CHANGE IN THE SEROTONIN CONTENT OF THE BLOOD OF RABBITS FOLLOWING TYPHOID INTOXICATION

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Researchers have recently shown increasing interest in the study of the physiological and pharmacological properties of the very active biogenous compound serotonin (5-hydroxytryptamine, 5-HTA), as well as in explanation of its role in various pathologic conditions [3, 19, 31, 35]. M. O. Raushenbakh and G. A. Chernov [2], for example, believe 5-HTA to be very important in the pathogenesis of acute radiation sickness; 5-HTA possesses a histamine-like effect and is evidently one of the phlogogenic substances which play a large part in the pathogenesis of infectious diseases. Shimamoto and co-workers [41,42] believe 5-HTA to be a toxicity factor in dysenteric intoxication. These [40, 41, 42] and other [16, 25] authors have established that bacterial endotoxins cause the liberation of 5-HTA from thrombocytes. The lethality of the dysenteric endotoxin has been reduced by the preliminary administration of 5-HTA antagonists [40] or reserpine [44] to animals. The administration of 5-HTA to mice increases their sensitivity to the causative agent of whooping cough [24, 28, 33]. Erspamer [20], however, believes that 5-HTA is a histogenous hormone which is active at its formation site, and considers the proposal that surplus 5-HTA plays a part in the genesis of various diseases to be poorly substantiated.

We therefore decided to determine how the serotonin content of the blood and of organs with a fairly high 5-HTA content changes during the development of bacterial intoxication.

The work was carried out on 42 male rabbits weighing 2.5-3 kg each. The animals were intravenously injected with heat-killed typhoid vaccine, prepared from the laboratory strain No. 495 of E. typhosa, in a dose of 30 billion microbes per 1 kg body weight. Determination of 5-HTA in the blood was carried out before the vaccine was administered, and then 5-HTA was determined in the blood and organs 15 and 30 min, 1, 3, 5, 12 and 24 hr after the administration of the vaccine. Two or three ml of blood was taken from the marginal vein of the rabbit's ear or from the heart; the rabbits were then exsanguinated by transecting the neck vessel under the light ether anesthesia, after which the brain, lungs, the last 50 cm of the small intestine and a 5 × 5 cm skin flap from the middle of the right side were immediately removed from the animals. As the control, we used the same organs, taken from rabbits which had not received the vaccine. Homogenates of the experimental organs were prepared. The serotonin content per 1 g each organ's homogenate and per 1.5 ml blood was determined. We used 0.1 ml of a 3.8% sodium citrate solution per 1 ml blood to prevent clotting. The method of Udenfriend and co-workers [46] was used to extract 5-HTA from the blood and organs. Quantitative determination of 5-HTA was done by the biological method, using a rat's isolated colon [15]. Gaddum's fluid was used to nourish the isolated colon and to dilute the serotonin extracts. We used the Flyuk Company's (Italy) creatinine sulfate 5-HTA as the standard.

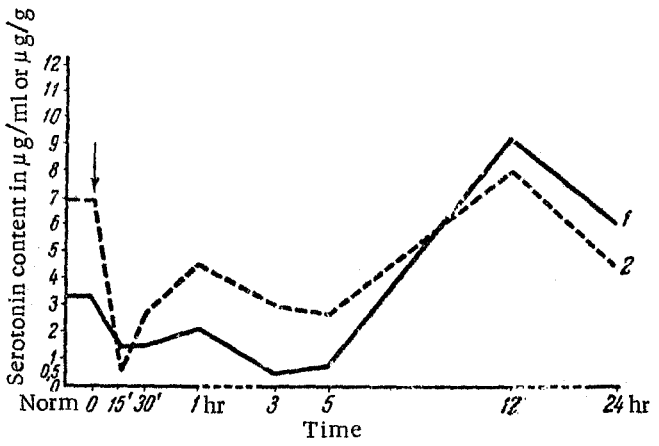

Fig. 1. Change in serotonin content of rabbits' blood and lungs following typhoid intoxication. 1) Blood; 2) lungs; ↓) administration of typhoid vaccine.

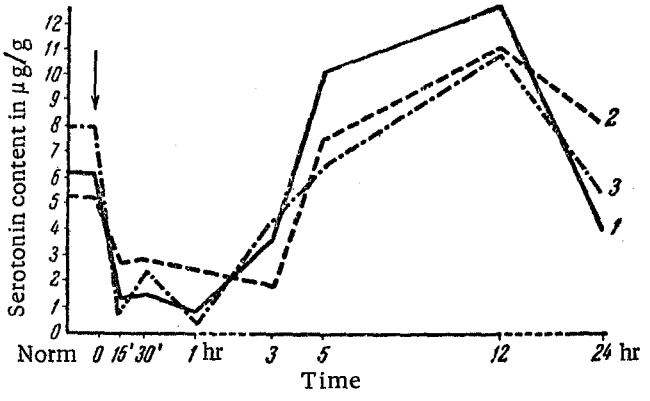

Fig. 2. Change in serotonin content of brain, small intestine and skin of rabbits following typhoid intoxication. 1) Brain; 2) small intestine; 3) skin; ↓) administration of typhoid vaccine.

The average data of the results obtained are shown in Figs. 1 and 2. Figure 1 shows that the 5-HTA content of the blood undergoes phasic changes. A sharp decrease in the 5-HTA content of the rabbit's blood was observed 15 min after the administration of the typhoid vaccine. The 5-HTA content decreased to 2.3 times less than the original level (from 3.28 ± 0.47 μg/ml to 1.44 ± 0.24 μg/ml). The content of 5-HTA in the blood remained below the original level for a long time. Three to five hr after the typhoid vaccine was administered, the 5-HTA content was 1/8 – 1/5 the original. Twelve hours after the vaccine injection, when the animals' condition had considerably deteriorated and severe diarrhea had developed, the 5-HTA content of the blood increased sharply, to thrice the original level. After 24 hr the 5-HTA content began to decrease, but its level during this period was still twice as high as the original. The animals' death prevented further determination of the 5-HTA content of the blood at later periods.

The changes observed in the serotonin content of the lungs, brain, small intestine and skin were also phasic in nature. The curve showing the 5-HTA content of the lungs repeated the curve of the 5-HTA content of the blood (see Fig. 1). Figure 2 shows the data characterizing the changes in the 5-HTA content of the brain, small intestine and skin. Fifteen minutes after the vaccine injection, a sharp decrease in the serotonin content of these organs was observed. For example, the average 5-HTA content of the small intestine decreased to $\frac{1}{2}$ the original level, while in the brain and skin, the average 5-HTA content decreased to, respectively, $\frac{1}{4}$ and $\frac{1}{8}$ the original levels. The 5-HTA content continued to be rather low for an hour in the skin and brain and for three hr in the small intestine.

If the curves showing the 5-HTA content of the brain, skin and small intestine are compared with the curve of its content in the blood, it is evident that the 5-HTA of the organs undergoes the same changes during the initial period of the intoxication as the 5-HTA of the blood. The subsequent increase in 5-HTA content begins considerably earlier in the case of the organs than in that of the blood. Five hr after the administration of the typhoid vaccine, when the 5-HTA content of the blood was still very low, the 5-HTA content of the rabbits' brain and small intestine was higher than in the same organs of the control rabbits. Twelve hr after the typhoid vaccine injection, these organs contained twice as much 5-HTA as the corresponding organs of the control rabbits. In the experimental rabbits during this period, the 5-HTA content of the skin was also higher than the amount found in the skin of the control animals. After 24 hr , the 5-HTA content of the experimental organs decreased. The 5-HTA decrease was especially sharp in the brain, skin and lungs; in these organs, its content became considerably lower than in the corresponding organs of the control rabbits. In the intestine, the 5-HTA content remained fairly high, exceeding the control level. During this period, the condition of the rabbits was very serious. Adynamia, diarrhea and lack of reaction to extraneous stimuli were observed in the animals.

As a result of the observations conducted, several reasons have been established for the phasic nature of the changes in the 5-HTA of the blood following typhoid intoxication. During the first hr of typhoid intoxication, the change in the 5-HTA content of the blood can be related to change in the number of thrombocytes; subsequently, no direct relationship between these indices is observed. M. O. Raushenbakh and G. A. Chernov were also unable to observe a constant relationship between the 5-HTA content of the blood and the number of thrombocytes in different animals with acute radiation sickness [2]. The most important reasons seem to be the liberation of 5-HTA from the thrombocytes effected by the typhoid endotoxin and change in the adsorptive properties of the thrombocytes. There are reports in the literature that bacterial endotoxins prepared from Shigella sonnei [40, 41] and Clostridium Welchii [25] cause the liberation of 5-HTA from the thrombocytes. It is well known that 5-HTA is not synthesized in thrombocytes, but enters these cells by adsorption [11, 52] and that the influence of unfavorable factors causes the adsorptive ability of thrombocytes to decrease [2, 11, 26].

Change in the 5-HTA content of the blood and organs is undoubtedly affected by the processes of its formation, which depends on the activity of the enzyme 5-hydroxytryptophan carboxylase [9, 29, 38, 49], and decomposition, which depends on the activity of the enzyme monamine oxidase, which deaminates 5-HTA, forming hydroxyindoleacetic acid and 5-hydroxyindoleacetic acid [7, 9, 32, 47, 48]. There is every reason to believe that the activity of the latter enzyme changes during the development of typhoid intoxidation, as certain authors have observed it to following the irradiation of animals [1].

The sharp increase in the 5-HTA content of the small intestine and blood 5-12 hr after the administration of the typhoid vaccine could be the cause of the diarrhea observed in the rabbits during this period. There are many reports in the literature that an increase in the 5-HTA content of the organism intensifies intestinal peristalsis and causes the occurrence of diarrhea [10, 12, 21, 30].

The indirect results of our study indicate that serotonin is evidently formed or bound in the small intestine, brain and skin of the rabbit, creating depots in certain cells of these organs. In the literature, it has been shown that the argentaffine cells of the gastrointestinal tract mucosa contain a large amount of 5-HTA [5, 17, 18] and that in these cells, tryptophan is transformed into 5-hydroxytryptophan and from that into 5-HTA [18]. Several authors [9, 34, 50] believe that 5-HTA is formed in certain organs of the central nervous system. In the skin of rats and mice, the fat cells are a source of 5-HTA [27, 29, 37, 54], but in other animals and in man, the serotonin in the skin is not associated with the fat cells [6, 22, 39, 43, 44, 53, 54], but is probably bound by other structural elements. No accumulation of 5-HTA in the lungs has been established; therefore, the great similarity of the changes we observed in the 5-HTA content of the blood and lungs following typhoid intoxication (see Fig. 1) suggests that the 5-HTA content of the lungs depends to a large extent on the 5-HTA content of the blood. Certain authors, however, oppose this point of view [23, 26].

SUMMARY

The content of serotonin in the blood, brain, small intestine, lungs and skin undergoes phasic changes during the process of typhoid intoxication in rabbits. The amount of serotonin in the blood and organs drops markedly 15 min after intravenous injection of typhoid vaccine and remains below the initial level for a long period of time. The rise of serotonin level in the organs begins earlier than in the blood. In 12 hours after the

administration of the vaccine, serotonin concentration considerably exceeds its initial level in the blood and organs. Repeated reduction of serotonin content is seen in 24 hr.

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