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THE PERMEABILITY OF THE HEMATO-ENCEPHALIC BARRIER AND THE SORPTION CHARACTERISTICS OF BRAIN TISSUE IN EXPERIMENTAL THYROTOXICOSIS

/Following is the translation of an article by N.F. Shaposhnikova entitled "Pronitsayemost' Gemato- Entsefalicheskogo Bar'yera i Sorbtsionnyye Svoystva Tkaney Mozga pri Eksperimental'nom Tireotoksikoze" (English version above) in Problemy Endokrinologii i Gormonoterapii (Problems of Endocrinology and Hormone Therapy), Vol.VI, No.3, 1960, pages 91-94./

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The human and animal organism has at its disposal a number of barrier adaptations which prevent the entry and dissemination of disease-inducing agents within the organism. Among these formations is the hemato-encephalic (blood-brain) barrier (HEB), which is of considerable interest. At the present time the functional properties of this barrier have been well studied (9,14,4).

Demonstration has been given of its role in the activity of the nervous system (9). It has been shown that, in a number of pathologic processes -- shock (12,8), infection (10,16), radiation injury (15,2), brain trauma (13,3) -- the permeability of the HEB changes, which cannot but be reflected in the development and clinical picture of these diseases. Concerning the problem of the state of permeability of the HEB in endocrine diseases, there are only isolated reports in the literature, and the data are contradictory. The question of its permeability in thyrotoxicosis has been given little attention. Nonetheless, these data would be of considerable interest, since the most important clinical manifestations of thyrotoxicosis are associated with disturbances in the nervous system, especially of the central part.

Of experimental works in this direction, note should be taken of the studies of L.G. Velkina and A.I. Zlatoverov (1). Studying the permeability of the HEB upon injection of thyroidin into the organism, these authors discovered an increase in the permeability of the barrier to crystalloids (sodium ferrocyanide and sodium oidide), whereas with respect to colloids (trypan blue), the permeability of the HEB remains essentially unchanged. Removal of the thyroid gland, on the contrary, leads to increase in the permeability of the HEB with respect to colloids, while its permeability to crystalloids under these conditions shows almost no changes (11). These findings permit us to suggest that, under the influence of the thyroid hormone, the permeability of the HEB changes differently for different substances: with respect to some, it increases, while with respect to others it does not change.

It should be noted that, in the above-mentioned works, studies were made only of the cerebrospinal fluid, whereas the content and distribution of the indicator in the tissues of the brain substance under the influence of thyroidin were not investigated.

Starting with the data in the literature, we undertook to study the state of permeability of the HEB, and also the sorption-properties of certain structures of the brain, in experimental thyrotoxicosis.

The experiments were carried out on 55 rabbits. Thyrotoxicosis was induced by the injection of thyroidin (0.1 gm/kg body weight) for a period of six to 40 days. We evaluated thyrotoxicosis by the amount of oxygen required by the animals per unit time before and after the injection of thyroidin, by the general state of the animals, and also by the extent of weight loss. The amount of oxygen consumed was determined by the method of N.I. Kalabukhov (5). As a rule, the development of thyrotoxicosis was accompanied by considerable increases in oxygen consumption (by 22 to 97 percent). Only in five animals was the increase of oxygen consumption as slight as 12 to 19 percent, while in four it was 102, 108, 129, and 157 percent, respectively. The rabbits lost from 190 to 1000 gm.

The permeability of the HEB and the sorption properties of the brain tissue were studied by the method of radioactive isotopes. The latter has a number of advantages over other methods (the method of vital staining, etc.). It gives a precise quantitative characterization of the process and also permits appraisal of permeability with respect to substances originating in the organism itself. As indicators of permeability we used radioactive phosphorus in the form of a solution of $Na_2HP^{32}O_4$ and radioactive calcium in the form of a solution of $Ca^{45}Cl_2$.

The isotopes were injected intraperitoneally (22.5 microcuries/kg body weight). One hour later, blood was drawn from the heart in amounts of three to four ml for determination of the content of isotope in the serum. Then the animals were killed by the injection of ether into the ventricle, and were autopsied, and samples of the brain were taken for studies.

The degree of permeability of the brain barrier was evaluated by the amount of isotope which penetrated into the cerebrospinal fluid. Simultaneous studies were made of the content of the indicators in the cerebral cortex (region of the parietal lobes), ophthalmic tubercles, and medulla oblongata. The activity of the samples was determined with the use of the B-2 apparatus with an AS-2 scintillation counter enclosed in a lead casing. In experimentts involving the injection of Ca^{45}, the activity of the preparations was determined with a MST-17 scintillation counter. Upon determination of the activity of the preparations, computation was made of the absolute and the relative statistical errors of measurement. The relative error [? deviation] of measurement in our experiments did not exceed + percent.

The results obtained are expressed in the form of relative activity, i.e. the ratio of activity of the sample being studied to the activity of the serum, in percentages. The total number of experiments (including controls) was 69.

In the first series (14 control experiments), we became convinced that the indicators penetrated the brain: however, the content of them in the several elements of the brain was considerably lower than in the serum. In experiments with the injection of P^{32} -- the activity of the cerebrospinal fluid with respect to the activity of the serum varied from 4.0 to 8.7 percent (with an average of 6.4 percent). Even less P^{32} was found in the cerebral cortex -- from 4.1 to 7.4 percent (average 5.4 percent), ophthalmic tubercles -- from 3.5 to 7.9 percent (average five percent), and medulla oblongata -- from seven to 10.2 percent (average 8.2 percent).

Hence, in the cerebrospinal fluid and in the brain tissues, separated from the blood by the HEB, the content of P^{32} is approximately 16 times less than in the serum. This difference is even more marked with the use of Ca^{45}. In these experiments the activity of the cerebrospinal fluid with respect to the serum varied from 3.2 to 5.8 percent (average 4.6), of the cerebral cortex from 2.2 to 4.8 percent (average 3.2), of the ophthalmic tubercles from 3.4 to 5.8 percent (average 4.6), and of the medulla oblongata from 3.9 to 5.7 percent (average 5.1 percent).

In the second series, 55 animals were used for studying the permeability of the HEB in thyrotoxicosis. In the first group (17 experiments), the animals were in the initial stages of thyrotoxicosis, while in the second group (38 experiments), they had overt manifestations of the disease.

The early form of thyrotoxicosis is characterized by a slight loss of weight (190-325 gm) and by increase in oxygen consumption by 12 to 75 percent per kg body weight per hour. In the group with overt manifestations of toxicosis there were animals with considerable weight loss (300-560 gm). The increase in the oxygen consumption in this group varied from 14 to 97 percent, and in two rabbits by 102 and 108 percent. The severe form of thyrotoxicosis included animals with more serious general manifestations (in some there were adynamia and intestinal disturbances), and increase in oxygen consumption varying from 22 to 92 percent, in two rabbits by 129 and 157 percent. Loss of weight varied from 500 to 1000 gm.

In animals with the early form of thyrotoxicosis the relative activity of the elements of the brain was close to the corresponding indices for controls. Only the activity of the CSF in these animals was slightly higher than in normal animals. Thus, in experiments with the injection of P^{32}, the relative activity of the CSF in animals with the early form of thyrotoxicosis varied from 6.4 to 12.6 percent (average 9.1), with the activity of the CSF in the controls ranging from four to 8.7 percent (average 6.4). The same was observed in the case of Ca^{45}: the relative activity of the CSF under ordinary conditions varied from 3.2 to 5.8 percent (average 4.6), while in the early form of thyrotoxicosis it varied from 4.4 to 10.5 percent (average 7.8 percent). Hence, even in the early form of thyrotoxicosis there was a slight increase in the permeability of the HEB to P^{32} and Ca^{45}.

In animals with overt manifestations of thyrotoxicosis the relative activity of the parts of the brain for P^{32} and Ca^{45} was higher than in controls and than in those with the early form of the process. Thus, in experiments with P^{32} the relative activity of the CSF in normal animals varied from four to 8.7 percent (average 6.4), in animals with the early form of thyrotoxicosis from 6.4 to 12.6 percent (average 9.1), while with overt disease the variation was from 9.8 to 19.2 percent (average 12.8 percent).

From these data it is evident that an increase in the content of P^{32} in animals with overt thyrotoxicosis (as compared with controls) occurs not only in the CSF but also in the brain tissues. While the activity of the cerebral cortex in control animals varied from 4.1 to 7.4 percent (average 5.4), of the ophthalmic tubercles from 5.5 to 7.9 percent

(average five percent), and of the medulla oblongata from seven to 10.2 percent (average 8.2), in animals with overt toxicosis the relative activity of the cerebral cortex varied from 6.2 to 15.5 percent (average 9.6 percent), of the ophthalmic tubercles from 6.4 to 16.6 percent (average 9.8), and of the medulla oblongata from 8.3 to 17.4 percent (average 11.7 percent).

Almost the same phenomenon was observed in the experiments with Ca^{45}. With a relative activity of the CSF in animals with overt thyrotoxicosis of six to 14.5 percent (average 9.7), in animals with the early form of toxicosis it varied from 4.4 to 10.5 percent (average 7.8), and in control animals from 3.2 to 5.8 percent (average 4.6 percent). In animals with overt thytotoxicosis, more Ca^{45} penetrated into the brain tissues studied here, also.

An especially marked increase in the permeability of the HEB was seen in rabbits with severe manifestations of the disease.

About three and a half times more P^{32} penetrated into the CSF if animals with severe thyrotoxicosis, than in the case of normal controls, and about two and a half times more than in the case of early disease. The same difference was seen in the cerebral cortex, the optic tubercles, and the medulla oblongata. The activity of the brain in animals with severe disease averaged 14.6 percent, of the optic tubercles 15.1 percent, and of the medulla oblongata 19.5 percent, whereas in animals with less severe toxic manifestations the values were, respectively, 9.6, 9.8, and 11.7 percent (normal controls showed values of 5.4, five, and 8.2 percent). Similar results were seen in the experiments with injection of Ca^{45}.

On the basis of these data it may be concluded that, with increase in severity of thyrotoxicosis, the permeability of the HEB and also the sorption properties of the brain structures for phosphates and calcium are enhanced. The most pronounced changes are seen in severe thyrotoxicosis.

As to the mechanism of these disturbances, it is necessary to keep in mind a number of factors, primarily the increase in the permeability of vessels of the brain under the conditions of thyrotoxicosis, due to the toxic effects of thyroidin on the vasomoto nervous system. In favor of this hypothesis are the morphologic changes of the vessel walls in acute thyrotoxicosis, especially swelling and fusion of the argyrophilic substance, with loss of its impregnation properties (6). This process of quick "fusion", as shown by A.I. Smirnova-Zamkova (7), is connected with stimulation of the parasympathetic or with suppression of the sympathetic nervous system. Taking into account the sympathomimetic properties

of thyroxin, it may be said that the increase in permeability of the vessels of the brain in our experiments is associated with vasodilator changes in them, due to toxic paralysis of the sympathetic nervous system caused by the injection of thyroidin into the organism.

These studies permit us to conjecture that the pathogenesis of functional disorders on the part of the nervous system and the irregularities of psychic phemomena in patients with thyrotoxicosis are connected, to a certain extent, with the penetration into the brain of toxic substances and other substances not related to brain metabolism, due to an increase in the permeability of the HEB.

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