

Studies on Lysergic Acid Diethylamide (LSD-25)

III. Attempts to Attenuate the LSD-Reaction in Man by Pretreatment with Neurohumoral Blocking Agents

HARRIS ISBELL, M.D., C. R. LOGAN, and E. J. MINER, Lexington, Ky.

Interest in possible chemical transmission of impulses in the central nervous system has been increasing. The neurohumors involved include acetylcholine,^{1,2} norepinephrine,^{2,4} and serotonin.⁴⁻⁶ These theories of central chemical synaptic transmission have led, in turn, to hypotheses which ascribe the psychosis induced by lysergic acid diethylamide (LSD-25) and other psychotomimetic drugs to derangements in central nervous system function because of competition with one or another of the neurohumors or, on the contrary, to accentuation of the effects of the neurohumors by the psychotomimetic agents. The greatest interest has centered on possible interactions of serotonin and LSD. Woolley and Shaw⁵ and Gaddum⁶ independently evolved a hypothesis which ascribes the LSD psychosis to competition between LSD and serotonin for receptor sites on or in neurons. This hypothesis, which might be termed the serotonin-deficiency theory, is based in part on the following evidence: Serotonin is found in brain,^{6,7} and the concentration of serotonin in tissue is reduced⁸ by reserpine, a drug with powerful effects on the central nervous system; in certain concentrations, serotonin and LSD have antagonistic effects on isolated smooth-muscle preparations⁹; reserpine and serotonin prolong sleeping time induced by hexobarbital in mice, and LSD abolishes this enhancement of hexobarbital sleeping time.¹⁰

It is also possible to hypothesize that LSD induces a psychosis by enhancing the

effects of serotonin.^{11,12} This possibility is favored by the following evidence: Low concentrations of LSD increase serotonin-induced contractions in isolated smooth-muscle preparations rather than reducing them¹³; elevation of the serotonin content of brain brought about either by feeding the precursor of serotonin, 5-hydroxytryptophan,¹⁴ or by giving iproniazid, followed by reserpine,⁴ produces symptoms in animals resembling those induced by LSD; injection of serotonin into the lateral ventricles of the brain causes abnormal behavior in animals,¹⁵ and LSD and serotonin both inhibit postsynaptic transmission in a transcallosal synapse.^{16,17}

It is also possible to hypothesize that the LSD psychosis is due to disturbances in central adrenergic mechanisms. The following facts suggest such a possibility: A number of drugs with adrenergic effects (cocaine, amphetamine, and methamphetamine) will, if taken in sufficient dose, cause a toxic psychosis; a number of the signs and symptoms seen after administration of LSD in man (pupillary dilatation, elevation of blood pressure, goose flesh, anorexia, insomnia, and anxiety) suggest hyperactivity of the sympathetic (adrenergic) division of the autonomic nervous system; LSD and a number of adrenergic drugs have the same kind of inhibitory effect on transcallosal postsynaptic transmission^{2,16}; Rothlin and co-workers^{17,18} state that LSD produces a state of central vegetative (autonomic) stimulation. Chlorpromazine partially ameliorates the LSD reaction¹⁹⁻²¹; and since chlorpromazine is a peripheral,²² and possibly a central,²³ adrenergic blocker, one might hypothesize that chlorpromazine

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U. S. Department of Health, Education and Welfare, National Institute of Mental Health, Addiction Research Center, P. H. S. Hospital.

attenuates the LSD psychosis by virtue of adrenergic blocking effects. Some interesting findings in experimental animals support the adrenergic concept. Elder et al.²⁴ surveyed antagonists to LSD and found that pretreatment with chlorpromazine reduced LSD-induced hyperthermia in rabbits and "feline mania" in cats. In addition, phenoxybenzamine (Dibenzylamine), an adrenergic blocker with no known central effects, attenuated "feline mania." Gogerty et al.²⁵ studied the interactions of LSD and reserpine in rabbits. If LSD was given to rabbits two hours after reserpine, hyperthermia was accentuated. At this particular time reserpine-induced release of norepinephrine from brain,²⁶ as well as of serotonin, should be occurring. If LSD was given 10 hours after reserpine, hyperthermia after LSD was reduced. At this time the norepinephrine and serotonin content of brain is almost zero.

A hypothesis relating the LSD psychosis to central interactions with acetylcholine may be suggested by the following: The cholinergic blocking drugs, atropine and scopolamine, can cause toxic psychoses. Acetylcholine and inhibitors of cholinesterase (physostigmine, isoflurophate U. S. P., etc.) stimulate the brain-stem reticular formation,²⁷ leading to an "alert" electroencephalographic pattern, whereas the cholinergic blocking drug, atropine, reduces activity in the reticular formation and induces a "sleep" pattern in the EEG (even though the animal may be awake). In the rabbit, LSD causes an "alert" EEG pattern, similar to that induced by acetylcholine²⁸; so one could speculate that this LSD-induced activation of the EEG is due to some effect of LSD on cholinergic transmission in the reticular formation. Marrazzi¹⁶ suggests that a balance exists in the central nervous system between synaptic excitation by acetylcholine and inhibition by adrenergic neurohumors, so that disturbance of either chemical member of this balanced system may result in abnormal mental function.

Pfeiffer and Jenney²⁹ postulated that since the Rauwolfia alkaloids and chlorpromazine have persistent acetylcholine-like actions, cholinergic drugs that pass the blood-brain barrier should have effects on behavior which resemble those induced by the tranquilizers. These authors demonstrated that arecoline, pilocarpine, and physostigmine reduced or abolished a conditioned avoidance response in rats protected from the peripheral effects of the cholinergic drugs by methyl atropine, a cholinergic blocker which presumably does not cross the blood-brain barrier. In this hypothesis, a "muscarinic" drug is regarded as being an antipsychotic agent, whereas muscarinic blockers are regarded as psychotomimetic. Some of the actions of LSD (pupillary dilatation, facial flush, and elevation of temperature) are similar to those of atropine. Pfeiffer and Jenney, therefore, imply that the LSD psychosis possibly might be due to central muscarinic blocking actions of LSD.

In view of these alternatives, it seemed of interest to determine whether neurohumoral blocking agents would attenuate or enhance the LSD reaction in man. The purpose of this communication is to show that pretreatment with an acetylcholine blocker, scopolamine; an adrenergic blocker, phenoxybenzamine (Dibenzylamine*), and a serotonin antagonist,³⁰ 1-benzyl-2-methyl-5-methoxytryptamine (BAS†), had no significant effect on the mental reactions induced by LSD in man.

Methods

Subjects.—All were adult Negro men who volunteered for the experiments and who were serving sentences for violating Federal narcotic laws. Their ages ranged from 21 to 50 years. All subjects were in excellent physical health, and all had been abstinent from opiates for a least several months before participation in the experiments. There was no evidence of psychosis in any of the patients.

* Supplied through the courtesy of Mr. Theodore Wallace, Smith, Kline & French Laboratories, Philadelphia.

† Supplied through the courtesy of Dr. Frederick K. Heath, Merck Sharp & Dohme, Philadelphia.

and all were diagnosed as having character disorders. The effects of LSD in such subjects have been shown to be similar to the effects observed in other groups of subjects from a different environment and background.⁴¹ Different groups of patients were used in evaluating the various blocking drugs.

Means of Measurement and Analysis.—Methods previously described³⁰ were used. The patellar reflex, pupillary size, and resting systolic blood pressure were measured hourly for two hours prior to and eight hours after administration of LSD (or LSD placebo). In the experiments involving phenoxybenzamine, additional measurements of resting pulse rate and of pulse rate after standing for one minute were made. The average of the two pre-LSD measurements was used as a base line, and the area under the time-action curve was measured with a planimeter,⁴² or was calculated by the method of Winter and Flataker.⁴³ The mental effects of LSD were assessed by administering a modification of the questionnaire of Abrahamson et al.⁴⁴ hourly, twice before and eight times after LSD or LSD placebo. The number of positive responses after LSD or LSD placebo was counted, eliminating any positive answers that were also scored positively prior to administration of the drug. The intensity of the reaction was graded on a scale of 0 to 4, using criteria previously described.³² The grade was based on a short psychiatric examination carried out either hourly or at the height of the reaction.

Drugs.—All drugs were given orally. LSD and scopolamine were given in a solution in which the taste of the scopolamine was masked with a cherry syrup. BAS was given in tablet form, and phenoxybenzamine was administered in capsules. Appropriate identical placebos were used to control all experiments. The doses and times of administration of each of the drugs are described below under the separate experiments. Preliminary experiments, in which BAS or phenoxybenzamine was given alone, were carried out prior to beginning the critical experiments in order to establish effective dosage schedules for these blocking drugs. Experiments were conducted at weekly intervals in order to prevent the development of tolerance to LSD.

Experimental Design.—A "cross-over" design, in which each person served as his own control, was used. The blocking experiments always involved four separate drug combinations in the same group of subjects: LSD placebo plus blocker placebo; LSD plus blocker placebo; LSD plus blocker, and LSD placebo plus blocker. Both patients and observers were unaware of the nature of the medications administered during a particular experiment ("double blind" procedure). The order in which the various combinations of blockers and

LSD were administered was randomized by using a table of random numbers and a Latin-square design. Means and standard errors of means were calculated by standard statistical techniques. Significance of differences was, however, evaluated by the *t*-test for paired observations.⁴⁵

Results

BAS. In preliminary experiments 15 patients were given BAS or BAS placebos. In initial trials, small single doses were used, and the amounts given were gradually increased as experience with the drug accumulated. Patients were then given two doses, and finally three doses, at intervals of six hours. The patients did not report any subjective effects until two doses of 100 mg. of BAS had been given. These sensations did not appear until 8 hours after the first dose of BAS (2 hours after the second dose), were most pronounced 12-16 hours after the first dose, and persisted for 48-72 hours after the last dose. The outstanding subjective effects included fatigue, drowsiness, abdominal discomfort, blurring of vision, and dizziness. Nasal stuffiness was seldom reported. These symptoms were present in all of the 11 patients who received two or three doses of 150 to 200 mg. of BAS. Symptoms resembling those induced by LSD were not reported. There were no significant changes in pulse rate, blood pressure, temperature, pupillary size, or tendon reflexes. No symptoms were reported after placebos in this group of subjects.

Ten of the patients who had received BAS alone were used in the experiment in which combinations of BAS and LSD were studied. In this experiment, patients received 150 mg. of BAS (or BAS placebo) 24, 16, 10, and 2 hours prior to LSD or LSD placebo. The dose of LSD varied from 0.5 to 1.5 μ g/kg. (average 0.95 μ g/kg.).

The results are presented in Table 1. Although BAS prevented the characteristic rise in systolic blood pressure after LSD, the other aspects of the LSD reaction, including the mental effects, were unchanged in intensity or duration. The drowsiness,

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TABLE 1.—Effect of BAS on the LSD Reaction

Measure	Drugs			
	BAS Placebo plus LSD Placebo	BAS Placebo plus LSD	BAS plus LSD	BAS plus LSD Placebo
Patellar reflex *	+0.13±0.14	+2.02±0.43	+2.04±0.29	+1.17±0.17
Pupillary size *	-0.11±0.22	+4.54±0.28	+3.79±0.35	+1.37±0.55
Systolic blood pressure *	+0.59±0.18	+2.48±0.46	+0.76±0.36	+0.12±0.31
Number of positive answers †	0.7±0.9	42±13	43±12	5±0.3
Clinical grade †	0±0	1.3±0.1	1.1±0.1	0.3±0.3

* Expressed as the mean ± the standard error of the area under curves (square inches). A positive (+) figure indicates an increase; a negative figure, a decrease, as compared with predrug controls.

† Means ± standard errors. For number of subjects, doses, and methods, see text.

fatigue, etc., reported after BAS in the preliminary tests were also prominent in this experiment. No significant degree of miosis was observed with BAS alone.

Phenoxybenzamine.—Two preliminary experiments were conducted with phenoxybenzamine. In one of these experiments, four patients received a placebo and 0.4 to 0.6 mg. of epinephrine before and two to three hours after oral administration of 1.0 mg/kg. of phenoxybenzamine hydrochloride. The pulse rate and systolic and diastolic blood pressures were determined twice before and at intervals of 5, 10, 15, 20, 30, 40, and 60 minutes after epinephrine or epinephrine placebo. The rise in systolic pressure after epinephrine was less after phenoxybenzamine, but the difference was not sufficiently great to be significant statistically. The decrease in diastolic pressure after epinephrine was enhanced by phenoxybenzamine. In another experiment, eight patients were "challenged" with a placebo and with 0.6 mg. of epinephrine subcutaneously before and at three and five hours after administration of the last of three doses of phenoxybenzamine (0.5, 1.0, and 1.0 mg/kg. of phenoxybenzamine hydrochloride at 8 a. m. and 6 p. m. on the day prior to epinephrine injections and at 6 a. m. on the day of "challenge"). In this experiment the epinephrine-induced increase in systolic blood pressure was significantly reduced five hours after the last dose of phenoxybenzamine, whereas the decrease in diastolic

pressure and the increase in pulse rate after epinephrine were enhanced both three and five hours after the last dose of phenoxybenzamine. In addition, a marked degree of postural hypotension and tachycardia was present. No symptoms suggestive of central effects of phenoxybenzamine were reported by the patients.

Four patients received 0.5μg/kg. of LSD, and six patients received 1.0μg/kg. of LSD two hours after a single dose of 1 mg/kg. of phenoxybenzamine hydrochloride. Since the results of these experiments were almost identical with the findings of the experiment described below, even though the degree of adrenergic blockage was not as great, they will not be reported in detail.

Ten patients received 0.5, 1.0, and 1.0 mg/kg. of phenoxybenzamine hydrochloride 24, 11, and 2 hours prior to administration of 1.0μg/kg. of LSD. The results are shown in Table 2. Miosis, marked postural tachycardia, and postural hypotension with fainting on standing of 5 of the 10 patients after phenoxybenzamine alone indicated that a considerable degree of adrenergic blockage was present. Pupillary dilatation after LSD was partially blocked by phenoxybenzamine, but no other aspect of the LSD reaction was altered significantly. LSD reduced the postural tachycardia and hypotension caused by phenoxybenzamine.

Scopolamine.—Eleven patients received 0.42, 0.64, and 0.85 mg. of scopolamine hydrobromide simultaneously with

TABLE 2.—Effect of Phenoxylbenzamine on the LSD Reaction

Measure	Drugs			
	Phenoxylbenzamine Placebo plus LSD Placebo	Phenoxylbenzamine Placebo plus LSD	Phenoxylbenzamine plus LSD	Phenoxylbenzamine plus LSD Placebo
Pulse rate, recumbent	+2.08±0.52	+5.6±1.87	+7.74±1.3	+4.8±1.01
Pulse rate, standing	+3.63±1.85	+1.2±2.32	+1.60±3.98	+15.7±4.5
Systolic blood pressure, recumbent	+0.68±0.64	+1.75±0.23	+1.88±0.27	+0.96±0.32
Pupillary size	+0.79±0.33	+3.55±0.38	+2.38±0.18	-0.35±0.89
Patellar reflex	-1.25±0.43	+1.66±0.3	+2.09±0.4	+0.23±0.28
Number of positive answers	0.2±0.08	33±12	47±15	0.1±0.9
Clinical grade	0±0	1.65±0.37	1.85±0.37	0±0

* Expressed as the mean ± the standard error of the area under curves (square inches). A positive (+) figure indicates an increase; a negative figure, a decrease, as compared with predrug controls.

† Means ± standard errors. For number of subjects, doses, and methods, see text.

1.0µg/kg. of LSD. Since the results with these doses of scopolamine were not essentially different from the results obtained with 1.3 mg. of scopolamine hydrobromide combined with LSD, they will not be described in detail. Side-effects attributable to scopolamine (dry mouth, blurred vision, difficulty in swallowing, and pupillary dilatation) occurred with the smallest dose (0.42 mg.) used and became more pronounced as the dose was increased. Mental confusion, depersonalization, hallucinations, and delusions did not occur with any of the doses of scopolamine.

Twelve patients received 1.2 mg. (1/50 grain) of scopolamine hydrobromide combined with 1.0µg/kg. of LSD. The results are shown in Table 3. Although dryness of the mouth, blurred vision, and sleepiness were pronounced, the patients did not report the marked changes in visual perception after scopolamine alone that are so

characteristic of the LSD psychosis, and they did not report any hallucinations or delusions. Pupillary dilatation after the combination of scopolamine and LSD was greater than after LSD alone. The characteristic LSD-induced rise in blood pressure was blocked by scopolamine. Assessment of the mental effects of the combination of scopolamine and LSD was somewhat complicated. The mean number of positive answers increased from 65 after LSD alone to 116 after the combination of LSD and scopolamine. The mean number of answers after scopolamine alone, however, was 42. Counts of the number of times specific symptoms were reported showed that dryness of the mouth, dryness of skin, blurring of vision, and sleepiness accounted for almost all (95%) of the positive responses after scopolamine alone. Increases in frequency of these particular symptoms also accounted for most of the increase in the

TABLE 3.—Effect of Scopolamine on the LSD Reaction

Measure	Drugs			
	Scopolamine Placebo plus LSD Placebo	Scopolamine Placebo plus LSD	Scopolamine plus LSD	Scopolamine plus LSD Placebo
Patellar reflex	+0.83±0.42	+3.08±0.36	+3.26±0.46	+1.44±0.38
Pupillary size	+0.54±0.24	+3.45±0.32	+4.65±0.27	+2.00±0.31
Systolic blood pressure	+0.78±0.62	+2.00±0.37	+0.43±0.52	-0.51±0.6
Number of positive answers	10±4	65±16	116±42	42±20
Clinical grade	0±0	1.1±0.34	1.5±0.4	0.36±0.37

* Expressed as the mean ± the standard error of the area under curves (square inches). A positive (+) figure indicates an increase; a negative figure, a decrease, as compared with predrug controls.

† Means ± standard errors. For number of subjects, doses, and methods, see text.

number of answers after the combination of LSD and scopolamine. The frequency of the more specific symptoms of the LSD reaction (visual-perceptual distortions, depersonalization, and optical hallucinations) was as great after the combination of LSD and scopolamine as after LSD alone, but no greater. The clinical grade of reaction after LSD and scopolamine was somewhat higher than after LSD alone, but the increase was not significant statistically. Occasional reports of anxiety and nervousness in 4 of the 11 patients account for the positive clinical grade with scopolamine alone. The data, therefore, did not suggest any specific accentuation of the mental effects of LSD by scopolamine. They seem more compatible with simple addition of different symptoms caused by two different drugs.

Comment

There was no definite evidence of any attenuation or accentuation of the mental aspects of the LSD reaction after pretreatment with any of the neurohumoral agents. The data, therefore, do not favor any of the hypotheses which attribute the LSD psychosis to derangements in neurohumoral mechanisms within the central nervous system. These experiments do not, of course, disprove these hypotheses, since unknown factors, such as varying penetration of the blood-brain barrier, relative affinity for receptor sites, etc., might account for the negative results.

The results with the serotonin antagonist, BAS, are of especial interest. Although BAS did induce symptoms suggestive of effects on the central nervous system (sedation), it did not cause any mental reaction resembling that seen after LSD. Wilkins³⁵ has also reported sedation after BAS. Similar results have been reported with a congener of LSD, 2-bromo-*d*-lysergic acid diethylamide (BOL-148). This compound is as potent as LSD in antagonizing serotonin-evoked contractions in isolated smooth-muscle preparations³⁶ or in reversing enhancement of hexobarbital sleeping

time in mice,³⁷ but, unlike LSD, is not a potent psychotomimetic drug.³⁸ It is, therefore, apparent that antagonism to serotonin is not correlated with the ability of a drug to produce a psychosis. Since BOL-148 should penetrate the blood brain barrier readily, the hypothesis that a deficiency of serotonin is responsible for the LSD psychosis no longer seems plausible.

Recently Ginzel and Mayer-Gross have reported that pretreatment of patients for two days with BOL-148 attenuated the LSD reaction.³⁸ This finding could possibly be interpreted as favoring the hypothesis that an excess of serotonin-like effect is responsible for the LSD reaction. Such an interpretation must be regarded with caution, since Ginzel and Mayer-Gross found that one day's pretreatment with BOL-148 does not completely block the effects of LSD and, also, that BOL-148 will not reverse the LSD reaction once it has been developed. These results are more suggestive of cross tolerance between LSD and BOL-148 than of blockade of the effect of LSD because of serotonin antagonism by BOL.

Failure to confirm in man the amelioration of the LSD reaction observed in animals²⁴ after pretreatment with phenoxybenzamine might be due to the relatively enormous doses of LSD necessary in animal experimentation, to difficulty in equating behavioral changes in animals with psychoses in man, or to a combination of these factors.

Summary

Pretreatment with the neurohumoral blocking drugs phenoxybenzamine (Dibenzylinc), scopolamine, and 1-benzyl-2-methyl-5-methoxytryptamine (BAS) did not attenuate or accentuate the lysergic acid diethylamide (LSD-25) psychosis in man.

N. I. M. H. Addiction Research Center, U. S. P. H. S. Hospital.

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