EFFECT OF SERA WITH BRAIN ANTIBODIES ON PENETRATION OF A THERAPEUTIC SUBSTANCE INTO RAT BRAIN TISSUE

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Sera of rabbits immunized with rat brain tissue and sera of patients with nervous and mental diseases containing brain antibodies, if injected into rats simultaneously with isoniazid, modify the rate of penetration of this drug into the brain.

* * *

Brain antibodies have been shown to have the power of localizing microbial infection in the brain tissues and also of modifying the action of viral antisera in relation to infection with neurotropic virus [4, 6]. It was therefore interesting to study the action of brain antibodies on the penetration of therapeutic substances into the brain.

The antituberculous drug isoniazid (isonicotinic acid hydrazide), a substance penetrating readily through the tissue barriers and easily determined in the tissues, was used in the present investigation.

EXPERIMENTAL METHOD

The action of immune and normal rabbit sera and the sera of patients with nervous and mental diseases was investigated [3-5]. The content of brain antibodies was determined by means of the complement fixation reaction with antigen preparations from rat brain tissue [3, 5]. Three rats of the same sex and weight were given an intramuscular injection of 1% isoniazid solution (50 mg/kg body weight) accompanied by the test serum or physiological saline (control; 1 ml/150 g body weight). Injections were given daily for 6 days, enabling maximal changes to be detected in the intensity of penetration of isoniazid into the brain. The animals were sacrificed 2 h after the last injection and the isoniazid content in the brain tissues determined by the method described in [1], using the FEK-M photoelectric colorimeter. The isoniazid content was expressed in μg/g weight of brain and also as a percentage of the control value.

EXPERIMENTAL RESULTS

In the experiments of series I the rate of penetration of isoniazid into the brain under the influence of large doses of immune sera was investigated. The sera were inactivated at 63° and treated with 0.4% rivanol solution [9] in a ratio of 1:1 to reduce the protein content. The action of four series of immune sera with titers of brain antibodies between 1:80 and 1:320* and of four series of normal rabbit sera was investigated. It was found that brain antisera, given in this dosage, reduced the penetration of isoniazid into the brain tissues compared with the control values and also with the action of normal serum, on the average by 32 and 25.8% respectively ($P < 0.01$†; Fig. 1).

Since it is well known that tissue antisera in small doses exert an action on tissue function which is directly opposite to the action of large doses [8], the rate of penetration of isoniazid into the brain was also

*The titer was taken to be the dilution in which a reaction of not less than ++ was obtained.
†See the paper by L. S. Kaminskii [2].

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TABLE 1. Effect of Serum of Patients with Various Immunologic Characteristics on Penetration of Isoniazid into Rat Brain Tissues

Exp. No.	Patient	Diagnosis	Results of CFR with rat brain preparation			Content of isoniazid in brain tissues (in percent of control)
			I	II	III	
1	Sh	Psychopathia	—	1:20 +++	1:40 +++	153.8
	G	Schizophrenia	—	—	—	123
2	K	Schizophrenia	—	1:40 ++	1:40 ++++	200
	S	Mentally healthy	—	—	—	144
3	K	Schizophrenia[1]	1:80 ++	1:10 (++)	1:20 ++	145
	D	" "	—	—	—	122.7
4	M	Severe psychopathia	—	1:40 ++	1:40 ++(+)	220
	U	Schizophrenia	—	—	—	122.7
5	O	Alcoholism, rheumatic fever	1:40 ++	1:40 ++	0	144.4
	B	Schizophrenia	—	—	0	100
6	M	Residual effects of head injury[3]	1:80 +++(+)	—	0	181.2
	R	Schizophrenia	—	—	0	125
7	M	Schizophrenia[2]	1:80 ++	0	0	150
	Sh	" "	—	0	0	116,6

Legend: I) saline extract; II) mitochondria; III) lipoid extract; 0) not investigated. 1, 2, 3) treatment with insulin, chlorpromazine, and stelazine respectively.

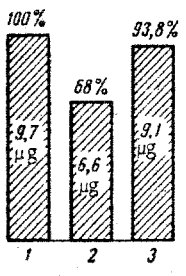

Fig. 1. Action of large doses of immune and normal rabbit sera on penetration of isoniazid into the brain. 1) Content of isoniazid in brain tissues of control rats; 2) after injection of immune sera; 3) after injection of normal sera.

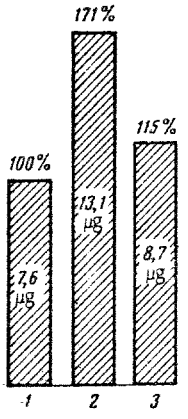

Fig. 2. Action of small doses of immune and normal rabit sera on penetration of isoniazid into the brain. Legend as in Fig. 1.

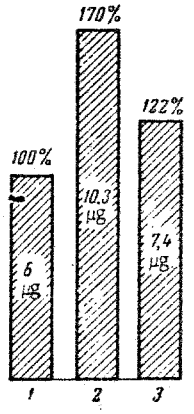

Fig. 3. Mean data showing action of patients' sera on penetration of isoniazid into the brain. 1) Isoniazid content in brain tissues of control rats; 2) after injection of sera containing antibodies; 3) after injection of sera without antibodies.

investigated under the influence of smaller concentrations of sera, namely 1:50 (in some experiments 1:20-1:800). Seven series of immune sera with titers of brain antibodies ranging from 1:40 to 1:800 were tested in 22 experiments. The action of 6 series of normal rabbit sera and one series of liver antiserum was studied in 12 control experiments. These experiments showed (Fig. 2) that the rate of penetration of isoniazid into the brain under the influence of brain antisera was higher than in the control series and also higher than the rate of its penetration into the brain under the influence of normal sera and of liver antiserum on the average by 71 and 56% respectively ($P < 0.01$). Normal rabbit sera increased the penetration of isoniazid into the brain by only 15% (mean value) compared with the control ($P < 0.01$).

The results of investigation of the serum of 14 persons admitted to hospital for nervous and mental diseases are illustrated in Table 1 and Fig. 3 (7 sera with complement-fixing antibodies against rat brain preparations, 7 sera without antibodies).

The sera were inactivated at 56° and injected in a dilution of 1:5. Sera with antibodies were found to increase penetration of isoniazid into the brain on the average by 70 and 48% compared with the control and with the action of sera without antibodies ($P < 0.01$). However, the latter also increased the penetration of isoniazid into the brain to some extent compared with the control (on the average by 22%; $P < 0.01$).

The results of this investigation thus showed that sera with brain antibodies can modify the rate of penetration of a drug into the brain. The mechanism of this effect is not yet clear, just as the essential mechanism of the effect of tissue antibodies on the function of the tissues has not yet been discovered. This action may perhaps be based on some effect of antibodies on metabolic processes in subcellular structures containing the corresponding organ-specific antigens [7].

It is probable that so-called normal antibodies may have some action on the rate of penetration of a drug into the tissues, and this may partly explain our results indicating changes in the isoniazid content in the brain tissues under the influence of normal sera.

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