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A. I. Krasnova

INFLUENCE OF THE BLOOD SERUM OF SCHIZOPHRENICS ON CARBOHYDRATE EXCHANGE IN THE ERYTHROCYTES OF CHICKENS

Although many investigations have been devoted to carbohydrate exchange in schizophrenics, the changes characteristic of this illness have not yet been discovered. Experimental investigations have been more successful. It has been established that changes at various points of carbohydrate exchange occur in living single-celled organisms or isolated mammalian cells under the influence of the blood serum of schizophrenics. For example, it has been demonstrated that the blood serum of schizophrenics inhibits breathing in yeasts and glucose absorption in experiments on the diaphragm and retina in rats in vitro (1-4).

Frohman et al (5-7) showed that the blood serum of schizophrenics incubated with chicken erythrocytes evokes disturbances in carbohydrate exchange in the latter. The authors consider this phenomenon to be characteristic of schizophrenics. However, these data were not confirmed by later experiments (8, 9).

In this investigation we have attempted to elucidate the biological characteristics of the blood serum of schizophrenics as compared with the serum of healthy people, as well as to characterize certain traits of the biologically active factor present in the serum of schizophrenics. The index of the latter was the content of the intermediate products of glucose exchange – pyroracemic and lactic acid. By studying the content of these products of exchange, it is possible to a degree to estimate the intensity of glucose disintegration.

Taking into account the heterogeneity of the data obtained by various authors regarding this problem and assuming that the reason for it may be a difference in the clinical principles of the choice of material for investigation, we put the primary emphasis on the clinical aspect. Schizophrenia was divided into two basic types: chronic (nuclear forms and paranoia)

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and periodic (oneirodynia catatonia, circular, and depressive-paranoid).

Of those studied, 160 were patients with various forms of schizophrenia, 22 were healthy, and 54 were patients with other mental illnesses.

Blood was taken in the morning before the subjects had eaten, and was defibriginated; the serum was immediately separated by a centrifuge under 4° in the course of 30 minutes at 1500 rotations/minute. Not more than an hour passed from the moment the blood was taken to the beginning of the experiment. The patients were studied before the beginning of treatment or after a pause in treatment of not less than two weeks. Patients were chosen who did not exhibit signs of somatic disturbances.

The chicken erythrocytes were prepared in the following way: 12 to 13 ml. of blood were taken from the comb of chickens. It was put into a test tube with three ml. of 3.2% solution of sodium citrate. The blood was immediately centrifuged, the plasm removed, and the erythrocytes washed thoroughly once by three volumes of physiological solution. After a ten-minute centrifugation, the saline solution was removed and the cells were weighed in two volumes of Krebs-Ringer solution; four ml. of this suspension were added to one ml. of the subject's serum.

In the control trial one ml. of serum was added to four ml. of a mixture consisting of one volume of physiological solution and two volumes of Krebs-Ringer solution. The purpose of the control test was to determine the contents of lactic and pyroracemic acid in the serum itself.

The experimental and control tests were incubated in a thermostat at 37° for one hour. After incubation the protein in the experimental and control tests precipitated to equal volumes of ten per cent solutions of trichloroacetic acid and the content of lactic and pyroacemic acid was determined in the non-protein filtrate (10, 11). The product of lactic and pyroracemic acid was found according to the difference between the experimental and control solutions as well as the correlation between them, i.e., the coefficient of lactate/piruvate was calculated.

The results were analyzed, using the variation statistics (12), for which the coefficient of reliability T was calculated. If the coefficient of reliability of the difference between two compared groups is no greater than 2, we can speak of chance changes; if it is greater than 2 but smaller than 3 – of probable changes. If the coefficient is greater than 3, the results are considered reliable.

Our results are presented in Table 1.

As can be seen from the table, the same amount of pyroracemic acid (48.1 ± 4.2 μg) is formed under the influence of the serum of healthy chicken erythrocytes in an incubated combination and the serum of patients of the control group (46 ± 6.0 μg). When the erythrocytes are incubated with the serum of schizophrenics, less pyroracemic acid is formed (32.3 ± 1.8 μg); this comparative decrease is statistically reliable.

The mean magnitude of lactic acid production under the influence of blood serum of schizophrenics was somewhat greater than in the control.

Lactate/piruvate coefficient changes were more marked. Under the influence of the serum of schizophrenics, the mean magnitude of this coefficient (7.2 ± 0.4) reliably increased (at the expense of reduction of pyroracemic acid formation) in comparison with the coefficient under the influence of serum of the healthy (4.2 ± 0.4) and patient control groups (4.9 ± 0.8).

It is interesting to examine the changes of this coefficient under the influence of the serum of various groups of schizophrenics (Table 2). The magnitude of the coefficient scarcely differed from the healthy group in those under the influence of the serum of the patient control group (epileptics, alcoholics, and those with Pick's disease). Among the epileptics we studied patients in a state of twilight dullness of consciousness and the epileptic state, as well as those in the interparoxysmal period. Chronic alcoholics were studied in delirium and chronic hallucinosis. The magnitude of the coefficient in all cases did not exceed the normal coefficient.

Table 1

Influence of Blood Serum of Investigated Groups on Carbohydrate Exchange in Chicken Erythrocytes (Mean Data)

	Healthy	Patient control group	Schizophrenics
Number of subjects	22	54	160
Products of lactic acid (in μg to 1 ml cells)	180 ± 24	207 ± 21	215 + 17
Products of pyroracemic acid (in μg to 1 ml cells)	48.1 ± 4.2	46.2 ± 6.0	32.3 ± 1.8
Coefficient lactate/ piruvate	4.2 ± 0.4	4.9 ± 0.8	7.2 ± 0.4

Table 2

Influence of the Serum of Patients on Coefficient Changes of Lactate/Piruvate

Control group	Number of subjects	Coefficient
Healthy	22	4.2 ± 0.4
Pick's disease	8	3.9 ± 0.7
Manic-depressive	9	6.2 ± 0.7
Epilepsy	8	4.5 ± 0.5
Chronic alcoholism	8	4.6 ± 1.1
Others	21	5.9 ± 0.6
Schizophrenics		
Periodic	66	7.4 ± 0.4
oneirodynic catatonia	19	8.9 ± 0.6
circular	25	6.1 ± 0.7
depressive-paranoid	22	6.8 ± 0.8
Chronic		
paranoid form	33	6.9 ± 0.8
paranoial stage	7	8.9 ± 0.7
paranoid stage	21	7.0 ± 0.7
final paranoid stage	5	5.9 ± 1.3
Nuclear forms	61	6.6 ± 0.4
weakly flowing	16	6.4 ± 0.9
hebephrinic	10	7.9 ± 0.9
simple	12	5.1 ± 0.6
early paranoic	23	6.7 ± 0.5

With the serum of manic-depressives a probable but not reliable increase in the coefficient was established in comparison with its magnitude under the influence of blood serum of healthy subjects (T = 2.5). In a series of cases a high coefficient was observed, but the difference influenced by depressive and manic fits did not lend itself to analysis.

In comparing the influence of the serum of patients with periodic and acute types, it appeared that although the coefficient of lactate / piruvate was somewhat greater than when under the influence of the serum of healthy subjects, the difference was unreliable. In the former situation both high and low coefficients were observed in individual cases. Therefore, the results of the investigation were compared according to various clinical forms within the framework of these two large groups.

The largest coefficient (8.0 ± 0.6) was established for patients with periodic schizophrenia during oneirodynic catatonia. This was reliable in comparison with the group of healthy subjects (T = 6.6). A slightly lower coefficient was noted under the influence of the serum of patients with a depressive-paranoid form (6.8 ± 0.8). This coefficient was almost reliable (T = 2.9) when compared with healthy subjects. There was almost no difference in the lactate/ piruvate coefficient (6.1 ± 0.7) between circular schizophrenics and normal subjects.

In the analysis of the group with chronic schizophrenia, the following was noted. In the paranoid form the highest coefficient (8.9 ± 0.7) was established in the paranoial stage. This coefficient was reliable (T = 5.7) in comparison with healthy subjects. In the paranoid stage the coefficient (7.0 ± 0.7) was also raised in comparison with healthy subjects (T = 3.4) However, it was not possible to establish reliable differences of the indices for patients at the paranoial and paranoid stages (T = 2.1). At the final stage of paranoid schizophrenia the coefficient (5.9 ± 1.3) was lower.

Thus, within the paranoid form of schizophrenia we were able to discover a relation between the size of the coefficient lactate/ piruvate and the stage of the schizophrenic process. Patients at the beginning stage of the disease had a larger coefficient. As the disease developed the coefficient decreased.

The coefficient lactate/ piruvate was not established in all cases among patients with nuclear forms of schizophrenia. The greatest coefficient was noted in hebephrenic (7.9 ± 0.9) and early paranoid (6.7 ± 0.5) forms. This was statistically reliable in comparison with the index of healthy subjects (T = 3.7 and 3.9, respectively). In inertly flowing forms the coefficient lactate/ piruvate was somewhat higher (6.4 ± 0.9) than in healthy subjects (T = 2.2); in patients with simple form this coefficient (5.1 ± 0.6) did not differ from healthy subjects.

Consequently, in especially malignant schizophrenic processes, namely, hebephrenic and early paranoid forms, the coefficient was higher than in inertly flowing forms.

Five pairs of twins were also investigated (three pairs of identical twins and two pairs of fraternal twins). The identical twins were schizophrenic and exhibited the same form of schizophrenia. Of the fraternal twins, one in each pair was schizophrenic, the other was practically healthy. According to the preliminary data the lactate/ piruvate coefficient was in the mean significantly higher in all five pairs of twins (8.2 ± 1.0) than in healthy subjects, but higher in the identical twins than in the fraternal twins. For the identical twins it was, respectively, 12.4 and 10.8, 9.5 and 12.7, 8.9 and 4.5; in the fraternal twins: 6.0 and 4.2, 7.8 and 4.8 (the lowest coefficient in both cases was noted under the influence of the serum of the healthy twin). In individual cases the practically healthy parents of the twins were investigated. They did not exhibit heightened lactate/ piruvate coefficient. These were the preliminary data. At the present time the work is being continued (a wider group of parents is being investigated, both directly and indirectly).

In this work an attempt was also made to elucidate certain biologically active factors of the blood serum of schizophrenics which evoke changes in the carbohydrate exchange in chicken erythrocytes. The serum was initially subjected to various physical and chemical influences.

Table 3

Influence of the Storage Period of Serum on the Size of the Lactate/ Piruvate Coefficient

Storage Temperature	Patient	Coefficient		Duration of Storage
		Fresh Serum	Stored Serum	
4°	G-na	5.7	5.6	1 day
	S-r	9.0	9.2	3 days
	K-va	6.6	6.6	3 days
	G-ra	5.4	5.9	4 days
	I-aia	4.0	4.6	4 days
	Kh-n	11.6	12.1	5 days
			7.7	14 days
	T-o	7.8	5.4	8 days
	K-pa	12.1	3.8	14 days
	G-d	6.9	2.5	20 days
	A-va	13.1	3.7	29 days
	G-va	7.4	3.2	35 days
	G-n	9.7	6.0	6 days
			3.0	9 days
	A-va	10.4	8.6	10 days
			3.5	30 days
	L-ts	9.3	6.1	11 days
	S-o	9.9	5.2	27 days
Room	P-va	3.7	3.4	3 hours
	A-va	9.9	10.1	3 hours
			5.9	24 hours
	L-va	7.5	4.2	24 hours
	A-n	8.5	3.5	24 hours
56°	D-n	9.6	5.7	30 minutes
	F-ov	6.5	4.6	30 minutes
	G-ov	7.8	6.3	30 minutes
	Z-ov	6.3	3.0	30 minutes
	K-ov	5.1	3.3	30 minutes
-30°	L-va	7.5	4.0	30 minutes

The biologically active factor in the blood serum of schizophrenics turned out to be thermolabile. Its influence disappeared when the serum was heated for 30 minutes at 56° and when it was frozen at 30° (Table 3).

Storage of serum at 4° led to gradual reduction of its biological action. If the biological activity of the serum did not change in the course of the first three to five days, it was reduced when kept in storage under these

conditions for a longer period, and within five to six days completely disappeared (see Table 3). The serum's activity was reduced even more quickly when stored at room temperature: it was retained for three hours under these conditions but disappeared within 24 hours.

In view of the instability and thermolability of this factor, we can assume that its activity may be linked with proteinic substances.

The attempt was made to determine the nature of the factor of blood serum which evokes the disturbance of carbohydrate exchange in chicken erythrocytes. The method of preparative electrophoresis was conducted in the pure form α-, β- and γ- globulins of the blood serum.* Each of the proteinic fractions obtained from the blood serum of healthy subjects and schizophrenics was tested for its influence on the carbohydrate exchange. The concentration of protein in each fraction was identical. The data of this series of experiments are presented in Table 4. It is apparent from this table that the lactate/ piruvate coefficient for the α- and γ-globulin fractions is the same for both healthy subjects and schizophrenics. A marked difference is observed only in the β-globulin fraction. For that fraction the coefficient was 5.0 for the healthy subjects and 16.2 for the schizophrenics – i.e., three times higher.

Thus it may be assumed that the effect discovered in the blood serum of schizophrenics is linked with the β-globulin fraction.

The data permit us to draw a preliminary conclusion: blood serum of schizophrenics, as distinguished from that of healthy subjects and patients with a series of other mental illnesses, evoked disturbance of carbohydrate exchange that manifests itself in an increased lactate/ piruvate coefficient in an incubated mixture of chicken erythrocytes. The compared results of the respective groups of patients indicated that increase in the coefficient does not depend on the acuity of the psychosis, since it appears under the influence of the serum of patients with

*Fractionation of serum proteins was conducted by D. V. Lozovskii on an apparatus for preparative electrophoresis type EFP-2.

Table 4

Influence of Various Proteinic Fractions of the Blood Serum on the Lactate/ Piruvate Coefficient

	Healthy	Schizophrenics
	Coefficients	
Fresh serum	4.7	11.3
α-globulin	2.6	3.2
β-globulin	5.0	16.2
γ-globulin	3.7	3.7

oneirodynic catatonia, as well as hebephrenic and early paranoid forms.

The mean magnitude of the action of the serum from the control patient group did not differ from the action of the serum of healthy subjects. However, serum action of certain manic-depressives, progressive paralytics, and chronic alcoholics was the same as that of the schizophrenics. Therefore, increase of lactate/piruvate coefficients cannot be considered as strictly specific to schizophrenics. At the same time it is characteristic of that disease, since it was noted reliably more often in patients with this disease than in patients with other mental illnesses.

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