CHARACTERISTICS OF ANTI-BRAIN HETEROANTIBODIES IN THE SERUM OF PATIENTS WITH NERVOUS AND MENTAL DISEASES

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Previous investigations have shown that the sera of certain patients with nervous and mental diseases contain antibodies reacting selectively with saline extracts of heterologous brain [1, 4, 5]. Rat's brain tissues were used for the preparation of these antigens. In the present study we investigated the activity of sera towards antigens from the brain tissue of other species of animals and also certain properties of these heteroantibodies: their ability to undergo absorption by brain tissues, and also their distribution in the serum protein fractions.

EXPERIMENTAL METHOD

The antigens were saline extracts of the brain of man and certain species of animals; for control purposes extracts of liver and, in some cases, other tissues were investigated. The technique of obtaining the extracts was described previously [3]. Antigens from human brain were obtained separately from various morphological structures; to obtain extracts from the dog's brain tissues were taken from the hemispheres (white and gray matter together), and the whole brain of the small animals was taken.

The investigation made use of the method of complement fixation in the cold; the total volume of ingredients was 1 ml, and the dose of complement was 170% of the titer determined in warm conditions. The results were read after hemolysis had taken place in the controls. The test serum was investigated in various dilutions with a constant dose of antigen – about 0.4 mg of protein/ml; in some experiments the serum was investigated in a dilution of 1:20 with different doses of antigen containing protein in amounts of about 1.6, 0.8, 0.4, and 0.2 mg/ml (designated I, II, III, and IV respectively in the tables). In the absorption experiments, to one volume of residue of repeatedly washed tissue homogenate was added 4 times its volume of noninactivated test serum in a dilution of 1:5, and after 1 h the mixture was centrifuged at 4000 rpm. Before the experiment the absorbed and initial sera were heated to 56° for 30 min.

To study the distribution of antibodies in the serum protein fractions the method of treatment of the serum with rivanol [6] was used. To one volume of noninactivated serum was added 3.5 volumes of 0.4% rivanol solution, and after 10 min the mixture was centrifuged. The supernatant fluid (fraction I) was treated with powdered activated charcoal, and the residue (fraction II) was dissolved in a definite volume of physiological saline with a phosphate buffer (pH 7.4) in the presence of charcoal; the charcoal was removed by centrifugation. Before the experiment, both fractions and the original serum were heated to 56° for 30 min.

EXPERIMENTAL RESULTS

The results of the investigation of the sera of 7 patients and of one immune serum (No. 178), obtained from a horse after injection of a suspension of mouse brain and containing antibodies to the brain of several different species of animals [2], are given in Table 1. The investigation of this immune serum and also of the serum of patient I, which reacted specificially with antigens from the brain of various species of animals (except fish), was carried out

TABLE 1. Complement-Fixing Activity of Sera in Relation to Saline Extracts of Brain Tissues of Various Species of Animals

Serum	Dilution of serum	Dose of antigen	Antigens from brain of a								
			rat	mouse	hamster	man	dog	rabbit	guinea pig	bird	fish (carp)
Ch	1:10	III	+++(+)	++++		–[1]	–	±	–		
	1:20		++(+)	++++		±	–	±	±		
	1:40		++	+++		–	–	±	±		
	1:80		++	++		–	–	–	–		
S	1:10	III	++++			+[1]				–[3]	
	1:20		+++			±				–	
	1:40		++(+)			±				–	
	1:80		+			–				–	
R	1:9	III	++++			–[2]			–		
	1:18		++++			–			–		
	1:36		++++			–			–		
	1:72		++								
M	1:10	III	++++			–[1]				–[3]	
	1:20		++++			–				–	
	1:40		+++			–				–	
	1:80		+			–				–	
	1:20	I	+++(+)	+++		+[1]					–
		II	+++	++(+)		–					–
		III	+++	++		–					–
		IV	++(+)	++		–					–
G	1:10	III	++++	++++		–[2]		–			
	1:20		++++	++++		–					
	1:40		++	++(+)		–		–			
	1:80		–	–		–		–			
	1:20	I	++++	+++	+++(+)	–[2]	–	–	++++	–[3]	–
		II	++(+)	++(+)	++	–	–	–	++(+)	–	
		III	+(+)	++	+(+)	–	–	–	–	–	
		IV	±	+	+	–	–	–	–	–	
Rv	1:20	I	++(+)	+++(+)	+++	±[2]	+			++[4]	–
		II	+(+)	++(+)	++(+)	–	–			±	–
		III	+	+(+)	+	–	–			–	–
		IV	±	+		–	–			–	–
Control Serum of patient I	1:20	I	++(+)	++++	+++	+++[2]	+++(+)			+++(+)[4]	–
		II	++	+++(+)	++(+)	++(+)	+++			+++	–
		III	+(+)	+++	+	++	++			+(+)	–
		IV	±	++	–	+	+			+	–
No. 178	1:20	I	++++	++++	++++	++++[2]	++++			+++(+)	++++
		II	++++	++++	++++	++++	+++(+)			+++(+)	++++
		III	++++	++++	++++	+++	+++			+++(+)	+++
		IV	++++	++++	++++	++(+)	++			++	++(+)

Notes (for all tables). 1. The doses of antigen containing protein in amounts of 1.6, 0.8, 0.4, and 0.2 mg/ml are designated I, II, III, and IV respectively. 2. The degrees of the positive reaction are denoted by ++++, +++(+), +++, ++(+), ++, +(+), and +, a doubtful reaction by ±, and a negative reaction by –.

[1]Antigen from the frontal lobe.

[2]Antigen from the thalamus.

[3]Antigen from the brain of a duck.

[4]Antigen from the brain of a hazel hen.

TABLE 2. Immunological Activity of Serum in Relation to Antigens from the Brain of Different Species of Animals from Results of Absorption Experiments

Serum	Dilution of serum	Dose of antigen	Antigens from brain of a					
			rat	mouse	guinea pig	rabbit	dog	man
Original	1:20	I	++++	++++	++++	−	+(+)	−
		II	++++	++++	+++	−	±	−
		III	+++	+++	±	−	−	−
		IV	++	+(+)	−	−	−	−
After absorption by tissues of the	1:20	I	−	−	−	−	−	−
		II	−	−	−	−	−	−
		III	−	−	−	−	−	−
		IV	−	−	−	−	−	−
Mouse's liver	1:20	I	+++	+++(+)	−	−	−	−
		II	++	++	−	−	−	−
		III	+	+	−	−	−	−
		IV	−	±	−	−	−	−
Duck's brain	1:20	I	++++	+++(+)	++++	−	−	−
		II	++++	+++	++(+)	−	−	−
		III	++(+)	++(+)	−	−	−	−
		IV	+	++	−	−	−	−
Human brain	1:20	I	++++	+++(+)	++++	−	+(+)	−
		II	++++	+++	+++	−	±	−
		III	++(+)	++(+)	−	−	−	−
		IV	+	++	−	−	−	−

TABLE 3. Immunological Activity of Fractions Obtained by Rivanol Treatment of Serum

Serum	Electrophoretic characteristics	Antigens from rat's tissues	Dilution of serum			
			1:9	1:18	1:36	1:72
Original	Albumins, α-, β-, and γ-globulins	Brain	++++	++++	+++	+
		Liver	−	−	−	−
Fraction I	γ- and, partly, β-globulins	Brain	+++(+)	+++	++	+
		Liver	−	−	−	−
Fraction II	Albumins, α- and β-globulins	Brain	±	−	−	−
		Liver	−	−	−	−

to verify the activity of the antigens. It is clear from Table 1 that the sera of specimens Ch–Rv did not react with antigens from human brain, but reacted well with extracts of the brain of the rat (Ch–Rv), mouse (Ch, M, G, Rv), and hamster (G and Rv). The sera did not react with antigens from the brain of the dog (Ch, G, Rv), rabbit (Ch, G), bird (S. M, G), or carp (M, Rv); with antigens from the brain of the guinea pig the reaction either was absent (Ch, R) or was weaker than with the antigens from the brain of the rat, mouse, and hamster (G). It was concluded from the negative results of the investigation of the sera with antigens from the liver of the rat and mouse, and also with the extracts of the kidney, spleen, intestine, and testis of the rat, that the reaction with antigens from the brain was specific.

Experiments (the result of one of which is given in Table 2) showed that the brain tissues of those species of animals, extracts of whose brain tissues reacted with the patients' sera, possessed absorptive activity.

The anti-brain heteroantibodies in the serum of the patients were evidently bound with γ-globulins, as demonstrated by the results of investigation of the fractions obtained by the method of treating the serum with rivanol (Table 3).

Hence, it was found that the serum of certain patients with nervous and mental diseases contains antibodies showing selective activity towards saline extracted antigens from the brain tissues of various species of animals – mouse, rat, and hamster. The suggestion has previously been made [4, 5] that destructive processes in the brain tissue at various stages of the disease may lead to autoimmunization of the organism by brain antigens of different nature. It may be postulated from the results described above that the human brain contains, not only antigens common to all species of animals, but also antigenic substances having the greatest degree of resemblance to the brain antigens of certain species of animals, namely the rat, mouse, hamster, and possibly other species not yet investigated. It is possible that the metabolic products of human brain tissue in certain pathological states resemble the specific antigens of the brain of these species of animals. Whether anti-brain heteroantibodies appear as a result of autoimmunization with the normal heteroantigens of the diseased brain or with heteroantigens arising in pathological conditions is not yet certain. Nevertheless, the very fact that these antibodies do appear is, in our opinion, of more than theoretical interest: it requires further study to assess the stage and intensity of the pathological process in nervous and mental diseases.

SUMMARY

Anticerebral heteroantibodies, found in the serum of some patients with nervous and mental diseases; show an elective activity with respect to antigens produced from the brain of rats, mice and hamsters and are inactive or slightly active against antigens contained in the brain of humans, guinea pigs, dogs, rabbits, birds and fish. The above antibodies appear mainly a serum γ-globulin fraction. It is presumed that the cerebral tissue of mice, rats, hamsters includes a specific heterogenic antigen, similar to some, as yet little known antigenic brain structures in man. The appearance of anticerebral antibodies against human serum comes as a result of destructive processes, affecting corresponding heterogenic substances of the human brain. The selective reaction of the sera obtained from patients with brain extracts of mice, rat and hamsters is caused by the high level of these heterogenous antigens in the cerebral tissue of these animal species.

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