The increase in uptake and degradation of pepsin-modified ^{125}I-LDL by macrophages may indicate their greater atherogenicity. This conclusion is supported by the parallel, described in the literature, between protein degradation processes and intracellular accumulation of cholesterol esters in macrophages incubated with acetylated LDL [9].

The use of pepsin to modify LDL is convenient in the respect that it is inactivated by simple neutralization of the medium; consequently, there is no need to remove it before adding the LDL to the cell culture. At the same time, as had already been stated, pepsin is a close analog of cathepsin D. We know that cathepsin D acts on LDL [2] and may modify lipoproteins when cells are destroyed as a result of inflammatory and other pathological processes [12].

The results are thus evidence in support of the view that enzymatically modified LDL possess higher atherogenicity than native.

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ANTENATAL PREVENTION BY LITHIUM HYDROXYBUTYRATE OF DEVELOPMENTAL CHANGES INDUCED IN THE RAT BRAIN BY SERUM FROM SCHIZOPHRENIC PATIENTS

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KEY WORDS: lithium hydroxybutyrate; serum from schizophrenic patients; antenatal period; rat brain.

The antenatal effects of most drugs are generally assessed from the standpoint of their possible adverse effects on the pregnant mother and fetus. Data on the stimulating effect of lithium hydroxybutyrate (LHB), administered in the antenatal period, on ontogeny of the CNS [1], have suggested the possible use of LHB in the prevention of dysfunction and dysregulation of maturation of the CNS associated with the action of endotoxins and exotoxins.

The specific disturbance of metabolic mechanisms in schizophrenia is responsible for the appearance of factors of toxic nature in the blood [3, 14]. The so-called "maternal effect" — the significant increase in the number of children affected with schizophrenia in the progeny of an affected mother compared with the frequency of affected children in fami-

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TABLE 1. Effects of Antenatally Administered LHB and SSP on Body Weight, Development of Muscular Strength, and Posture Regaining Reflex in 5-Day-Old Rats, and Also on Body Weight, Locomotor Activity, and Edge Avoidance Reflex in 10-Day-Old Rats (M ± m)

Age of rats, days	Parameter	Control		LHB		LHB + SSP		SSP	
		males	females	males	females	males	females	males	females
5	Body weight, g	7,6±0,3	7,4±0,4	10,1±0,4	8,3±0,4	8,4±0,2	8,7±0,3	8,2±0,2	8,5±0,2
	Duration of holding on to horizontal rod, sec	5,8±0,6	5,3±0,8	11,6±1,3*	11,6±1,2*	19±1,3*	20,1±2,5*	8,6±2,3	10,3±1,7
	Rotation time on flat surface,	4,6±0,8	5,8±0,9	2,3±0,2*	2,8±0,3*	2,3±0,1*	2,1±0,1*	7,4±1,2	4,9±1,1
	Number of animals	14	13	25	22	17	8	12	8
10	Body weight, g	11,0±0,6	12,4±0,7	12,8±0,6	11,2±0,5	11,2±0,2	11,6±0,4	10,3±0,2	11,0±0,3
	Number of crossings from one square to another	2,4±0,4	1,3±0,3	5,8±0,8*	4,3±0,4*	9,3±0,8*	7,7±1,2*	2,5±0,3	1,7±0,4
	Edge avoidance reflex, %	92,3	91,7	100,0	100,0	100,0	100,0	66,7	100,0
	Number of animals	13	12	22	21	17	9	12	8

Legend. *P < 0.05 compared with control, **P < 0.05 for comparison of series III and IV.

lies in which only the father has schizophrenia [8] — is associated with these factors. The cytotoxic properties of the serum of schizophrenic patients (SSP) in relation to various cell cultures, especially of nerve cells [3, 5, 14], phenomena of neurotoxicity on injection of SSP into laboratory animals [9], and disturbances of catecholaminergic neurotransmission in the CNS [4] are known.

These data motivated the present investigation, the aim of which was to study the neuroembryotoxic effects of SSP in pregnant rats and the possibility of their prevention by LHB.

EXPERIMENTAL METHOD

Experiments were carried out on 27 noninbred albino rats weighing 180-220 g and on 145 young rats from their progenies.

There were four series of experiments: I) control: four pregnant rats, and their progeny of 37 young rats; II) six pregnant rats receiving LHB, and their progeny of 52 young rats; III) four pregnant rats receiving LHB and SSP, and their progeny of 36 young rats; IV) four pregnant rats receiving SSP, and their progeny of 20 young rats.

LHB was given *per os* by means of a tube in a dose of 5 mg/100 g body weight from the 1st through the 19th days of pregnancy. SSP was injected intraperitoneally in a dose 0.1 ml/100 g body weight every 3 days, starting with the 3rd day of pregnancy (six injections altogether).

On the 20th day of pregnancy the rats were transferred into individual cages. The animals of series I, II, and IV were born on the 22nd day of pregnancy, whereas the duration of pregnancy in the animals of series III was 23.30 ± 0.25 days. On the 5th day after birth the young rats were weighed; their muscular strength and movement coordination were studied by means of tests involving holding on to a horizontal rod and rotation on a flat surface. On the 10th day of postnatal development the young rats were weighed again and tested in a small open field: the number of crossings between squares was counted, the edge avoidance reflex determined, and the trend of the first rotations immediately after the young rats were placed in the open field identified. All the tests mentioned above were conducted during the first half of the day at 24-26°C with natural daylight.

The effects of the sera (SSP were obtained from the No. 3 Republican Psychiatric Hospital) from four male patients with schizophrenia (paranoid form, progressive type of course, mentally defective state), aged 42-67 years. The duration of the disease varied from 10 to 16 years. Serum from each donor was injected into one pregnant rat in series III and IV of the investigation.

EXPERIMENTAL RESULTS

It was found that SSP have toxic properties, and the degree of toxicity of the different sera varied. Serum No. 3 was the most toxic. In the rat receiving it (series IV) pregnancy

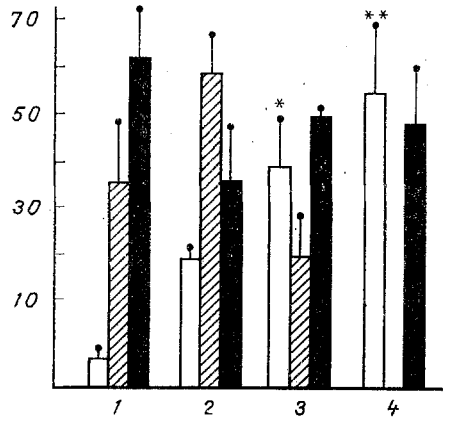

Fig. 1. Effect of antenatal LHB and SSP on distribution of 10-day-old rats depending on direction of first turns. Ordinate, number of rats (in %). Unshaded columns, rats turning left; obliquely shaded, symmetrical; black columns, rats turning right. 1) Control; 2) LHB; 3) LHB + SSP; 4) SSP. *P < 0.05 for comparison of series III and I, and III and II; **P < 0.05 for comparison of series IV and I.

was interrupted on the 14th-15th day, and in series III the rat died on the 3rd day after giving virth to young. The effect of the three other sera was identical, and the results of these experiments are pooled.

The number of young rats in the litter of the animals of series I, II, and III was 9.0 ± 0.8, 9.0 ± 0.4, and 8.3 ± 0.3, respectively, whereas in rats receiving only SSP during pregnancy, it was 6.7 ± 0.3.

The sex ratio in the litter of the experimental animals showed specific differences. In the animals of series III and IV there was a tendency for the absolute number of females in the litter to decrease (2.7 ± 0.9 and 2.7 ± 0.8, respectively) compared with rats of the control series (4.3 ± 0.3) and rats receiving LHB only (5.0 ± 0.6).

Compared with the control, the body weight of the 5-day-old rats of series II, III, and IV had a tendency to increase (Table 1). LHB significantly increased the length of times the rats held on to the horizontal rod (series II). Muscular strength had a tendency to increase also under the influence of SSP (series IV). In animals under the combined influence of LHB and SSP during antenatal development, muscular strength received its highest level, and as regards the duration of holding on to the horizontal rod, it amounted to the sum of the corresponding effects in the animals of series II and IV. SSP disturbed movement coordination of young male rats and increased the time of regaining the original posture when turned over on to their back. LHB, if given alone, shortened the time of this reflex. A similar effect was preserved against the background of SSP.

At the age of 10 days the rats of series II and III had greater motor activity than rats of series I and IV. Potentiation following combined administration led to the sum of corresponding effects of isolated administration of LHB and SSP to be exceeded. Progenies of rats treated with SSP in the antenatal period did not behave uniformly in the edge avoidance test; although this test was completely normal when performed on female rats, it was reproduced by only some of the male rats. LHB, given alone or together with SSP, completely preserved the edge avoidance reflex.

Investigation of the character of the first turns showed that SSP significantly disturbed the symmetry of behavior of 10-day-old rats (Fig. 1). In the litter of females receiving SSP during pregnancy there were no young rats with a symmetrical type of behavior, the relative number of rats turning to the left was considerably increased, and the number of rats turning to the right showed a tendency to increase. LHB corrected to some extent these effects of SSP, by reducing the number of left turners and causing the appearance of a group of rats with a symmetrical type of behavior.

SSP thus modified the antenatal ontogeny of the progeny of the rats. Besides evidence of embryotoxicity, inequality of development of individual CNS functions was observed. These effects of SSP were to a certain extent sex-dependent. A decrease in the number of females in the litter of rats receiving SSP could be due to injury and death of some fertilized ova. LHB did not influence this effect of SSP. "Selection" of the females in this way in the early stage of intrauterine development was responsible for increaed resistance of the rest to the action of SSP. Unlike females, SSP disturbed movement coordination and the perception of space in males, which could be corrected by antenatal administration of LHB.

The action of stressors or drugs stimulating skeletal muscle activity in the period of intrauterine development accelerates the formation of physiological functions in early postnatal ontogeny [2]. The presence of a "stressor" factor in the composition of SSP, leading to activation of spinal motor centers [7] provide an explanation of the mechanism of the stimulating effect of antenatally administered SSP and LHB on the muscular strength and motor activity of young rats.

We know that certain pathological processes in the CNS are either directly connected with dysfunction of one hemisphere or are directly related to the character of abnormal interhemispheric asymmetry [13]. In this connection, changes in lateralization of behavior in the progeny of the rats reflect the specific neuroembryotoxic action of SSP when administered antenatally. A similar effect of SSP may lie at the basis of dysfunction and dysregulation of CNS maturation in the progeny of schizophrenic mothers (the maternal effect). The peptide nature of CNS lateralization [6] and the effect of lithium on the distribution of brain peptides [10] indicate a positive causative connection between changes in the lateralization of behavior under the influence of SSP and their modulation by LHB. Meanwhile other possible mechanisms of the protective action of LHB against the neuroembryotoxic effect of SSP cannot be ruled out, such as the ability of lithium ions to correct disturbances of catecholaminergic neurotransmission, caused by antibrain antibodies of SSP [4], and to stabilize the enzyme systems of nerve tissue membranes [11, 12].

LHB, administered during pregnancy, can thus prevent to a certain extent disturbances of CNS maturation induced by SSP, through the more rapid formation of several motor and behavioral functions. Although the biological nature of this phenomenon requires further study, the results provide experimental justification for the possibility of antenatal prevention of some manifestations of disturbances of CNS ontogeny induced by SSP.

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