CONTENT OF COPPER IN BRAIN TISSUE UNDER NORMAL CONDITIONS AND IN SOME DISEASES OF THE NERVOUS SYSTEM

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The brain is one of the richest copper-containing organs of the human. Highest values have been observed in the cerebral cortex, subcortical nodes and the optic thalamus [2, 13]. In the left hemisphere the content of copper is higher than in the right [1, 5]. About 90% of the copper found in the brain is joined to proteins [1, 16]. Injection of sedative substances into the organism increases the concentration of copper in the brain [8], while excitation of the nervous system and convulsive states decreases copper concentration [1]. However at the present time almost nothing is known about the relative significance of copper in nervous system activity.

Our objective was to determine the copper content in functionally different parts of the human nervous system and changes in its concentration in the brain in some diseases.

EXPERIMENTAL METHOD

Copper was determined by emission spectra analysis. The spectrograms were analyzed on a spectroprojector and MF-2 microphotometer. A calibration curve was constructed on the basis of a salt mixture similar in composition to the brain ash [1, 2]. As an internal standard, the spectral line of cobalt was used, artifically added to the combustion mixture. The tissue ash was burned in an activated arc of an alternating current. Reproducibility of the investigation was ±8%.

EXPERIMENTAL RESULTS

Initially the copper content in brain tissues of essentially healthy individuals, accidentally killed, was determined. The reason for death in 5 cases was asphyxiation; in 2, electric trauma; in 3, destruction of organs important for life by mechanical trauma. All the dead were aged 18-32 years. Parts of the brain were taken for investigation only in thoses cases when no signs of brain disease could be found. Results of the determinations are presented in Table 1.

The highest amount of copper in the brain calculated on a fresh weight basis was found in the globus pallidus and caudal nucleus, followed in decreasing order by brain cortex, optic thalamus, and hypothalamic formations. The least copper was in the white matter of the brain hemisphere. When calculated on a dry weight basis the same relationships were maintained. Variation in copper concentration in the lobes, parietal and occipital parts of the brain cortex did not exceed 80%. A somewhat higher copper content (10-12%) was noted in

TABLE 1

Copper Content of Investigated Tissues

Investigated material	In tissues of healthy, accidentally killed individuals		In tissues of a patient with hepatolenticular degeneration		In tissues of patients with brain tumor	
	in milligrams/ /100 g fresh matter	in milligrams/ /100 g dry matter	in milligrams/ /100 g fresh matter	in milligrams/ /100 g dry matter	in milligrams/100 g fresh matter	in milligrams/100 g dry matter
Brain cortex	0.6 (0.43-0.92)	3.33 (2.3-3.7)	1.64	10.4	0.76 (0.41-0.9)	3.62 (3.2-4.4)
White matter	0.5 (0.4-0.7)	1.52 (1.2-2.0)	1.32	4.49	0.46 (0.26-0.8)	1.66 (1.5-1.8)
Optic thalamus	0.56 (0.51-0.71)	2.49	1.45	7.01	–	–
Caudal body	0.64 (0.49-0.75)	3.37 (3.1-3.5)	1.38	6.42	–	–
Hypothalamus	0.53 (0.31-0.71)	2.71 (2.1-3.5)	–	–	–	–
Globus pallidus	1.31 (0.73-1.68)	4.31 (3.9-4.6)	2.89	18.71	–	–
Cerebellum	–	–	1.43	8.25	–	–
Spinal cord (cervical swelling)	–	–	0.98	3.99	–	–
Spleen	–	–	0.58	2.96	–	–
Muscle	–	–	0.25	1.07	–	–
Liver: Acutely infected lobe	–	–	3.20	13.69	–	–
Liver: Less infected lobe	–	–	1.66	5.92	–	–

Note: Limits of individual variation are placed in parentheses.

the anterior hypothalamic region (sections near the intersection of the optic nerves and the anterior portion of the tuber cinereum) in comparison with the posterior (region of the mammillar bodies and the posterior section of the tuber cinereum). The lateral portions of the optic thalamus contained 0.48 mg % of copper and the medial portions 0.64 mg %.

We then investigated the copper content in tissues of a patient dying from hepatolenticular degeneration. The patient had the tremulus-rigid form of hepatolenticular degeneration. Kayser-Fleischer's ring was present, as well as disturbance of the copper metabolism. On autopsy, changes in liver and brain characteristic of hepatolenticular degeneration were found.

The copper content in the brain of the patient with hepatolenticular degeneration (see Table 1) when compared to the level of copper in the corresponding brain sections of healthy individuals accidently killed

TABLE 2

Content of Copper in Brain Tumors (in milligram-percent/100 g tissue)

Investigated tumor	Form of investigated material	In the whole tumor (average of the copper concentration in the center and on the periphery of the tumor)	In the center of the tumor	On the periphery of the tumor
Arachnoid-endothelioma	Fresh	0,221 (0,145-0,357)	0,237 (0,137-0,555)	0,206 (0,134-0,39)
	Dry	1,145 (0,91-1,57)	1,049 (0,83-1,42)	1,24 (0,85-1,88)
Benign neuroectodermal tumor	Fresh	0,44 (0,138-1,05)	0,366 (0,152-0,985)	0,507 (0,23-1,12)
	Dry	1,418 (1,045-1,755)	1,209 (1,070-1,31)	1,627 (0,84-2,20)
Malignant neuroectodermal tumor	Fresh	0,823 (0,575-1,011)	0,45 (0,184-0,802)	1,19 (0,77-1,58)
	Dry	4,955 (4,7-5,15)	2,53 (1,0-4,060)	7,38 (6,24-8,52)

when calculated on a fresh weight basis, was 274% in the cortex , 264% in the white matter, 259% in the optic thalamus, 220% in the globus pallidus and 216% in the nucleus caudatus. A similar comparison of the copper concentration in the relative parts of the brain calculated on a dry weight basis showed a somewhat different relationship: 191% in the nucleus caudatus, 281% and 292% respectively in optic thalamus and white matter, 312% in brain cortex and 434% in globus pallidus.

Due to the fact that a patient with hepatolenticular degeneration is rarely autopsied, copper determination in the cerebellum,spinal cord, liver and muscles of this patient are also presented in Table 1.

Finally, in the last series of investigations we determined the copper content in neoplasms and tissues of the nervous system in brain tumors.*

Twenty-one tumors were investigated, of which 11 were arachnoidendothelial, 8 were neuroectodermal tumors of various forms (3 spongioblastoma multiforme and 5 astrocytomas), one was a tumor of hypophysis (chromophilic adenoma), one was an epidermoid cyst. Sections of the brain not infected with tumor were investigated in 9 cases. Tissues free of vessels and decomposed matter were used in the determination.

A small amount of copper (Table 2) was found in tumors of the membrane-vascular system (arachnoidendothelial). In intracerebral benign tumors (astrocytomas) the amount of copper approached that in white matter of the brain. The most copper was contained in the malignant neuroectodermal tumors (spongioblastoma multiforme). This difference was maintained when the copper content was calculated on a dry weight basis. In the case we investigated of intracerebral tumors with a noncerebral origin (epidermoid cyst), the copper content exceeded somewhat the concentration in arachnoidendothelial tumors (0,246 mg %). A very small quantity of copper was found in the chromophobic adenoma of the hypophysis (0,104 mg % calculated on fresh tissue and 0,320 mg % by dry weight).

* Parts of the brain were obtained at the time of operation, when access to the tumor was accompanied by the necessary removal of uninfected tissue, and in some cases brain sections were obtained at autopsy. The specimens were obtained from the Neurosurgical Department (Director, Dr. Med. Sci. I. M. Irger) of the Scientific Research Institute of Psychiatry of the Acad. Med. Sci. USSR, in the S. P. Botkin Base Hospital.

Different groups of tumors also differed with respect to distribution of copper in various parts of the neoplasms. In arachnoidendotheliomas the variation in copper content in various parts did not exceed 10-15% as a rule. In benign neuroectodermal tumors the copper content on the periphery of the tumor was 29% higher on the average than in the center. In malignant penetrating tumors of the brain this difference attained 62% by wet weight, and 290% calculated by dry weight.

The copper content (see Table 1) in the white matter not infected with tumor (in milligram-percent fresh weight) was lower and in the cortex (in 5 observations out of 6) it was higher than the average copper concentration in the brain of healthy individuals. The copper content (dry weight) of both cortex and white matter exceeded the average copper content in healthy, suddenly-killed individuals.

The values presented above for copper in the brain of suddenly-killed, essentially healthy people verifies data obtained by other investigators [2, 13] regarding the unequal copper content in various parts of the brain. The high content of copper in the brain of the patient dying from hepatolenticular degeneration verifies existing observations of the disturbance of copper metabolism in this disease [7, 12, 13].

The unequal accumulation of copper in various parts of the brain should be noted. The highest concentration of copper in normals and in hepatolenticular degeneration was noted in the globus pallidus and the nucleus caudatus.

In order to determine the significance of copper in tissues of the nervous system it is appropriate to compare the data presented above regarding the high copper concentration in the subcortical nodes of the brain with the facts indicating the ability of the copper-containing proteins of the blood serum to acidify some catecholamines (adrenalin, noradrenalin and others [4, 15]) and observations of the relationship of the serum copper content to changes in the tonus of the sympathetic nervous system [3, 4]. It is also known that in disease of the ganglia at the base of the brain secretion of catecholamines from the urine are appreciably increased. Isolated destruction of the globus pallidus in such patients leads to still higher increase in the synthesis of these amines in the urine. Analogous activity in other parts of the brain does not have such an affect [11]. Injection of drugs which act on the metabolism of catecholamines in the brain (aminazine and ganglioblocking agents) leads to the development of a syndrome of injury to the subcortical ganglia of the brain in those patients who have a high copper blood level at the time of treatment [10]. As our investigation showed, patients with organic disease of the subcortical ganglia of the brain have an increased copper blood level.

It is difficult to imagine that this chain of events is the result of accidental coincidence. It is more probable that there is a relationship between the copper-containing proteins in the brain and the catechol amines, adrenalin and noradrenalin in particular, in subcortical ganglia. From this point of view, interest is drawn to the fact noted above that the copper content is significantly higher in medial sections of the optic thalamus than in the lateral sections. It was shown [17] that the content of sympathins (adrenalin and noradrenalin) in medial sections of the optic thalamus is also higher than in lateral sections.

An almost equivalent amount of copper (only 2-4% higher than experimental error) in the anterior and posterior sections of the hypothalamus coincides with a uniform distribution of sympathins in these formations [17]. Therefore, definite correlation between copper content and catecholamines occurs in other parts of the nervous system.

Some increase in copper, which we noted in parts of the cerebral matter not infested with neoplasm in patients with brain tumors, was entirely insignificant and occurred in small samples.

The copper content of brain tumors with varying histogenesis varied within wide limits. The smallest amount was noted in tumors of the membrane-vascular series and benign neuroectodermal neoplasms. In spongioblastoma multiforme the copper concentration exceeded that of the cortex and on a dry weight basis it was higher than the maximum copper content in globus pallidus. If the concentration of copper in the center of the tumor did not exceed the value for white matter of the brain, then the peripheral part of the tumor contained approximately 200% more copper than the surrounding tissue. In malignant neuroectodermal tumors the amount of copper in the periphery was 2.9 times higher than in the center.

These data cast doubt on the opinion expressed by some authors [6] that increase in the copper concentration in tumors is related to the development of foci of necrosis in them. As is known, the intensity of cellular growth, anaerobic glycolysis and the content of nucleic acids is higher in malignant tumors, and also larger in the

periphery of neoplasms [9]. Comparison of the results obtained with data in the literature lead us to the conclusion that the parts of the tumors with increased copper content are at the same time tissues with the most intensive metabolism and cellular growth, which is evidence of the importance of copper and copper containing proteins for metabolic processes proceeding in tumors.

SUMMARY

Copper content was determined spectrographically in various portions of the brain in 10 healthy patients who died accidentally, in the brain of a patient with hepatolenticular degeneration, as well as in various tumors of the brain and areas of the nervous system not affected by neoplasms. The greatest copper content was noted in the globus pallidus, nucleus caudatus and the cortex of the large hemispheres. The copper concentration in the brain of patients with hepatolenticular degeneration is considerably higher than in the accidentally dead persons. As shown, less copper is contained in the lateral portions of the optic thalamus than in the medial portions. The concentration of copper was almost even in the anterior and the posterior portions of the hypothalamic area. Copper content is increased in the areas of the brain not affected by neoplasms. Copper content in the brain tumors of membranous-vascular genesis is lower than in the white matter. Much copper was detected in benign neuroectodermic tumors. The highest copper content was noted in malignant neuroectodermal tumors (higher than in the brain tissue richest in copper). In malignant tumors copper content was higher at the periphery of the neoplasm, in the area of intensive cellular growth and glycolysis. The significance of copper for the actvity of the nervous system and metabolism in tumors is discussed.

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