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National Institute of Mental Health, Addiction Research Center, U. S. Public Health Service, Lexington, Kentucky

Relationships of Psychotomimetic to Anti-Serotonin Potencies of Congeners of Lysergic Acid Diethylamide (LSD-25)

By

HARRIS ISBELL, E. J. MINER und C. R. LOGAN

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It has been postulated that LSD induces a psychosis by creating a relative deficiency of serotonin within the brain (GADDUM 1953; WOOLEY and SHAW 1954a). The converse hypothesis—that LSD creates a psychosis by acting like serotonin in brain—has also been formulated (WOOLEY and SHAW 1954b; RINALDI et al. 1956). Evidence for and against both hypotheses has recently been reviewed (PAGE 1958). Serious doubt of the validity of the deficiency hypothesis was created by the finding that D-2-Brom-diethylamide of lysergic acid (BOL-148), which is as potent or more potent than LSD in blocking serotonin in isolated smooth muscle preparations, was not a psychotomimetic drug (CERLETTI and ROTHLIN 1955; ROTHLIN 1957), or only a very weak one (SCHNECKLOTH et. al. 1957). Availability of a number of congeners of LSD-25 with varying potencies as antagonists of serotonin on isolated uterine muscle of the rat made possible a more detailed examination of the relationship of potency of drugs of this type as serotonin antagonists to potency as psychotomimetics. In addition, availability of these compounds provided an opportunity to study the relationship of chemical alterations in the LSD molecule to psychotomimetic effect.

Methods

Drugs. The congeners of LSD studied[1] are listed in Table 2, which also shows the code designations of the various substances. Fresh solutions of all drugs in distilled water were given orally to patients in a fasting state. Doses were calculated on the basis of body weight (micrograms per kilogram) and were expressed as the weight of the salts. Subjects were always unaware of the identity of the drugs (though they expected that they would experience LSD-like effects) and, when detailed comparisons were made, neither the subjects nor the observers knew the nature of the drugs under study ("double-blind" procedure).

[1] These drugs were made available through the courtesy of Dr. R. BIRCHER, Sandoz Pharmaceuticals, Hanover, N. J. The code designations are those of the Sandoz Company.

Subjects. The persons who served as subjects were all Negro male prisoners whe were serving sentences for violation of the narcotic laws, and whoe volunteered for the experiments. All were healthy physically and presented no symptoms suggestive of psychotic disorder. All patients had received LSD prior to entering on these experiments and were familiar with the subjective effects induced by that drug. Because of the large numbers of drugs studied and the long length of time over which the investigations were carried out the same group of subjects did not receive all the drugs. For this reason, estimates of the comparative potencies of the various drugs are affected by possible variation between groups, and can be considered only as approximations.

General Conditions. Experiments were conducted in a special ward devoted to clinical research. Patients entered the ward on the afternoon prior to the experimental day and remained until all drug effects had subsided. They were housed in individual rooms, but were allowed to leave them and to mix with other patients in a common dayroom if they so desired. Experiments were done at weekly intervals in order to prevent the development of tolerance.

Observations. The following observations were made, by methods previously described (ISBELL, et al. 1956), at hourly intervals, twice before and eight times after administration of the drugs: threshold for the kneejerk, systolic blood pressure after resting in bed for ten minutes, and pupillary diameter. Beginning thirty minutes before the drug was given, a modification[1] of the questionnaire of ABRAMSON et al. (1955) was administered hourly, once before, and eight times after the drug was given. Short mental status examinations were performed after the questionnaires had been completed and "clinical grades" of the LSD reaction assigned on a scale of 0—4 according to the system described by ISBELL[2] et al. (1956).

[1] The questionnaire consists of 57 questions covering various symptoms frequently reported after LSD-25. Typical questions are: Are you nervous? Do you feel strange? Does any part of your body feel different? Have you seen any colored lights with your eyes closed? Do the lights form any pictures that you can name? Is someone controlling your mind?

The questionnaire has several disadvantages: It may suggest symptoms; few positive responses are given to many questions; and it does not cover all the mental phenomena reported after LSD.

The questionnaire has the advantages that a systematic record is obtained and the number of positive responses is highly correlated with the dose of LSD.

[2] The grades are assigned on the basis of the presence of the following symtoms:

Grade 0: Absence of any reaction,

Grade 1: Anxiety and nervousness without perceptual distortion or hallucinations,

Grade 2: Anxiety, nervousness and perceptual distortion but without "true" hallucinations,

Experiments. Since most of the drugs had not previously been studied in man, it was necessary to carry out preliminary experiments to determine the dosage which would induce a reaction roughly equal to that produced by 1.0 mcg/kg of LSD. Such preliminary experiments were not "double-blind" since the observers were, for reasons of safety, aware of the drug and the dose. In this phase of the study placebos were not used. The dosage in the first trial of a new drug in the preliminary phase was always 0.5 mcg/kg. If no effect was observed, the dose was doubled in the next experiment with a different subject and the procedure repeated until LSD-like effects began to be observed, or until a dose of at least 50 mcg/kg had been reached without evidence of any psychotomimetic action. The number of subjects used in preliminary trials varied from 5, in the case of ALD-52, to 58, in the case of LAE-32. No psychotomimetic effects were observed with L-LSD (maximum dose 70 mcg/kg), I-LSD (50 mcg/kg), and MBL-61 (175 mcg/kg), so that further comparisons of these drugs with LSD were not undertaken.

After the preliminary experiments were completed, the drugs which has psychotomimetic properties were compared with LSD in more detail. The observations and general methods were those described above. Six groups of subjects were used. Each group received a placebo, LSD, and one to three of the new drugs. Order of administration of the various compounds and of the various doses was randomized and the "double-blind" procedure followed throughout, with identity of the drugs and the doses used being unknown to both subjects and observers. The six groups of patients, the number of patients in each group, and the doses of the drugs are shown in Table 2.

Analysis of Data. The areas under the time-action curve over the eight-hour period after administration of drugs was calculated by the method of WINTER and FLATAKER (1950), as described elsewhere (ISBELL et al. in press) in the cases of threshold for the kneejerk, systolic blood pressure and pupillary diameter. The positive responses on the questionnaire were counted over the entire eight hour period, eliminating answers which were also scored positively prior to drug administration. The highest "clinical grade" observed was used in tabulating the results, regardless of the time at which it occurred. Means and standard errors of means were calculated according to standard techniques. In

Grade 3: Anxiety, nervousness, and "true hallucinations" (an hallucinatory experience which the patient can definitely name as an object or a sound as contrasted with perception of lights, meaningless patterns or simple hyperacusis). In this grade, insight is maintained (patients state that effects are due to the drug).

Grade 4: Same as Grade 3 with insight lost (patient does not realize that effects are due to the drug).

Table 1. *Comparison of psychotomimetic and antiserotonin potencies*

Code	Compound	Dose approximately* equivalent to 1.0 mcg/kg of LSD-25	Relative psychotomimetic activity (LSD-25 = 100)	Relative** antiserotonin activity (LSD-25 = 100)	Remarks
		A. Stereoisomers			
LSD-25	d-Lysergic acid diethylamide	1.0	100	100	
L-LSD	l-Lysergic acid diethylamide	>70	0	0	No psychotomimetic effect in doses used
I-LSD	d-Iso-lysergic acid diethylamide	>50	0	0	No psychotomimetic effect in doses used
		B. Variations in amide group			
DAM-57	d-Lysergic acid dimethylamide	10	10	23	Effect similar to LSD, onset quicker and course shorter
LAE-32	d-Lysergic acid monoethylamide	20	5	12	Effect similar to LSD; course shorter
LPD-824	d-Lysergic acid pyrrolidide	10	10	5	Effect similar to LSD; course shorter
LSM-775	d-Lysergic acid morpholide	9	11	2	Effect similar to LSD; course shorter
		C. Substitutions in ring system			
MLD-41	d-1-Methyl lysergic acid diethylamide	3	33	370	Effect similar to LSD; onset slower
ALD-52	d-1-Acetyl lysergic acid diethylamide	1	100	210	Effect similar to LSD; course similar
BOL-148	d-2-Brom-lysergic acid diethylamide	>86	<2	103	Only partial LSD effect; course shorter
MBL-61	d-1-Methyl-2-brom-lysergic acid diethylamide	>175	<1	533	No spychotomimetic effect in doses used
		D. Substitutions in rings and variations in amide			
MLA-74	d-1-Methyl-lysergic acid monoethylamide	25	4	835	LSD-like; short course
ALA-10	d-1-Acetyl-lysergic acid monoethylamide	15	7	39	LSD-like; short course
MPD-75	d-1-Methyl-lysergic acid pyrrolidide	>20	<5	130	Only partial LSD effect; short course

* See text for method of estimation.

** Taken from data of CERLETTI and DOEPFNER.

Table 2. *Comparative effects of congeners of LSD*

Drug	No. pts.	Dose mcg/kg	Patellar* reflex	Blood* pressure	Pupillary* size	Number of positive answers	Grade
Placebo	9		0.9 ±1.2	50.7±18	−1.8 ±1.1	0 ± 0	0 ± 0
Placebo	8		0.4 ±1.7	29 ±25	4.3 ±1.8	0 ± 0	0 ± 0
LSD-25	9	0.75	5.7 ±1.6	80 ±20	15.8 ±2.4	10 ± 4	0.2 ±0.2
LSD-25	9	1.5	8.7 ±1.2	94 ±15	18 ±2.3	53 ±21	2.4 ±0.4
LPD-824	9	7.5	0.6 ±1.3	50 ±16	9.4 ±1.5	7 ± 3	0.4 ±0.2
LPD-824	9	15.0	2.2 ±0.95	55 ±14	6.6 ±1.4	19 ± 7	1.1 ±0.1
DAM-57	9	7.5	5.1 ±0.8	76 ±15	19.7 ±7	26 ± 9	1.8 ±4
DAM-57	9	15.0	5.1 ±1.6	105 ±23	13.3 ±2.2	51 ± 6	2.9 ±1
LSM-775	9	4.5	2.5 ±1.1	68 ±18	6.3 ±2.2	7 ± 4	0.55±0.2
LSM-775	9	9.0	1.4 ±1.5	65 ±13	9.4 ±2.5	16 ± 8	0.8 ±3
Placebo	10		1.5 ±0.8	36 ± 6	3.8 ±1.6	1.0± 3	0 ±0
LSD	10	1.0	9.6 ±1.3	98.5±14	17.7 ±1.3	36 ±13	1.0 ±0.35
LSD	8	2.0	10.4 ±1.3	106 ± 6	19.3 ±1.9	48 ±15	1.8 ±0.37
MLD-41	6	3.0	12.3 ±1.4	114 ±15	18.2 ±2.6	19 ±22	1.0 ±0.55
MLD-41	10	4.0	12.4 ±1.1	115 ±16	17.2 ±1.8	34 ±19	1.3 ±0.3
MLD-41	6	6.0	11.4 ±2.0	127 ±20	18.5 ±2.0	42 ±13	2.0 ±0.3
Placebo	6	—	3.0 ±1.3	38 ±14	3.3 ±1.2	5 ± 5	0 ±0
LSD	6	1.0	9.2 ±2.0	93 ±14	17.4 ±1.9	50 ± 7	1.5 ±4
LSD	4	1.5	9.8 ±2.8	87 ±38	16.8 ±1.6	21 ± 9	1.0 ±7
ALD-52	6	1.0	10.7 ±1.8	115 ±11	17.2 ±2.2	54 ±11	2.0 ±0.4
ALS-52	4	1.5	13.0 ±2.4	137 ±25	17.0 ±3.2	53 ±18	2.5 ±0.7
Placebo	8		2.8 ±5.2	49 ±19	3.0 ±0.8	0 ± 0	0 ±0
LSD-25	8	1,5	10.7 ±1.8	142 ±19	15.7 ±4.5	86 ±18	2.1 ±0.3
MLA-74	8	25	4.7 ±1.9	77 ±20	9.0 ±2.6	22 ± 6	0.9 ±0.3
ALA-10	8	15	3.0 ±1	88 ±26	3.5 ±1.5	30 ±10	1.1 ±0.47
Placebo	8		1.9 ±0.9	27 ±18	0.7 ±2.3	0 ± 0	0 ±0
LSD-25	8	1.5	9.8 ±1.5	96 ±15	15.9 ±1.1	58 ±12	1.8 ±0.1
MPD-75	8	20	0.16±0.5	57 ±14	4.2 ±1.6	11 ± 3	0.4 ±0.2
LAE-32	8	20	0.8 ±0.7	42 ±12	6.7 ±1.2	2.6± 9	1.0 ±0.16
Placebo	15		0.75±0.6	27.2± 8	−0.48±0.7	2 ± 1.2	0 ±0
LSD-25	15	0.5—1.5	9.2 ±1.3	108 ±16	15.7 ±1.4	61 ±11	2.0 ±0.3
BOL-148	15	75—110	2.52±0.8	38 ±12	6.1 ±1.3	13 ±47	0.6 ±0.15

* Figures given are mean ± standard errors of areas under time-action curves and are expressed as "millimeter-hours" (blood pressure, pupils) and "degree-hours" (kneejerk). The double horizontal lines indicate the six groups of patients used in assessing psychotomimetic potency. All patients within a group received all the drugs in all the doses listed in that group.

the case of BOL-148, data for doses ranging from 75—110 mcg/kg were combined and compared with data for various doses of LSD-25 (0.5—1.5 mcg/kg).

The approximately equivalent psychotomimetic doses shown in Table 1 were chosen by inspecting the data on number of positive answers and clinical grade in Table 2, and selecting the dose of the new drug which most nearly approximated the effect seen or expected from 1.0 mcg/kg of LSD. Though the method is inexact, it is felt that

the dosages assessed in this way reflect the relative psychotomimetic potencies of the new drugs with sufficient accuracy to permit meaningful comparisons of potencies as psychotomimetics with potencies in antagonizing serotonin.

The data for each measurement made on each dose of each drug were tabulated and averaged for each hour before and after administration of the compound. These data on time-action of the various drugs are too voluminous to publish *in toto*, but the time courses as reflected by the average number of positive responses on the questionnaire after the largest doses of the drugs that had definite psychotomimetic effects is shown in Table 3.

Table 3. *Time course after highest dose of various drugs as reflected by average number of positive responses on the questionnaire*

Drug	Dose mcg/kg	Number of subjects	Hours before or after drug								
			−½	+½	+1½	+2½	+3½	+4½	+5½	+6½	+7½
Placebo	—	9	0	0.7	0.2	0	0	0	0	0	0
LSD-25	1.5	9	0	6.9	8.6	10.1	11.0	9.6	2.2	4.2	0.7
DAM-57	15	9	0	19.7	13.6	9.3	4.0	2.6	1.0	0.7	0
LAE-32	20	8	0	12	8	4	1.5	0.3	0	0	0
LPD-824	15	9	0	4.7	6.4	3.8	2.4	1.3	0.4	0.2	0
LSM-775	9	9	0	7.5	5.0	2.6	0.6	0.1	0.1	0	0
MLD-41	6	6	0	2	12	14	8	5	1	0	0
ALD-52	1.5	4	0	7.5	9.0	11.0	8.5	7.0	6.0	4.0	0
BOL-148	86*	15	0	5	3	2	2	1	0	0	0
MLA-74	25	8	0	9	5	4	2.2	0.8	0.3	0	0
ALA-10	15	8	0	16	8	7	4.5	1	0.3	0	0
MPD-75	20	8	0	28	3.8	2.6	0.9	0.3	0.1	0	0

* Average dose (range 75—110 mcg/kg).

Results

The combined data are presented in Table 2, and the approximations of equivalent psychotomimetic doses are compared with the potencies as serotonin antagonists in Table 1. Data on serotonin antagonism were taken from the paper of CERLETTI and DOEPFNER (1958). The only alteration in the LSD molecule which did not reduce psychotomimetic potency was substitution of an acetyl group on the indole nitrogen (ALD-52). All other alterations resulted in diminished activity. Inactivation was greatest in the case of the two compounds, BOL-148 and MBL-61, in which a bromine atom replaced a hydrogen at position two of the indole ring. Alterations in the amide group all reduced activity and shortened the time course. The stereoisomers of LSD did not possess any significant psychotomimetic potency.

In general, the changes in the patellar reflex, blood pressure, and pupillary size parallelled the "mental" effects (questions and grade).

The greatest deviations from such parallelism occurred with the compounds with short-lengths of action (on the kneejerk, in the case of MLA-74, ALA-10, MPD-75 and LAE-32; and on pupillary diameter, in the case of ALA-10). This lack of parallelism in these cases is partly an artefact of the method of analysis. The means for effects on the patellar reflex, pupillary size, and blood pressure are computed over a period of eight hours. The length of action of these four drugs is four hours or less. Therefore, the total degree of change over the entire eight-hour period of observation is less than is the case with LSD, which has effects persisting for at least eight hours.

Discussion

There are very few reports in the literature concerning the effects of these congeners of LSD in man. SOLMS (1953, 1956) found that 0.5 to 0.75 mg (total dose) subcutaneously of LAE-32 induced a psychosis characterized by pseudo-hallucinations and illusions. In smaller doses, an apathetic, adynamic state was often seen. In our experiments, the apathy described by SOLMS was never observed, and the dose of LAE-32 approximately equal to 1 mcg/kg of LSD was 20 mcg/kg, a total dose 1.4 mg for a 70 kg man. These differences in our experiments and those of SOLMS may be due in part to the different routes of administration. JARVIK et al. (1955) also found that LAE-32 was much less active than LSD as a psychotomimetic. Geronimus et al. (1956) reported that L-LSD induced no psychotomimetic effect in a dose (total) of 100 mcg orally. MURPHREE et al. (1958) reported that L-LSD was inert in does of 4 mg. Our data on L-LSD agree with both these groups of authors. I-LSD has not been previously studied. MURPHREE et al. state that 800 mcg of LPD-824 had a fleeting effect equal to about one-tenth as much LSD. Our data confirms this estimate. GOGERTY and DILLE (1957) found that 75 mcg (total dose) of LSM-775 induced short-lasting effects in 2 subjects, which seemed equivalent to those following 50 mcg of LSD. In contrast, we found LSM-775 to be approximately one-tenth as active as LSD. ROTHLIN (1957) states that DAM-57 did not induce any psychic changes but did cause autonomic disturbances in man. In our experiments, DAM-57 was one-tenth as active as LSD, and induced both psychic and autonomic changes when given in this dose. Our data confirm ROTHLIN'S statement that ALD-52 is as active a psychotomimetic as is LSD. ABRAMSON et al. (1958) reported that MLD-41 is approximately one-third as potent as LSD as a psychotomimetic, which agrees with our estimate.

BOL-148 deserves special comment. CERLETTI and ROTHLIN (1955), and ROTHLIN (1957) state that BOL-148 did not have psychotomimetic effect in doses 20 times as great as the psychotomimetic dose of LSD.

JARVIK et al. (1955), likewise, reported little effect from 5 to 7 mcg/kg of BOL. SNOW et al. (1955) observed no mental symptoms in patients with malignant carcinoid who had received as much as 7.5 mg of BOL. SCHNECKLOTH et al. (1957), however, noted LSD-like mental effects after intravenous infusion of 18 to 22 mcg/kg of BOL. In our experiments, BOL did not have any psychotomimetic effects in doses less than 50 mcg/kg. However, doses greater than 70 mcg/kg did consistently induce mild mental changes, although a complete spectrum of LSD-like effects was never observed.

The data show that a high degree of activity as a serotonin antagonist in isolated smooth muscle preparations is not necessarily correlated with high psychotomimetic potency. Thus MBL-61 had no psychotomimetic effect in doses of 175 mcg/kg even though it is five times as potent as LSD as a serotonin blocker on the isolated uterine muscles of the rat uterus. Other dissociations between potency as serotonin antagonists and potency in inducing psychoses are apparent in the cases of MLD-41, BOL-148, MLA-74, and MPD-75. There is, however, no example of low potency as a serotonin antagonist being associated with high potency as a psychotomimetic. The data, therefore, do not support the hypothesis that LSD (and similar drugs) causes a psychosis by competing with serotonin within the central nervous system, but do not disprove it.

Summary

1. The psychotomimetic potency of 13 congeners of LSD-25 has been approximately determined in man.

2. With the exception of acetylation of the indole nitrogen, all the changes made in the LSD molecule reduced psychotomimetic potency. Bromination at carbon 2 caused the greatest inactivation.

3. High potency as a serotonin antagonist in isolated smooth muscle preparations was not correlated with high potency as a psychotomimetic.

4. The data do not support but do not disprove the "serotonin deficiency" hypothesis of the LSD psychosis.

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HARRIS ISBELL, M. D., Director of Research,
NIMH Addiction Research Center, U. S. Public Health Service Hospital,
P. O. Box 2000 Lexington, Kentucky/USA