidently associated with their action on the host and not on the agent responsible for the infection. It may be assumed that the mechanism of this action is complex, for serotonin has a stimulating action on the hypothalamo-hypophyseo-adrenal axis [19], which is of major importance in the pathogenesis of infection. The difference between the effect of serotonin and 5-hydroxytryptophane on the local inflammatory reaction may be explained by the difference in the time of the concentrations of serotonin in the blood and tissues created when the compounds were injected by their particular method.

The administration of serotonin led to an increased serotonin concentration in the blood and to spasm of the vessels, which could inhibit the development of the inflammatory reaction during the first 24 hours. Administration of 5-hydroxytryptophane raised the serotonin level in the skin and the central nervous system, and this could facilitate the development of the local inflammatory reaction.

The adverse effect of serotonin on the mortality among the animals with typhoid toxemia was possible associated with the increased susceptibility of the animals to typhoid endotoxin as a result of the action of serotonin, which is in agreement with the results of Shimamoto and co-workers, obtained with dysentery endotoxin [24, 25].

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
