

# EFFECT OF VETRAZINE, CHLORACIZINE, AND CHLORPROMAZINE ON HISTAMINE AND SEROTONIN CONTENT IN ORGANS OF RABBITS WITH *Bacterium prodigiosum* BACTERIEMIA

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Bacteriemia due to *Bacterium prodigiosum* itself had no significant effect on the histamine and serotonin concentrations in the organs and blood of rabbits. However, when rabbits infected with *B. prodigiosum* were treated with vetrazine, chloracizine, and chlorpromazine, much more severe disturbance of the histamine and serotonin content in the tissues was found than when uninfected animals were given the same doses of these compounds. Under the influence of these drugs the serotonin/histamine ratio for the blood and organs as a rule was lowered both in healthy rabbits and in rabbits infected with *B. prodigiosum*.

Like iproniazid and indopan [5, 7, 8], vetrazine, chloracizine, and chlorpromazine [6, 11] accelerated and intensified the lethal effect of pneumococcal infection and of the bacteriemia produced by *Bacterium prodigiosum*. One possible cause of this effect could be aggravation of the imbalance between histamine, serotonin, and the catecholamines under the influence of these substances.

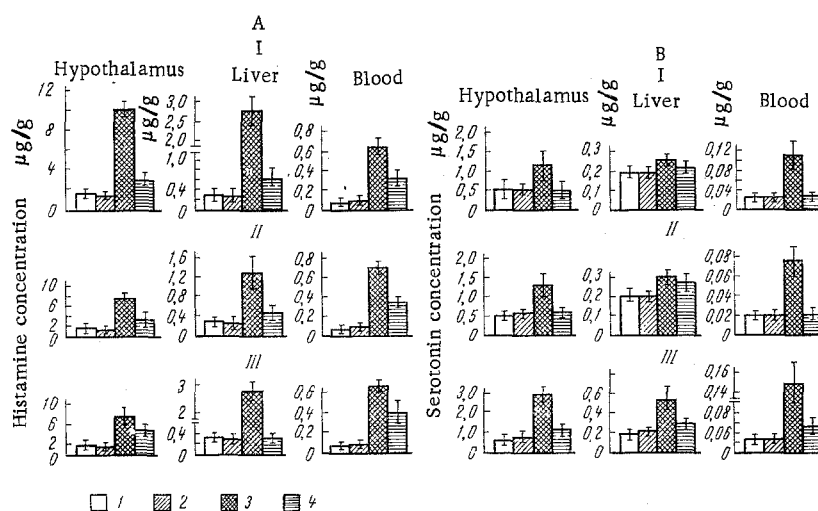


Fig. 1. Effect of vetrazine (I), chloracizine (II), and chlorpromazine (III) on changes in histamine (A) and serotonin (B) concentrations in blood and organs of normal rabbits (1) and rabbits 18 h after injection of *B. prodigiosum* (2), *B. prodigiosum* together with the compound (3), and the compound alone (4). Vertical lines show confidence limits.

Department of Infectious Pathology and Experimental Therapy of Infections, N. F. Gamaleya Institute of Epidemiology and Microbiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR Kh. Kh. Planel'es.) Translated from *Byulleten' Éksperimental'noi Biologii i Meditsiny*, Vol. 71, No. 5, pp. 51-54, May, 1970. Original article submitted October 2, 1969.

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It was therefore decided to examine whether the nonpathogenic micro-organism Bacterium prodigiosum, like the pneumococcus, can cause changes in the serotonin and histamine content in the tissues and whether the balance between these amines can be disturbed by the action of vetrazine, chloracizine, and chlorpromazine, in rabbits infected by this microorganism.

#### EXPERIMENTAL METHOD

The choice of B. prodigiosum from other species of nonpathogenic micro-organisms was determined by the ability of this microorganism to form a bright red pigment, so that the number of its colonies can easily be counted in Petri dishes after seedings are taken from the organs and blood of animals, and in the case of possible contamination from the air, B. prodigiosum can be differentiated.

The investigations were carried out on 96 male rabbits weighing 2.5-3 kg, divided into 8 equal groups: group 1 consisted of intact animals, group 2 of animals infected with B. prodigiosum, groups 3-5 consisted of animals receiving one of the test compounds, and group 6-8 of animals infected with B. prodigiosum and treated with one of the compounds.

Vetrazine (3, 4-dimethoxybenzylhydrazine) [2], in a dose of 50 mg/kg, and chlorpromazine in a dose of 20 mg/kg were given intramuscularly. Chloracizine (10- $\beta$ -diethylaminopropionyl-2-chlorophenothiazine hydrochloride) [13], in a dose of 60 mg/kg, was injected intraperitoneally. The rabbits received the compound in a single dose. Vetrazine was injected 10 min before, chlorpromazine 30 min before, and chloracizine 2 h before injection of the bacteria. B. prodigiosum (laboratory strain No. 1266) was injected intravenously in a dose of 5 billion bacterial cells. The content of histamine and serotonin in the blood, hypothalamus, and liver of the rabbits was determined 18 h after infection. The animals of the control group were killed by air embolism simultaneously with the experimental rabbits. Histamine [14] and serotonin [3] were determined by fluorometric methods. The fluorescence of histamine and serotonin was measured with a redesigned ISP-53 apparatus with FEP-1 attachment. Histamine dichloride (British Drug House Ltd.) and serotonin-creatinine sulfate (Reanal) were used as the standards. The numerical results were subjected to statistical analysis [1, 4].

#### EXPERIMENTAL RESULTS

In the intact animals the histamine concentration in the hypothalamus was  $1.7 \pm 0.36 \mu\text{g/g}$ , in the liver  $0.28 \pm 0.028 \mu\text{g/g}$ , and in the blood  $0.05 \pm 0.006 \mu\text{g/ml}$ , while the serotonin concentrations were  $0.5 \pm 0.021$ ,  $0.19 \pm 0.014 \mu\text{g/g}$  and  $0.022 \pm 0.001 \mu\text{g/ml}$ , respectively.

Unlike pneumococcal infection, which substantially modified the histamine [10] and serotonin [9] concentrations in the body, the bacteremia due to B. prodigiosum, which is nonpathogenic to rabbits, had no effect on the serotonin level in the blood and organs, and increased the histamine concentration (by 1.5 times) only in the blood of the animals.

Vetrazine and chloracizine had approximately the same action on the histamine level, increasing it by 6.6 times in the blood and by 1.5-2.2 times in the hypothalamus and liver of the uninfected rabbits. Under the influence of chlorpromazine the histamine concentration in the blood of the uninfected animals was increased by 8 times, in the hypothalamus by 2.5 times, while in the liver it was unchanged. Vetrazine and chloracizine had no significant effect on the serotonin concentrations in the tissues investigated, while chlorpromazine doubled the serotonin concentrations in the blood and hypothalamus, and increased it by 1.4 times in the liver (Fig. 1).

TABLE 1. Changes in Serotonin/Histamine Ratio as a Result of Various Procedures

Organ	Normal	Treatment with				
		B. prodigiosum	vetrazine	vetrazine + B. prodigiosum	chloracizine + B. prodigiosum	chlorpromazine + B. prodigiosum
Hypothalamus . . . . .	$0.34 \pm 0.067$ $0.68 \pm 0.075$	$0.34 \pm 0.041$ $0.85 \pm 0.081$	$0.18 \pm 0.0065$ $0.4 \pm 0.055$	$0.15 \pm 0.01$ $0.1 \pm 0.011$	$0.16 \pm 0.017$ $0.22 \pm 0.034$	$0.41 \pm 0.0043$ $0.19 \pm 0.0196$
Liver . . . . .						
Blood . . . . .	$0.4 \pm 0.043$	$0.24 \pm 0.033$	$0.078 \pm 0.0095$	$0.18 \pm 0.02$	$0.11 \pm 0.01$	$0.23 \pm 0.028$

In rabbits infected with B. prodigiosum and treated with vetrazine, the histamine level in the hypothalamus was 3.3 times higher, in the liver 4.3 times higher, and in the blood 2.0 times higher than the histamine level in the corresponding organs of the uninfected animals receiving the compound. Despite the fact that vetrazine and B. prodigiosum themselves had no significant effect on the serotonin concentration in the animals, under the influence of the compound on the infected rabbits, the serotonin concentration was found to be increased by 3 times in the hypothalamus, 1.4 times in the liver, and 5 times in the blood compared with the corresponding normal values (Fig. 1).

Injection of chloracizine into the infected animals led to an increase of 2.2 times in the histamine concentration in the hypothalamus, of 3.0 times in the liver, and 2.1 times in the blood compared with the corresponding values in uninfected rabbits receiving chloracizine.

The serotonin concentration in the hypothalamus of these animals was 2.24 times higher, and in the blood 3.25 times higher than in uninfected rabbits receiving chloracizine.

After administration of chlorpromazine the histamine concentration in the hypothalamus of the rabbits infected with B. prodigiosum was 1.7 times higher, in the liver 11 times higher, and in the blood 1.6 times higher than the corresponding values in uninfected animals receiving this compound.

The serotonin concentration in rabbits infected with B. prodigiosum and receiving chlorpromazine was 2.72 times higher in the hypothalamus, 1.9 times higher in the liver, and 3.26 times higher in the blood than the corresponding values in animals receiving chlorpromazine alone.

Because of the unequal increases in the concentrations of the biogenic amines through the action of the compounds on rabbits uninfected and infected with B. prodigiosum, the normal ratio between the serotonin and histamine concentrations in the blood and certain organs was disturbed. In most cases the serotonin/histamine ratio was lowered by several times compared with its value in intact rabbits, mainly because of a larger increase in the histamine concentrations than in the serotonin concentration (Table 1).

Unlike the pneumococcus, B. prodigiosum thus has no significant effect on the histamine and serotonin concentrations in rabbits. However, in bacteriemia due to B. prodigiosum, much greater disturbances of the histamine and serotonin concentrations in the body are produced by the action of vetrazine, chloracizine, and chlorpromazine than by the action of the same doses of these compounds on uninfected animals.

The accumulation of biogenic amines most probably takes place on account of inhibition of monoamine oxidase and of stimulation of the synthesis of the amines, for the results show that these compounds potentiated the accumulation of histamine and serotonin in the tissues of rats with pneumococcal infection [12], but under these conditions they depressed the excretion of 5-hydroxyindolylacetic acid equally in healthy rats and rats infected with pneumococci.

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