CHANGES IN THE CONTENT OF 5-HYDROXYTRYPTAMINE IN ORGANS AND TISSUES OF RABBITS WITH DIPHTHERIC INTOXICATION

(UDC 616.931-07 : 616-008.9-092.18 : 612.015-348]-092.9)

B. M. Rozenman

Division of Toxicology (Head—Candidate of Medical Sciences, K. A. Vyatchannikov) Belorussian Scientific Research Institute of Sanitary Hygiene (Director—Candidate of Medical Sciences A. P. Rusyaev) and Department of Infectious Diseases of of the Belorussian Institute for the Advanced Training of Physicians, Minsk
(Presented by Member of the Academy of Medical Sciences, USSR, S. E. Severin)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 59, No. 3, pp. 54-57, March, 1965
Original article submitted February 14, 1964

During certain experimental infections and intoxications, changes in the content of the biogenic amine 5-hydroxytryptamine (serotonin) are detected in a number of internal organs and tissues, [3, 4, 22, 23]. Preliminary administration of serotonin antagonists to animals lowers while an inhibition of the enzyme monoamine oxidase increases the sensitivity of animals to bacterial toxins [19].

Serotonin participates in the regulation of many physiological mechanisms [14, 18] and evidently plays an important role in the pathogenesis of bacterial toxin poisonings [5, 22, 23].

The purpose of this work was to study the dynamics of the serotonin content during experimental diphtheric intoxication of rabbits.

PROCEDURE

A model study of diphtheric intoxication was conducted on rabbits by a single injection of 0.0044 ml/kg of liquid diphtheric toxin (1 Dlm for a guinea pig 0.0034 ml). In preliminary experiments we studied the dynamics of the changes in the ECG and blood pressure, as well as the histological changes in the myocardium and adrenals. The serotonin content was determined according to Vane's method [25] in the organs and tissues of 18 healthy rabbits and 27 rabbits in various phases of intoxication.

A total of 690 determinations were made.

RESULTS

The introduction of diphtheric toxin into the blood causes severe intoxication, leading to the death of all the animals after 50 ± 12 h and was characterized by the development of the following three phases:

In the first phase 6-8 h after the administration of the toxin to animals in generally satisfactory condition, an increase in the frequency of respiration and heart contractions was observed as well as an increase in the blood pressure.

At the end of the first day, in the second phase of intoxication, the rabbits became sluggish, and refused food and water. Respiration became more infrequent, the blood pressure dropped moderately, and some of the animals showed sinus bradycardia.

Toward the end of the intoxication (third phase) salivation increased, apathy progressed rapidly, exhaustion developed, there was paresis of the limbs, bradycardia, blockage of the heart, and a sharp drop in the blood pressure. Death came suddenly, as a rule, against a background of tonospasms and clonospasms of the skeletal muscles, as a result of which first respiration, and then the heart ceased.

Serotonin Content in Organs and Tissues of Healthy Rabbits

Organ or tissue	No. of expts.	Serotonin content per g or ml of tissue (in micrograms)	
		M	±
Blood	15	8.496	± 0.845
Adrenal glands	15	0.305	± 0.06
Myocardium (left ventricle)	13	0.536	± 0.074
Myocardium (interventricular septum)	15	0.537	± 0.083
Kidney	10	0.854	± 0.166
Haunch muscle	10	0.046	± 0.006
Diaphragm muscle	10	0.317	± 0.035
Cerebral cortex	10	0.778	± 0.166
Hippocampus	9	0.639	± 0.164
Caudate nucleus	11	0.228	± 0.042
Thalamus	11	0.395	± 0.062
Hypothalamus	10	0.102	± 0.337
Central gray matter	11	0.961	± 0.198
Corpora quadrigemina	11	1.631	± 0.294
Pons Varolii	10	0.607	± 0.129
Medulla oblongata	11	1.428	± 0.197
Cerebellum	11	0.333	± 0.054
Spinal cord	9	1.021	± 0.163
Sciatic nerve	9	0.078	± 0.009

The nature of the functional changes, first of all on the part of the cardiovascular system, the rapidity of their increase, and the suddenness of death, as well as the morphological changes of the adrenal glands and myocardium permitted an evaluation of this variation of intoxication as a model of hypertoxic diphtheria in humans.

The table presents data on the serotonin content in organs and tissues of healthy rabbits, while Figs. 1 and 2 gives that of rabbits in a state of diphtheric intoxication.

Under the influence of diphtheric toxin, the serotonin content in whole blood progressively diminished, while in the adrenals, kidneys, myocardium, muscles of the diaphragm and haunches, and sciatic nerve, it increased (see Fig. 1). However, the degree and rate of increase of the serotonin content differed in the various organs and tissues.

In the adrenal glands and kidneys in the first phase of intoxication, the serotonin content did not change significantly, while in the second phase there was a statistically reliable increase above normal (5.7 and 5.9-fold, respectively). In the third phase, the serotonin content in the kidney remained increased, and in the adrenal glands it was especially sharply increased, exceeding the normal indices by 12.8-fold.

In the myocardium, muscles of the diaphragm and haunches, a statistically reliable increase in the serotonin content was observed only in the third phase of intoxication.

The changes in the serotonin content in the central nervous system were distinguished by nonequivalence for the various regions and were less pronounced than in the internal organs (in most regions they were statistically insignificant) (see Fig. 2). In the first phase of intoxication, the serotonin content was statistically significantly higher only in the pons Varolii. In the medulla oblongata, spinal cord, as well as in the hypothalamus—regions where in the norm a high serotonin content is observed—under the influence of diphtheric toxin, it is significantly lower (in the second phase of intoxication in the medulla oblongata it was 55%, and in the spinal cord, 38% of the normal level).

The differences in the rate and degree of changes in the serotonin content in the various organs and tissues correspond to their dissimilar affinity for diphtheric toxin. This is especially clearly manifested in the adrenals, the injury of which during the onset of diphtheria is especially early and is distinguished by the most pronounced

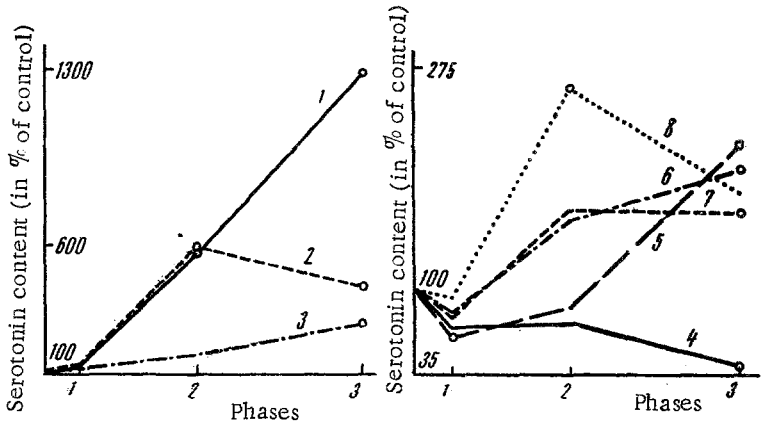

Fig. 1. Serotonin content in organs and tissues of rabbits during diphtheric intoxication: 1) adrenal glands; 2) kidney; 3) haunch muscle; 4) whole blood; 5) myocardium of left ventricle; 6) myocardium of interventricular septum; 7) diaphragm muscle; 8) sciatic nerve.

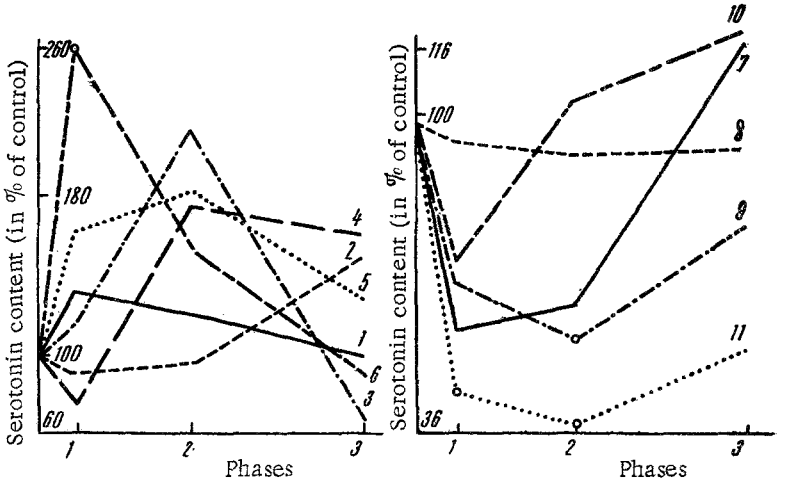

Fig. 2. Serotonin content in the central nervous system of rabbits during diphtheric intoxication: 1) cerebral cortex; 2) hypothalamus; 3) cordate nucleus; 4) thalamus; 5) central gray matter; 6) pons Varolii; 7) hypothalamus; 8) corpora quadrigemina; 9) medulla oblongata; 10) cerebellum; 11) spinal cord.

serotonin content in comparison with the other tissues. Evidently, changes in the serotonin content in the organs and tissues should be pathogenically linked with their injury by diphtheric toxin. Evidence of this, for example, is the ability of serotonin to cause acute edema in the tissues [20], a symptom so characteristic of diphtheria.

The above pertains to the problem of toxico-allergic pathogenesis of malignant diphtheria, since the symptoms of allergy and anaphylaxis are determined by the action of biologically active substances, among them, serotonin [11, 12] which are liberated during the joining of the allergen to the cells of the sensitized tissues [1]. The regeneration of malignant diphtheria by administration of small doses of diphtheric toxin to sensitized animals [7] is the result of a very rapid and firm bonding of it to the sensitized cells [2]. The administration of sufficiently large doses of toxin as it follows from the experiments conducted, causes a uniform effect and changes in the serotonin metabolism even without preliminarily sensitization of the animals.

The decrease in the serotonin content in the whole blood in the third phase of intoxication coincided with a pronounced decrease in blood pressure. This decrease may be connected with thrombocytopenia, characteristic of diphtheria. However, one should consider the liberation of serotonin from thrombocytes under the influence of bac-

terial toxins [10, 13, 21-23] and the destruction of free serotonin by the enzyme monoamine oxidase, as well as the local and reflex influence of free serotonin on the tonus of the vessels [9, 15-17].

In parallel investigations, carried out with the same laboratory animals, it was shown [6] that the functional disorders of the cardiovascular system are connected with a disruption of the cholinergic processes and selective blockage of the enzyme cholinesterase in the organs and tissues damaged by diphtheria toxin. Under the influence of serotonin, the activity of cholinesterase decreases [18]. Consequently, the accumulation of serotonin in the a adrenals and myocardium may also be important factors in the disruption of the functional state of these organs.

These functional changes should also be attributed to the central effects of serotonin [8, 24]. A decrease in its content in the brain stem and spinal cord in the first and second phases of intoxication probably was due to a liberation of serotonin from the bound state with the appearance of parasympathicotropic effects, as is characteristic of the action of reserpine [24].

LITERATURE CITED

1. P. F. Zdrodovskii, Problems of Infection, Immunity, and Allergy [in Russian] (Moscow, 1963).
2. V. I. Molchanov, Diphtheria [in Russian], (Moscow, 1960).
3. Z. A. Popenenkova, Byull. Éksper. Biol., 1961, No. 2, p. 32.
4. Z. A. Popenenkova and T. N. Zavanyagina, Byull. Éksper. Biol., 1961, No. 11, p. 43.
5. M. O. Raushenbakh and G. A. Chernov, Probl. Hematol., 1959, No. 3, p. 3.
6. B. M. Rozenman, Summary of Reports, Designed for Discussion at the Scientific Session of the Belorussian Institute for the Advanced Training of Physicians [in Russian] (Minsk, 1961), p. 18.
7. S. Ya. Feigina and F. E. Ageichenko, Pediatriya, 1940, No. 2-3, p. 9.
8. B. B. Brodie and P. A. Shore, Ann. N. Y. Acad. Sci., 1957, Vol. 66, Art. 3, p. 631.
9. J. H. Comroe Jr., B. Van Lingen, R. C. Stroud et al., Am. J. Physiol., 1953, p. 379.
10. R. B. Davis, J. Lab. clin. Med., 1959, Vol. 54, p. 344.
11. M. A. Fink, Proc. Soc. exp. Biol. (New York, 1956), Vol. 92, p. 673.
12. M. A. Fink and C. E. Gardner, Proc. Soc. exp. Biol. (New York, 1958), Vol. 97, p. 554.
13. E. Habermann and H. Springer, Naturwissenschaften, 1958, Bd. 45, S. 133.
14. D. M. Mac Canon and S.M. Horvath, Am. J. Physiol., 1954, Vol. 179, p. 131.
15. J. W. McCubbin, G. H. Green, G. C. Salmoiraghi et al., J. Pharmacol. exp. Ther., 1956, Vol. 116, p. 191.
16. B. Maupin, Biol. med. (Paris, 1960), Vol. 49, p. 75.
17. I. H. Page and J. W. McCubbin, Am. J. Physiol., 1953, Vol. 174, p. 436.
18. I. H. Page, Physiol. Rev., 1958, Vol. 38, p. 277.
19. R. M. Des Prez, N. Fallon, and E. W. Hook, Proc. Soc. exp. Biol. (New York, 1961), Vol. 107, p. 529.
20. D. A. Rowley and E. P. Benditt, J. exp. Med., 1956, Vol. 103, p. 399.
21. T. Shimamoto, H. Jamazaki, K. Ohno et al., Proc. Jap. Acad., 1958, Vol. 34, p. 444.
22. T. Shimamoto, M. Inoue, T. Konishi et al., Arch. inst. Pharmacodyn., 1959, Vol. 121, p. 342.
23. T. Shimamoto, H. Jamazaki, N. Sagawa et al., Arch. inst. Pharmacodyn., 1959, Vol. 121, p. 450.
24. P. A. Shore, S. L. Silver, and B. B. Brodie, Science, 1955, Vol. 122, p. 284.
25. J. R. Vane, Brit. J. Pharmacol., 1957, Vol. 12, p. 344.

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.
