PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

THE ROLE OF THE CEREBRAL CORTEX IN THE PATHOGENESIS OF HEMOLYTIC ANEMIA

COMMUNICATION II. THE EFFECT OF ACUTE DISTURBANCE OF HIGHER NERVOUS ACTIVITY ON THE COURSE OF EXPERIMENTAL PHENYLHYDRAZINE-INDUCED ANEMIA

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Various methods are available for the study of the role of the central nervous system in the regulation of various bodily functions under normal and pathologic conditions. Among such methods, one that has found extensive application is that of organic impairment or functional disturbance of one or other link in the nervous system, with subsequent observation of change in function or structure of the organ or system of organs under consideration [2-4, 8-10].

Investigation of the effect of disturbance of higher nervous activity on the course of phenylhydrazine-induced anemia, as well as reproduction of the phenylhydrazine anemia syndrome by way of conditioned reflexes, is among the more natural methods which make it possible to study the role of the cerebral cortex in the pathogenesis of experimental hemolytic anemia. If it were found that the usual reaction of the blood system to the introduction of phenylhydrazine into the body followed a different course in animals with disturbed higher nervous activity than in animals which were simply given phenylhydrazine, it would provide weighty evidence for participation of central mechanisms in the pathogenesis of the developing hemolytic anemia. The present investigation was undertaken with this hypothesis in view.

EXPERIMENTAL METHOD

Four series of experiments on 27 sexually mature white rats were carried out. Duration of each experiment – from 18 to 32 days. All the animals were maintained under uniform conditions of environment and diet.

In the 1st series of experiments (rats No. 1-5) a study was made of the spontaneous changes in red blood cells in white rats; in the 2nd series (rats No. 6-15) the course of anemia induced by administration of phenylhydrazine was followed; in animals of the 3rd series (rats No. 16-25) the course of phenylhydrazine-induced anemia was studied against the background of disturbed higher nervous activity and in the 4th series of experiments (rats No. 26-35) a study was made of the effect of disturbed higher nervous activity on the blood picture.

Disturbance of higher nervous activity was induced and maintained throughout the experiment. For this purpose daily use was made of extremely strong tactile-pain and auditory stimuli (current 40 v for 10-15 seconds with short intervals over a period of 3-10 minutes, accompanied by loud ringing), and the significance of conditioned stimuli in the stereotype pattern was altered.

The state of the higher nervous activity in animals of the 3rd and 4th series was judged by establishing a conditioned reflex stereotype prior to the beginning of trauma to the higher nervous activity; the stereotype consisted of two positive conditioned reflexes and differentiation with respect to them, established on the basis of an unconditioned tactile-pain stimulus – weak electric current.

On termination of observations on animals of the 4th series the brain of rats No. 30, 32, 33 and of 2 intact animals was examined microscopically for gross structural changes (necrosis, hemorrhage, lesions of the vascular wall). The appearance of such lesions is not excluded in cases in which electric current is used as unconditioned stimulus, and they could lead to the development of protective inhibition rebound in the cerebral cortex. The preparations were stained with hematoxylin-eosin. A total of 80 preparations from different parts of the brain was examined.

Phenylhydrazine was administered to the animals in a single dose of 0.02 g/kg subcutaneously, in the form of 1% aqueous solution. Before injection of phenylhydrazine the blood of the experimental animals was examined twice to determine the initial indices. The initial blood picture in animals of the 3rd and 4th series was determined after the establishment of the conditioned reflex stereotype before the beginning of trauma to the higher nervous activity, and after the development of a persistent neurotic state before administration of phenylhydrazine. Blood specimens were always taken from the experimental animals at the same time – after administration of phenylhydrazine; the number of erythrocytes, amount of hemoglobin, color index, and smear picture were determined.

EXPERIMENTAL RESULTS

Analysis of experimental data obtained from animals which were only given phenylhydrazine (series 2) shows that the number of erythrocytes in animals of this series reached minimal values on the 4th day after administration of the hemolytic poison (65.9%). As can be seen from the table, the hemoglobin content by this time also reaches the lowest figures (73.5%). On the 2nd day after administration of phenylhydrazine the peripheral blood shows all the signs characteristic for anemia: anisocytosis, macrocytosis, polychromatophilia and punctate basophilia of the erythrocytes. From the 4th day after phenylhydrazine injection, anemia development is replaced by intensive blood regeneration. The number of erythrocytes shows a progressive increase reaching 96.3% of the initial value by the 16th day. The increase in blood hemoglobin overtakes the increase in the number of erythrocytes and by this time reaches 102.6%. From the 9th day after injection of phenylhydrazine 4 out of 10 rats in this series of experiments show onset of normalization of the red cells, which is complete by the 13th day after phenylhydrazine administration. The color index throughout the period of observation is a little above 1; by the 6th day it reaches 1.17.

Animals of the 3rd and 4th series showed on the 8-10th day after the beginning of trauma to the higher nervous activity the development of persistent impairment of cortical dynamics, with predominance of inhibitory processes. As disturbances of higher nervous activity developed, positive conditioned reflexes disappeared, the animals' behavior underwent a change: the rats became untidy, sluggish, mostly sitting curled up with head tucked under; the coat lost its glossiness and smoothness and acquired a dirty yellow tinge.

In the case of the animals of the 3rd series, who were given phenylhydrazine after the development of a persistent neurotic state, the greatest drop in the number of erythrocytes and the amount of blood hemoglobin was also observed on the 4th day after injection of the hemolyzing agent. The number of erythrocytes by this time constituted 62% (see table) of the initial value, the amount of blood hemoglobin – 71.2%. Blood smears showed, on the 2nd day after phenylhydrazine injection, single polychromatophil erythrocytes in 7 out of 10 animals. On the 4th day of the development of anemia all the animals in this series showed marked anisocytosis, macrocytosis and large numbers of polychromatophilic erythrocytes. Blood regeneration which began at this time was much less intensive than in animals who were only given phenylhydrazine; on the 16th day after injection of phenylhydrazine the number of erythrocytes was on average only 76.2% and blood hemoglobin content 88% of the initial values. In 5 out of 10 animals the smears at this time showed all the changes characteristic for phenylhydrazine anemia. The color index was above 1 from the 4th day of anemia and remained within this range throughout the period of observation, reaching a maximum by the 9th day of anemia (1.26).

Under the influence of the disturbance of higher nervous activity, the animals of the 4th series showed development of moderate normochromic anemia which became more marked as the neurotic state became more profound (see table). The number of erythrocytes decreased gradually, amounting to 74.2% of the initial

value by the 16th day; the hemoglobin content was 73.7% of the initial value. No changes in the red cells could be seen in the blood smears apart from slight hypochromic tendency in the erythrocytes. The color index did not exceed 1 throughout the period of observation.

In animals of the 1st series (studies of red cell indices over a period of time corresponding to the duration of observations on animals of the 2nd, 3rd and 4th series of experiments) fluctuations in the indices under consideration did not extend beyond the limits of the initial values throughout the whole period of time.

No gross structural changes were seen on microscopic examination of the brain of rats No. 30, 32 and 33; the inhibition observed in animals of the 3rd and 4th series can therefore be regarded as a result of functional overstrain of processes of excitation in the cerebral cortex, and the results of these experiments considered from this viewpoint.

As can be seen from the table, the rebound inhibition developed as the result of overstrain of excitation processes exerts a definite influence on the course of experimentally produced hemolytic anemia, affecting particularly the phase of regeneration. Following administration of similar doses of phenylhydrazine, the animals with impaired higher nervous activity showed somewhat greater reduction in the number of erythrocytes and the amount of hemoglobin than that seen in intact animals. The development and disappearance of the blood picture characteristic for phenylhydrazine anemia were delayed in animals with impaired higher nervous activity as compared with animals who were only given phenylhydrazine. The increase in erythrocytes and hemoglobin in animals with impaired cortical activity followed a monotonous course with little tendency to normalization.

Dynamics of Change in the Number of Erythrocytes, Amount of Hemoglobin and the Color Index in Animals of the 2nd, 3rd and 4th Series

Days of observation following phenylhydrazine injection	Erythrocytes (in % of initial value)			Hemoglobin (in % of initial value)			Color index (absolute values)		
	series			series			series		
	2nd	3rd	4th	2nd	3rd	4th	2nd	3rd	4th
2nd	76,3	76,6	91,6	82,6	77,8	93,2	1,08	1,0	0,98
4th	65,9	62,0	87,8	73,5	71,2	93,0	1,06	1,18	1,0
6 th	69,7	65,8	90,8	84,4	75,8	93,5	1,17	1,2	1,0
9 th	83,6	68,1	86,1	92,4	80,6	82,2	1,09	1,26	0,9
13 th	91,5	75,3	81,8	94,4	88,0	77,1	1,03	1,2	0,9
16 th	96,3	76,2	74,2	102,6	88,0	73,7	1,03	1,1	1,0

Note: Figures cited are mean of 10 observations.

We tend to regard the development of normochromic anemia in animals of the 4th series as the result of profound impairment of trophic processes in the organism, including the hemopoietic tissue, consequent on disorganization of cortical activity. Our viewpoint finds confirmation in the work of T. V. Fokina [11] who observed increased hemoglobin breakdown and diminution of regeneration of red blood elements in experimental animals as the neurotic state became more profound. B. I. Baiandurov [3] and N. S. Dzhavadian [6] observed the development of "spontaneous" normochromic anemia, together with a number of trophic changes, in animals deprived of normal cortical stimuli (decortication, transection of the spinal cord). D. I. Gol'dberg [5] noted that animals deprived of their cerebral cortices showed a more severe course of phenylhydrazine anemia and delay in restoration of blood indices as compared with animals who were only given phenylhydrazine.

The results of our experiments agree with the experimental material presented in the work of M. A. Usievich et al., [9, 10] who conclude that the "inhibitory state of the cortical cells leads to exceedingly low levels of activity of the systems studied." Our data also coincide with the experimental results of V. N. Chernigovskii and A. Ia. Iaroshevskii [12], E. L. Kan and V. N. Chernigovskii [7] and G. I. Alekseev [1] who observed inhibition of erythropoiesis in animals with inhibited cortical activity.

The results of our investigations thus confirm the data presented in the literature concerning the role of cortical mechanisms in the pathogenesis of experimentally induced hemolytic anemia [5] and indicate the dependence of the erythropoietic function of bone marrow on the functional state of the cerebral cortex.

SUMMARY

The author studied the effect of acute disturbance of the higher nervous activity, caused by overstrain of the processes of excitation in the cerebral cortex, on the course of experimental hemolytic (phenylhydrazine) anemia. In animals with disturbed dynamics of the cortical function the course of anemia after administration of the same doses of hemolytic toxin was much more severe than in intact animals. With further development of disturbance of higher nervous activity the processes of blood regeneration became less intense. Moderate normochromic anemia develops in intact animals under the influence of disturbance of higher nervous activity. This anemia progresses with further development of disturbances of cortical dynamics. The results of these experiments demonstrate the role of cortical mechanisms in the pathogenesis of phenylhydrazine anemia. They confirm the literature data on the dependence of erythropoietic function of bone marrow on the functional condition of the cerebral cortex.

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