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- USSR -

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DESCRIPTION OF AN EXPERIMENTAL PSYCHOSIS INDUCED BY LYSERGIC ACID DIETHYLAMIDE

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[Following is a translation of an article by R.A.Ivanova, K.A. Laricheva and G.I.Mil'shteyn (Moscow) in the Russian-language journal Zhurnal nevropatologii i psikhiatrii imeni S.S.Korsakova (Journal of Neuropathology and Psychiatry imeni S.S.Korsakov), Vol 62, No 9, 1962, pp.1359-1365, Submitted 10 May 1962.]

An analysis of the literature leads to the conclusion that the most correct approach to a study of experimental psychoses is an all-round physiological and biochemical investigation, which must necessarily include an evaluation of animal behavior on the basis of instrument findings.

The project treated here aimed at studying the effect of diethylamide of lysergic acid on certain types of trained behavior in dogs and on biochemical indicators which would to a certain degree describe the status of serotonin, acetylcholine and adrenalin metabolism.

The project involved mature dogs weighing 10 - 15 kilograms. Two tests were used to evaluate the animals' behavior. The first, which we shall call the "dog labyrinth", is based on a motor habit elaborated on

the basis of a feeding reaction. The variant of the "labyrinth" which we used consists of 7 sections separated from each other by different types of barriers. A training period of 4 to 6 weeks produced in the dogs a motor habit which consisted in running rapidly through the labyrinth (in 5 - 6 seconds) to the food (meat) in the last section. A quantitative evaluation of the drug tested requires consideration of the following indicators: effective dose, speed of passage through the labyrinth, length of interruption in the reaction already produced.

Among the methods intended for the study of animal behavior, those methods based on the avoidance reaction have become very widely used. In this study we reproduced the set-up developed by S.S.Krylov and Ye.A.Snegirev. The apparatus consisted of two chambers: an outer soundproof shell and an inner chamber divided by a low fence. Each half of the inner chamber had a mesh floor through which a 50-80 volt electric current passed intermittently, combined with conditioning signals (bell and bright light). The action of two stimuli (buzzer and pale light) was not reinforced by the electric current. After a training period of 1 - 2 months the dogs developed a conditioned reaction of current avoidance which consisted in jumping over the barrier which divided the inner chamber in response to the conditioning stimuli. The apparatus had a hooked-in system which made it possible to give signals automatically according to a prearranged stereotype program and record both signals and animal response reactions on the tape of an ink oscillograph.

The serotonin in the blood and in the brain was determined by the biological method described by Garven [1]. Monoaminoxydase activity in the brain was studied by Hope and Smith's method [2]. The ceruloplasmin content of blood serum was judged from the amount of copper measured by L.N.Lapin's method [3] and from oxidase activity (with relation to paraphenylenediamine) determined by Ravin's method [4]. The oxidation rate of serum adrenaline was measured by Leach and Heath's method [5], the amount of acetylcholine in the different segments of the brain was determined by a biological method on the rectus abdominalis muscle of a frog, and acetyl- and butyrylcholinesterase activity was determined by A.A.Pokrovskiy's method [6].

An aqueous solution of d-diethylamide of lysergic acid tartrate (Sandoz brand) was injected intramuscularly. In order to examine the brain the animals were killed by electric current 60 - 90 minutes after injection of the chemical.

Intramuscular injection of a 0.1 mg/kg dose of lysergic acid diethylamide did not cause noticeable clinical changes in the majority of the animals. With doses of 0.2 mg/kg and higher all animals showed more or less pronounced symptoms - restlessness or, on the contrary, lethargy, absence of or inadequate reaction to external stimuli, periodic barking without cause, ataxia, weakness of the extremities, particularly of the hindquarters. Not infrequently the animal would be frozen in one position for a long period of time with his muzzle pressed against the wall and whining at the same time. The animals showed fear of ordinary well-known objects. Dealing

with barriers (detouring) was difficult. This state lasted for varying periods of time from 1 to several hours.

The behavior pattern (getting through the labyrinth) was interrupted when lysergic acid diethylamide was administered in doses which, as a rule, did not cause any visible clinical changes. From the data cited in Table 1 we can see that a dosage ordinarily not having a pronounced effect on the clinical state of the dog (0.1 mg/kg) caused a break in the elaborated skill in all test animals. Within 15 minutes after the injection, 2 of 6 animals took considerably longer to thread the labyrinth (55 - 80 seconds instead of the normal 5 - 7) while the skill had been completely disrupted in the other 4 dogs. At the end of 30 minutes the skill had disappeared in all animals. There was spontaneous recovery in 4 dogs after a day, in 1 dog after 2 days and in 1 dog on the 5th day.

Lysergic acid diethylamide had a definite effect on the behavior of dogs in the labyrinth when administered in a 0.05 mg/kg dose. Under these conditions 1 dog (out of 4) showed a breakdown in the acquired skill within 15 minutes after administration o f the preparation; recovery took place in 24 hours. Another dog showed a temporary slowness in passing through the labyrinth (20 seconds instead of 5).

In order to evaluate in more detail the effect of the preparation not only on the final summary effect but on the individual components of behavioral acts we studied the effect of lysergic acid diethylamide in a 0.1 mg/kg dose on acquired behavior based on conditioned and unconditioned avoidance reactions. In Table 2 we have average data showing the effect

TABLE 1

Effect of Lysergic Acid Diethylamide on Dog Behavior in a Labyrinth

Dose (mg/kg)	No. of animals	Time needed to pass through the labyrinth (in secs)							
		Before injection	After injection of chemical						
			15 mins	30 mins	1 hour	2 hours	1 day	2 days	3 days	5 days
0.01	2	5;5	5;5	5;6	5;5	5;5	5;5			
0.05	4	5;5;6;5	5;20;-;5	5;6;-;6	6;10;-;5	6;8;-;5	5;5;5;5			
0.1	6	5;10;5; 7;6;5	80;-;-; 55;-;-.	------- -------	------- -------	------- -------	5;-;-; 10;10;5	6;-	---	5

TABLE 2

Effect of Lysergic Acid Diethylamide (0.1 mg/kg) on Components of Skill Developed in Dogs

No. of animals	No. of experiments	Time after injection	Sound		Light		Current (reinforcing sound)		Current (reinforcing light)		Differentiation	
			Reaction	Latent period (secs)	Reaction	Latent period (secs)	Reaction	Latent period (secs)	Reaction	Latent period (secs)	Sound	Light
3	10	Original state	+	1±0.2	+	1.4±0.2					+	+
		30 mins	+		-		+	6.5±1	+	2.5±1	+	+
		60 mins	±	2.5± 0.4	±	1±0.2	+	1±0.2	+	0.7±0.3	+	+
		2 hrs	+	1±0.4	±	2.5±0.3			+	1±0.4	+	+
		3 hrs	+	1.7±0.1	±	3.2±0.4			+	3.5±0.9	+	±
		4 hrs	+	1.1±0.1	±	2.3±0.1			-	5±1	+	±
		2nd day	+	1.4±0.3	+	1.8±0.05					+	+
		3rd day	+	0.9±0.1	+	1±0.1						

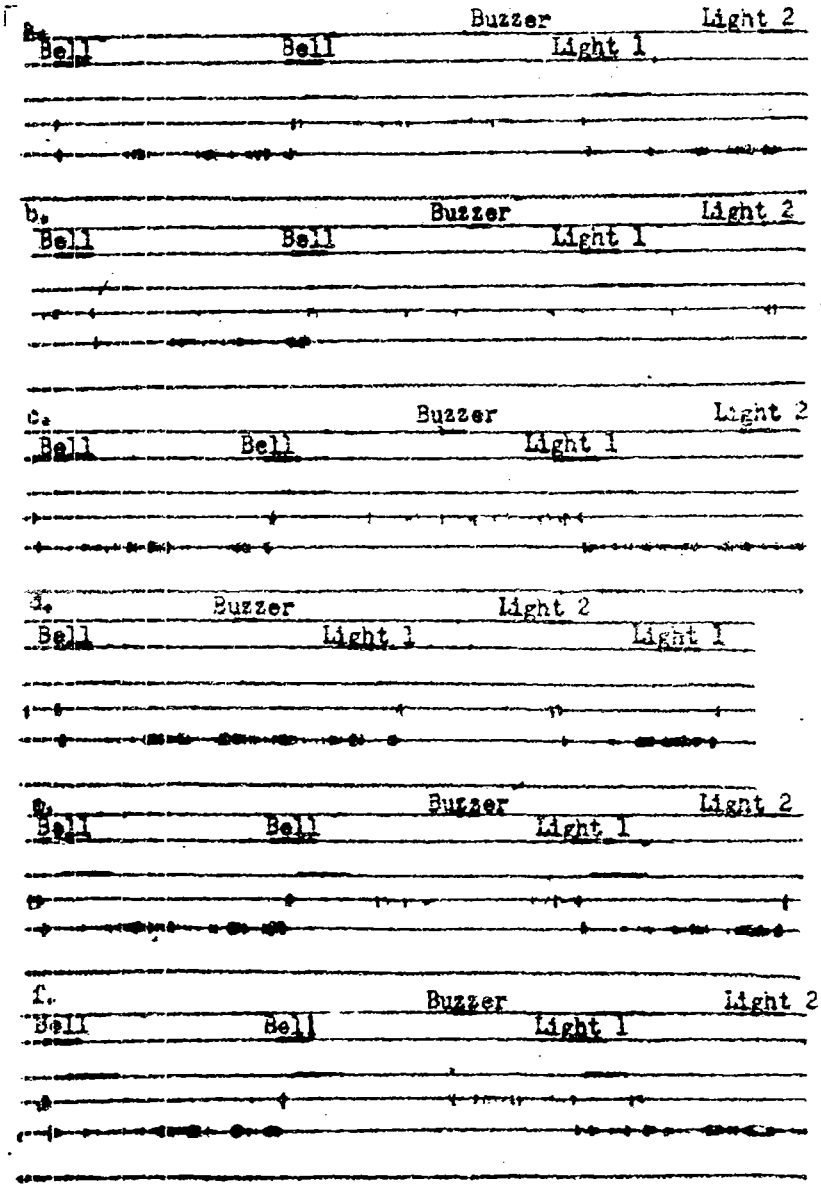

Figure 1. Effect of lysergic acid diethylamide on components of a habit developed in dogs.

Designation of tracings (from top to bottom): differential signal, conditioned signal, current, animal movement in right half of chamber, animal movement in left half of chamber, time mark (sec)

a - original state
b - 30 mins after intramuscular injection of LAD (0.1 mg/kg): no conditioned response to sound or light or unconditioned response to current reinforcing light.
c - 2 hrs after. Restoration of conditioned reaction to sound.
d - 3 hrs after. Disinhibition of light differentiation.
e - on 2nd day. All conditioned reactions restored. Light differentiation lacking.
f - on 3rd day. Original state restored.

of lysergic acid diethylamide on a number of indicators.

We should point out that different indicators describing the state of the higher nervous activity were not alike in their sensitivity to lysergic acid diethylamide. The reaction to light underwent the greatest changes: 30 minutes after injection of the preparation there was a drop in the conditioned response to light in all test animals; during the first 24 hours of observation the reaction was restored in some of the dogs while the latent period remained long. In other cases the reaction was not restored till the following day. The conditioned response to sound likewise dropped off in all experiments soon after the administration of the lysergic acid diethylamide but it returned much more rapidly and was complete within the first 2 hours.

The unconditioned response to the current, which could be detected only in case there was a disruption of the conditioned responses, was retained, as a rule. Only in specific instances did we record an absence of response to current reinforcing the light signal and that when there was a reaction to a current of the same intensity but following a sound signal. Most resistant to the action of lysergic acid diethylamide was sound differentiation which was not impaired in a single experiment. In some cases there was impairment of light differentiation 3 - 4 hours after administration of the chemical. In Fig.1 we have the oscillograms from one of the characteristic experiments.

In order to investigate the state of biological processes in the dogs we used doses of lysergic acid diethylamide leading not only to

disruption of behavioral skills but inducing clinical symptoms.

The injection of lysergic acid diethylamide in a number of cases led to a change in the serotonin content of the blood but the trend of these changes varied and a statistical processing of this material showed the fluctuations to be unpredictable (Table 3).

A determination of the serotonin content of the blood in the brain of experimental animals did not reveal marked deviations from the level observed in control experiments (Table 4).

Moncaminoxidase activity in the blood of experimental animals remained approximately within the limits observed in the control cases.

The effect of lysergic acid diethylamide on the condition of the catechin amines was determined from the activity of ceruloplasmin, an enzyme which participates in the oxidation of adrenaline, from the adrenaline and noradrenaline content of the blood and from the rate at which blood serum oxidizes adrenaline. Ceruloplasmin in animals following the injection of 0.2 mg/kg of lysergic acid diethylamide was determined from the copper content of blood serum; in addition the oxidase activity of the enzyme was determined from the its ratio to N-N1-dimethylparaphenylenediamine. The results for the last indicator are presented in the form of a difference in extinction measured in a photocolorimeter (FEK-M) after the end of the color reaction, in the blood serum of animals before and at various intervals after the injection of lysergic acid diethylamide (Fig.2).

TABLE 3

Serotonin Content of Dog Blood Following Injection of Lysergic Acid Diethylamide (0.2mg/kg)

No. of exp.	Serotonin in blood								
	Before exp.	After injection of lysergic acid diethylamide							
		30 mins		45 mins		60 mins		90 mins	
		microgram/ milliliter	% of norm	microgr/ milliliter	% of norm	microgr/ milliliter	% of norm	microgr/ milliliter	% of norm
1	0.39	-	-	0.44	113	0.49	126	-	-
2	0.33	-	-	0.35	106	0.33	100	-	-
3	0.25	-	-	0.1	40	0.3	120	-	-
4	0.11	0.11	100	0.12	109	0.16	145	0.11	100
5	0.16	0.33	203	0.20	125	0.23	143	0.18	113
6	0.22	0.24	109	0.22	100	0.18	82	0.2	91
7	0.15	0.1	67	0.1	67	0.16	107	0.16	107
8	0.12	0.18	150	0.13	108	0.1	84	-	-
9	0.3	0.33	110	0.33	110	0.2	67	-	-
t		0.19		0.194		0.39			
p		>0.5		>0.5		>0.5			

TABLE 4

Serotonin Content of Dog Brain 90 Minutes After Injection of Lysergic Acid Diethylamide (0.2 mg/kg)

No. of experiment	Serotonin (mg per g of brain tissue)			
	Control		After injection of LAD	
	Cortex	Midbrain	Cortex	Midbrain
1	0.33	0.10	0.11	-
2	0.12	0.16	0.16	-
3	0.12	-	0.16	0.15
4	0.20	-	0.20	-
5	0.19	-	0.16	0.1
6	0.12	-	0.14	0.14
7	0.11	-	0.36	0.28
8	0.15	-	0.33	0.27
9	0.46	0.36	0.34	0.33
10	0.33	0.19	-	0.1
11	0.33	0.34	-	0.1
t			0.22	1.21
p			>0.5	0.25

45-60 minutes after the injection of lysergic acid diethylamide 8 out of 11 dogs showed an increase in the copper content of the blood which reached 150-200%. The variation in the oxidase activity of the blood serum as a rule proceeded parallel with the increase in the copper level. Maximal changes in ceruloplasmin activity coincided with the period of the clinicallly most pronounced experimental psychosis. At the same time the amount of copper in the brain (cortex and thalamus) of test animals varied little from that in control dogs.

The injection of animals with lysergic acid diethylamide had no effect on the intensity of the oxidation of adrenaline by blood serum or on the amount of catechin amines (adrenaline and noradrenaline) in the blood.

In some segments of the brain, in the lamina quadrigemina, for instance, there was a marked increase in acetyl- and butyrylcholinesterase activity. In other segments of the brain (thalmus) there were no pronounced changes in enzyme activity. Only in the cerebral cortex was there some increase in acetylcholinesterase activity, lying on the very edge of predictability (Table 5). At the same time the amount of acetylcholine changed little when determined for the same areas of the brain.

The material obtained indicates first of all that lysergic acid diethylamide induces in dogs an experimental psychosis which is manifested both in the development of a certain clinical symptom picture and in a disruption of developed behavioral skills. The point of view of Abood and his coauthors must therefore be rejected [7] when it affirms that lyseric

TABLE 5

Cholinesterase Activity in the Dog Brain 90 Minutes After the Injection of Lysergic Acid Diethylamide (Dose: 0.2 mg/kg) in γ m acetylcholine per hour

No. of experiment	Control						After Injection of LAD					
	Cortex		Thalamus		Lamina quadrigemina		Cortex		Thalamus		Lamina quadrigemina	
	ACE*	BCE**	ACE	BCE	ACE	BCE	ACE	BCE	ACE	BCE	ACE	BCE
1	0.62	0.12	-	-	-	-	0.83	0.13	-	-	-	-
2	0.53	0.20					1.13	0.14				
3	0.53	0.14					0.83	0.15	1.50	0.40	3.50	0.71
4	0.50	0.16					0.92	0.18	2.40		2.08	0.32
5	0.46	0.14	0.93	0.35	1.60	0.35	0.37	0.10	1.25	0.38	1.95	0.66
6	0.25	0.12	1.33	0.34	1.36	0.35	0.34	0.09	1.25	0.35	1.64	0.63
7	0.93	0.21					0.93	0.17	1.23		1.42	0.35
8	0.39	0.11	1.69	0.78	1.04	0.28	0.70	0.15			2.70	
9	0.43	0.10	1.92	0.10	1.20	0.10	0.47	0.13	1.60		3.65	0.93

* ACE - acetylcholinesterase
** BCE - butyrylcholinesterase

acid diethylamide has no effect on dogs. Among the components entering into the reactions under study the most sensitive were, as might have been expected, conditioned reflex acts, primarily those connected with a conditioning light signal. In some experiments the suppresion of conditioned responses was followed immediately by the disappearance of the unconditioned reaction to the current reinforcing the light while the reaction to a current of the same intensity, but following the sound signal in the stereotype, was retained. Functional changes occurring under the influence of lysergic diethylamide persist for from several hours to several days but seem to be completely reversible.

The methodology employed can be recommended for further research on models of experimental psychosis induced both by lysergic acid diethylamide or other representatives of the psychogenic series of substances.

Among the biochemical indicators studied the most constant and pronounced was the increase in ceruloplasmin activity in blood serum which confirms the premise of a possible connection between this enzyme and the development of psychotic states [8-10]. Changes in the serotonin content were found only for blood but even there were irregular. Thus the point of view of certain authors [11,12] regarding the leading role of serotonin metabolism in the development of lysergic psychosis has not been confirmed. Attention must be given to a further analysis of data on the change in cholinesterase activity in certain cerebral structures since the importance of acetylcholine metabolism in the function of the nervous system is quite well known.

There can be no doubt but that a further biochemical and physiological analysis of a model of experimental psychosis, primarily that

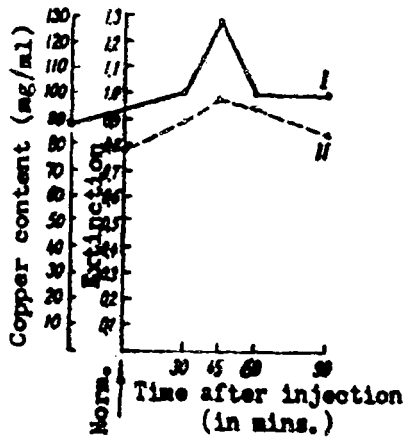

Figure 2. Copper content (I) and oxidase (II) in dog blood serum following injection of 0.2 mg/kg of lysergic acid diethylamide.

induced by lysergic acid diethylamide, can be useful in understanding the mechanisms of both normal and pathological psychic activity.

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