EFFECT OF LYSERGIC ACID DIETHYLAMIDE ON PERMEABILITY OF THE TISSUE-BLOOD BARRIERS IN RATS

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The study of the effect of lysergic acid diethylamide (LSD) on the permeability of the tissue barriers is of considerable interest both to the elucidation of the mode of action of the drug and to the assessment of changes in the barrier functions of the body in experimental psychotic states.

The information in the literature on the effect of LSD on the permeability of the tissue-blood barriers is scanty and conflicting [1, 6].

To assess the changes in the permeability of the blood-brain, blood-eye, and the parenchymatous barriers under the influence of LSD, the penetration of the radioactive isotope P^{32} into various parts of the brain, the aqueous of the eye, and the internal organs was studied in rats receiving different doses of this drug.

EXPERIMENTAL

Experiments were conducted on 18 male rats weighing 250-300 g with a stabilized conditioned running away reflex and on 12 control animals. LSD was given as a single intraperitoneal injection of the preparation Delysid (D-lysergic acid diethylamide tartrate) in doses of 0.1-3 mg/kg. Preliminary experiments showed that marked changes in behavior and motor activity and disappearance of the conditioned reflexes (with their reappearance 3 h later) took place only when LSD was given in a dose of 3 mg/kg. Doses of 0.1-1 mg/kg had a much smaller effect, and doses of 0.025-0.08 mg/kg had essentially no effect on the behavior, the motor activity, and the conditioned reflexes of the rats.

Control experiments showed that fixation on the bench and nociceptive stimulation (injections) had no effect on the stabilized conditioned reflexes.

After intravenous injection of P^{32} with a total activity of 8 μCi, the LSD solution was injected intraperitoneally. The animals' behavior was inspected in a transparent chamber, the spontaneous motor activity was investigated in a Knoll's motimeter [3], and the conditioned reflexes were studied.

One hour after injection of the isotope the animals were sacrificed by exsanguination, the vessels of the brain were perfused with physiological saline, and preparations from various parts of the brain, from the aqueous of the eye, and from the internal organs were made on targets 16 mm in diameter. The radioactivity of the samples was determined by means of a B-2 apparatus with a BFL-25 counter screened with lead. The ratio between the radioactivity of the tissue and the radioactivity of the blood taken at the same time was adopted, as the index of permeability.

EXPERIMENTAL RESULTS

In the experiment of series I on 10 rats, the action of LSD was studied in a dose of 3 mg/kg). The animals' behavior changed 1-3 min after the injection of LSD. They showed no orienting reaction, they performed frequent and random movements about the cell, the coordination of their movements was disturbed, and their tail was held out straight and rigid. The rats appeared timid, on guard, and sometimes aggressive; often they crowded into the corner of the cage, hiding behind one another. Their breathing was rapid and salivation was frequently observed. The spontaneous motor activity of eight rats was increased. The conditioned reflexes of all the animals were lost or disturbed: in response to 10 conditioned stimuli, between 5 and 10 conditioned reflexes failed to appear. Even after unconditioned reinforcement, the rats often failed to react to the next application of the conditioned stimulus.

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Penetration of P^{32} into Parts of the Brain and Internal Organs of Rats in Normal Conditions and after Injection of Various Doses of LSD (in % of activity in blood)

Tissue	Control	LSD in a dose of 3 mg/kg		LSD in a dose of 0.1 mg/kg	
Cerebral cortex	21,8±2,4	16,8±1,25	($P>0,05$)	27,6±4,55	($P>0,2$)
Olfactory lobes	26,7±3,2	21,5±1,47	($P>0,1$)	46,6±7,55	($P<0,05$)
White matter	12,4±1,6	10,6±1,57	($P>0,2$)	16,2±2,12	($P>0,1$)
Hippocampus	12,3±2,5	9,4±1,13	($P>0,2$)	20,2±3,22	($P>0,05$)
Hypothalamus	36,0±3,3	38,0±3,52	($P>0,5$)	66,0±6,56	($P<0,001$)
Pons	17,4±1,8	9,8±1,25	($P<0,01$)	16,4±2,82	($P>0,2$)
Medulla	11,6±1,1	12,5±1,89	($P>0,5$)	17,3±1,0	($P<0,01$)
Cerebellum	15,4±2,8	12,9±1,42	($P>0,2$)	29,2±3,77	($P<0,01$)
Corpora quadragemina	15,6±2,9	13,8±1,46	($P>0,5$)	27,9±3,52	($P<0,02$)
Basal ganglia	10,1±1,45	5,6±1,08	($P=0,02$)	22,2±4,45	($P<0,02$)
Brain homogenate	13,9±1,7	15,6±1,26	($P>0,5$)	26,5±4,62	($P<0,02$)
Pituitary	219±20,2	156±12,9	($P<0,02$)	281,0±18,7	($P<0,05$)
Aqueous of the eye	22,9±2,06	25,7±0,91	($P>0,2$)	26,3±3,95	($P>0,2$)
Kidney	914±66,2	524,3±24,5	($P<0,001$)	940±90,4	($P>0,5$)
Liver	999±107,2	604±72,5	($P<0,01$)	1 020±118,6	($P>0,5$)
Adrenals	469±30,1	462±46,3	($P>0,5$)	673±63,2	($P<0,01$)

The results of the investigation of the penetration of P^{32} into the brain showed that in nearly all parts there was a tendency for the P^{32} concentration to fall by comparison with its level in the control series. A statistically significant decrease in the accumulation of P^{32} was found in the basal ganglia, the pons, and the pituitary (see table). Hardly any of the isotope accumulated in the medulla. The concentration of P^{32} in the aqueous of the eye was considerably increased, while in the kidney and liver it was sharply reduced and in the adrenals it was unchanged after administration of LSD.

In the experiments of series II on eight rats, the action of a smaller dose of LSD (0.1 mg/kg) on the permeability of the tissue-blood barriers was investigated. After injection of the preparation, no significant changes were observed in the behavior of the animals. Usually, when untied from the frame the rats exhibited an orienting reaction both in the transparent cage and in the conditioned reflex chamber, after which they remained relatively still. No regular changes in motor activity could be observed. In the motimeter the spontaneous activity was depressed in 4 animals, increased in 3, and unchanged in one animal.

The rectal temperature in most animals was essentially unchanged, and it was raised in only two rats. The conditioned-reflex activity of the rats was undisturbed. In five animals the conditioned reflexes were completely intact, while in three rats between 1 and 3 of a group of 10 conditioned reflexes failed to appear.

Investigation of the P^{32} concentration in the brain showed a tendency for the accumulation of the isotope to be increased in nearly all its structures. The increase in radioactivity was greatest in the hypothalamus, the olfactory lobes, the cerebellum, the corpora quadrigemina, and the basal ganglia. The changes in the concentration of P^{32} in the cerebral cortex, the white matter and the hippocampus were not statistically significant ($P > 0.05$). Only in the pons was the relative radioactivity indistinguishable from its value in the control experiments. The concentration of P^{32} in the kidney and liver was essentially unchanged, while in the adrenals it was increased.

The results of these experiments show that the effect of LSD on the permeability of the tissue-blood barriers varies with the dose: in large doses inducing a psychosis-like state there was a tendency for the accumulation of P^{32} in the brain to be reduced; relatively small doses having no effect on the conditioned reflexes or behavior of the animals caused a marked increase in the incorporation of P^{32} into the brain structures. It may be assumed that the changes in the permeability of the blood-brain and other tissue-blood barriers under the influence of LSD are of essential importance in the mechanism of action of the preparation on the body.

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