CONTENT OF FREE AMINO ACIDS, RNA, AND DNA IN BRAIN TISSUE DURING PROLONGED ADMINISTRATION OF CHLORPROMAZINE

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Under the influence of chlorpromazine only transient changes take place in the content of various amino acids, RNA, and DNA in the rat brain.

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As a result of his experiments Decourt [4] found that chlorpromazine possesses a "narcobiotic" action and lowers the intensity of metabolic processes in the central nervous system. In this connection the quantitative determination of free amino acids in the brain tissue during prolonged administration of chlorpromazine is of considerable interest. This is especially true because some amino acids influence the conduction of nervous impulses and are the source of formation of biologically active substances [1, 5]. The study of the RNA and DNA levels in the brain during administration of substances lowering the intensity of metabolic processes in nerve tissue is also of theoretical and practical interest because nucleic acids are important factors in the regulation of protein synthesis.

The object of this investigation was to determine the content of free amino acids, RNA, and DNA in brain tissue during prolonged administration of chlorpromazine.

EXPERIMENTAL METHOD

Experiments were carried out on albino rats of both sexes weighing 180-200 g. The animals were kept on the usual diet. Three series of investigations were made: in series I free amino acids, RNA, and DNA were determined in the brain tissue of healthy rats (control), in series II they were determined 2, 4, 6, and 24 h after administration of chlorpromazine, and in series III at intervals of 5, 10, 20, and 30 days after daily administration of chlorpromazine. The drug was injected subcutaneously in a dose of 5 mg/kg.

Free amino acids were determined quantitatively by the method of unidimensional descending chromatography on paper [2], and the RNA and DNA levels by the method of Schmidt and Thannhauser [6] as modified by Tsanev and Markov [3].

EXPERIMENTAL RESULTS

As Table 1 shows, the brain of healthy rats has a high content of free amino acids, especially aspartic and glutamic acids, and also of threonine. During the 6 h after injection of chlorpromazine a significant increase was observed in the content of glycocol, alanine, serine, threonine, and aspartic acid and a decrease in that of leucine, arginine, histidine, tyrosine, and glutamic acid. During daily administration of chlorpromazine, on the 5th day the content of glycocol, alanine, leucine, and glutamic acid fell while the level of phenylalanine, tyrosine, histidine, and aspartic acid rose, although on the following days (until the 30th day) no appreciable changes were found in the concentration of free amino acids. However, a decrease in the content of glutamic acid and an increase in that of aspartic acid were observed during daily administration of chlorpromazine throughout the period of the experiment.

Table 2 shows that the rat brain contains more RNA than DNA. During the action of chlorpromazine the RNA content rose after 2 h and returned to its initial level after 4 h. In the course of administration of this drug for a long period the RNA level remained unchanged. So far as DNA is concerned, during

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TABLE 1. Content of Free Amino Acids in Brain Tissue at Various Times after Administration of Chlorpromazine (in mg%)

Amino acid	Control healthy animals	Time after administration of chlorpromazine						
		2 h	4 h	6 h	5 days	10 days	20 days	30 days
Glycocol	5.28±0.08	7.52±0.07[2]	8.83±0.15[2]	7.40±0.13[2]	4.59±0.08[2]	5.06±0.08	5.29±0.11	4.73±0.10[2]
Alanine	4.60±0.13	5.19±0.10[2]	5.23±0.07[2]	5.02±0.03[2]	4.21±0.08[3]	4.48±0.12[3]	4.43±0.12[3]	4.40±0.14[3]
Serine	5.07±0.15	6.52±0.22[2]	10.51±0.13[2]	11.85±0.11[2]	6.05±0.13[2]	4.46±0.35[2]	5.89±0.15[2]	5.95±0.08[2]
Threonine	7.20±0.18	9.50±0.14[2]	6.98±0.06[3]	8.30±0.10[2]	7.24±0.10[3]	5.65±0.11[2]	8.45±0.09[2]	8.16±0.11[2]
Leucine	2.08±0.04	1.39±0.08[2]	1.48±0.09[2]	1.35±0.07[2]	1.45±0.06[2]	1.29±0.09[2]	2.19±0.08[3]	1.98±0.06[3]
Arginine	3.0±0.07	2.42±0.09[2]	1.87±0.10[2]	1.63±0.08[2]	2.92±0.16[3]		Traces	
Aspartic acid	26.89±0.16	28.11±0.14[2]	28.08±0.06[2]	31.15±0.18[2]	33.90±0.10[2]	31.31±0.17[2]	26.18±0.14[2]	34.03±0.07[2]
Glutamic acid	44.98±0.45	35.75±0.95[2]	35.89±0.55[2]	37.04±0.02[2]	40.02±0.41[2]	37.02±0.11[2]	36.30±0.95[2]	35.14±0.09[2]
Phenylalanine	1.01±0.01	1.03±0.01[3]	1.02±0.02[3]	1.09±0.04[3]	1.69±0.03[2]	1.15±0.07[3]	1.18±0.06[2]	1.62±0.04[2]
Tyrosine	2.21±0.07	2.82±0.06[2]	Traces		2.58±0.06[2]	2.26±0.10[3]	2.52±0.8[2]	2.33±0.06[3]
Histidine	2.03±0.05	1.70±0.09[2]	2.93±0.03[2]	2.61±0.04[2]	2.86±0.14[2]			2.66±0.06[2]

Note. Number of animals given in parentheses. [2] $P < 0.01$; [3] $P > 0.05$.

TABLE 2. Content of RNA and DNA in Brain Tissue at Various Times after Administration of Chlorpromazine (in μg% P/100 mg tissue)

Nucleic acid	Control (healthy animals)	Time after administration of chlorpromazine			
		2 h	4 h	6 h	24 h
RNA	24.2±0.8	32.3±0.3[2]	24.5±1.0[3]	20.1±2.0[3]	22.2±0.3[2]
DNA	9.0±0.3	11.7±0.5[2]	11.3±0.6[2]	10.3±0.55[2]	10.2±0.4[2]
	(12)	(9)	(7)	(8)	(7)

Continuation

Nucleic acid	Control (healthy animals)	Time after administration of chlorpromazine			
RNA	24.2±0.8	26.6±1.3[3]	25.9±1.0[3]	27.1±0.9[2]	22.1±0.55[2]
DNA	9.0±0.3	9.2±0.3[3]	9.2±0.3[3]	9.8±0.15[2]	10.5±0.3[2]
	(12)	(11)	(11)	(11)	(11)

Note. Number of animals given in parentheses. [2] $P < 0.02$; [3] $P > 0.05$.

the 24 h after administration of chlorpromazine its concentration was higher than normal, but later it returned to normal. The results thus demonstrate that changes in the content of free amino acids, RNA, and DNA in brain tissue are most marked in the first hours after administration of chlorpromazine. The changes consist basically of an increase in the concentration of nonessential amino acids and a decrease in the concentration of essential amino acids. Prolonged administration of chlorpromazine had no significant effects on the level of amino acids, RNA, and DNA. The results obtained do not support conclusions previously reached according to which chlorpromazine depresses nitrogen metabolism in the central nervous system.

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