THE EFFECTS OF D-LYSERGIC ACID DIETHYLAMIDE ON CEREBRAL CIRCULATION AND OVER-ALL METABOLISM

By

Louis Sokoloff, Seymour Perlin, Conan Kornetsky, and Seymour S. Kety

Reprinted from
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Volume 66, Article 3, Pages 468-477
March 14, 1957

THE EFFECTS OF D-LYSERGIC ACID DIETHYLAMIDE ON CEREBRAL CIRCULATION AND OVER-ALL METABOLISM

By Louis Sokoloff, Seymour Perlin, Conan Kornetsky, and Seymour S. Kety

National Institute of Mental Health, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.

d-Lysergic acid diethylamide (LSD-25), a partially synthesized derivative of ergot, has recently been found to produce in minute doses marked aberrations in psychological and mental functions.[1, 2, 3] Because these disturbances simulate to some degree those observed in naturally occurring psychoses, there has been considerable interest in its mode of action. It has been suggested that the psychotomimetic action of lysergic acid is related to its reported antagonism to 5-hydroxytryptamine (serotonin),[4, 5, 6] a compound normally present in the brain.[7] Since serotonin is known to have powerful vasoconstrictor properties, it is conceivable that the antagonistic action of lysergic acid might be reflected in changes in the cerebral circulation. Furthermore, since the normal functions of the brain are completely dependent on a continuously obligatory consumption of oxygen and glucose, it might be supposed that disorders in the biochemical processes underlying the functions so grossly disturbed by LSD-25 would be reflected in alterations in the oxygen and glucose utilization by the brain. Mayer-Gross, McAdam, and Walker[8, 9] have found both *in vitro* and *in vivo* evidence for disturbances in carbohydrate metabolism produced by LSD-25. An increase in circulating hexosemonophosphate and glucose *in vivo* and a decreased breakdown of hexosephosphate in brain and liver *in vitro* have led these investigators to postulate that LSD-25 causes an increased metabolism of glycogen coupled with a block in the breakdown of hexosemonophosphate. Studies of the effects of lysergic acid on cerebral oxygen consumption have previously been done only *in vitro*, and these have led to contradictory results.[9-12]

In order to determine the effects of LSD-25 on the cerebral circulation and oxygen and glucose metabolism of individuals actively demonstrating the behavioral changes produced by the drug, measurements of these and related functions were undertaken in normal or nonpsychotic, conscious human subjects. Also, in consideration of the remote possibility that schizophrenic patients might react differently to the drug, similar studies were performed in a group of such patients.

Method

Cerebral blood flow (CBF) was measured by means of the nitrous oxide method[13] in 13 normal or nonpsychotic subjects and 9 chronic schizophrenic patients during a resting or control period and again during the height of action of intravenously administered LSD-25.* Eleven of the normal subjects were conscientious objectors or members of a religious sect who had volunteered to be experimental subjects in medical research. Of the remaining 2, both of

* LSD-25 supplied in 1 cc. ampules containing 0.1 mg. per cc. by Sandoz Chemical Works, Inc., Hanover, N. J.

whom had volunteered for this specific procedure, one (Rb. M.) was a normal working employee and the other (J. K.) a patient whose diagnosis was "anxiety neurosis." The schizophrenic patients were of most major types and had been selected from a hospitalized population on the basis of their anticipated cooperativeness during the procedure. Some of the patients, as well as the normal subjects, had been given trial tests with LSD-25 no less than 1 week previously in order to determine their responsiveness and the nature of their response to the drug. This screening was done to favor the occurrence of a definite reaction, but one not too violent to interfere with the procedure during the cerebral blood flow studies. The duration of the disease in the schizophrenic patients ranged from 5 to 22 years, and all exhibited mild to moderate deterioration. In addition to psychotherapy, almost all of the patients had received some form of shock or drug therapy, but in no case during the year preceding the time of these studies.

Each study consisted of two determinations of cerebral blood flow and associated functions, a control measurement followed by an experimental determination during the drug action. Immediately following the control measurements, the symptom questionnaire designed by Abramson and his co-workers[14] was administered to all the normal subjects and to those schizophrenic patients who were communicative. Following the completion of the questionnaire, 120 μg. of LSD-25 were injected intravenously in all but one normal subject (M. G. L.) and one schizophrenic patient (V. S.), in whom the dose injected was 100 μg. Administration of the symptom questionnaire was repeated at approximately 15, 40, 105, and 165 minutes following the drug injection. Because the mean number of symptoms appeared to be maximum at the 40-minute point, the experimental measurements of cerebral blood flow and associated functions were made at that time.

Mean arterial blood pressure (MABP) was measured with an air-damped mercury manometer connected by plastic tubing to the femoral arterial needle. Mean internal jugular venous pressure (MJVP) was determined by means of a Statham P23B strain gauge connected to the internal jugular venous needle and used in conjunction with a Brush Universal amplifier and oscillograph, the former modified to permit electrical integration of the venous pulse for the determination of mean pressure. Blood oxygen and carbon dioxide contents were determined by the manometric method of Van Slyke and Neill.[15] Arterial hemoglobin concentration was measured photometrically by a modification of the method of Evelyn and Malloy.[16] Blood glucose concentrations were determined as the mean of triplicate determinations by the Nelson method.[17] Blood *p*H was measured anaerobically at ambient temperature by means of the MacInnes-Belcher glass electrode and Cambridge Model R Potentiometer and was corrected to 37° C. by means of the factors of Rosenthal.[18] Blood oxygen saturation was determined spectrophotometrically by means of a modification of the method of Wyeth, Ecker, and Polis.[19] Blood carbon dioxide tension (pCO_2) was computed by means of the nomograms of Peters and Van Slyke.[20] Calculations of cerebral blood flow (CBF), oxygen consumption (CMR_{O_2}), glucose utilization (CMR_G), vascular resistance (CVR), and respiratory quotient (R.Q.) were made as previously described.[13]

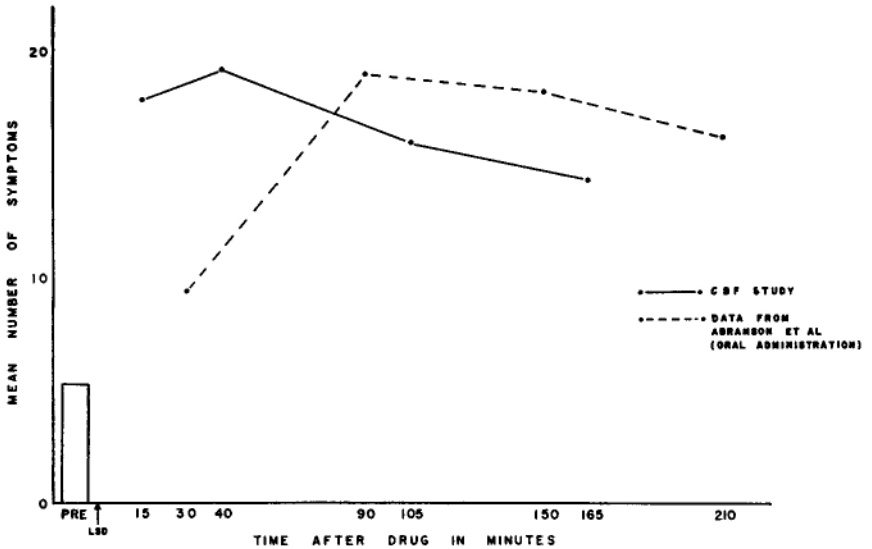

FIGURE 1. Graphic illustration of responses to symptom questionnaire of Abramson *et al.*[14] following oral and intravenous administration of LSD-25.

Results

In FIGURE 1 are graphically represented the results obtained in normal subjects with the symptom questionnaire when administered before and at various times subsequent to the intravenous injection of LSD-25. The results obtained by Abramson and his co-workers[14] following oral administration of the drug are similarly plotted for comparison. It is clear from FIGURE 1 that in normal subjects intravenous administration of LSD-25 does not result in any greater symptom formation than does oral administration, but the peak mean number of symptoms occurring at approximately 40 minutes following injection of the drug precedes the peak achieved with oral administration by nearly an hour. For this reason, the intravenous route of administration was chosen in these studies, and experimental data on cerebral circulation and metabolism and related functions were collected at approximately the 40-minute point. Since the symptom questionnaire could not be satisfactorily administered to schizophrenic patients, it was assumed that the timing of the LSD-25 effect was similar in this group, and the same schedule of experimental measurements was followed as in the normal subjects.

In TABLES 1, 2, and 3 are presented the data on the cerebral circulation and metabolism and related functions obtained in both the normal subjects and the schizophrenic patients. In both groups LSD-25 failed to produce any statistically significant change in pulse rate, respiratory rate, or oral temperature, although the change in pulse rate in the normal subjects from a mean control value of 78 to a mean experimental value of 91 beats per minute was only barely short of statistical significance ($p < 0.1 > 0.05$). In both normal subjects and schizophrenic patients slight but statistically significant in-

TABLE 1

EFFECTS OF LYSERGIC ACID DIETHYLAMIDE ON PULSE, RESPIRATION, AND BODY TEMPERATURE

Subject	Sex	Age	Interval in min.	Dose in μg.	Pulse per min.		Respiratory rate per min.		Oral temp. °C.	
					I	II	I	II	I	II
Thirteen Normal Subjects										
M. G. L.	M	19	91	100	68	78	18	20	36.2	—
W. W.	M	28	127	120	74	110	15	18	36.8	37.3
Rb. M.	M	30	100	120	82	80	21	24	36.6	36.6
A. R.	M	19	110	120	58	56	18	21	36.9	36.8
J. K.	F	46	120	120	83	80	19	16	36.6	36.2
D. B.	M	24	107	120	80	82	16	17	36.9	36.7
M. L.	F	22	150	120	90	85	20	17	36.8	36.7
L. N.	F	24	138	120	99	114	18	21	37.4	37.2
H. H.	M	25	116	120	76	166	10	14	37.4	37.5
C. S.	F	18	111	120	71	80	18	20	37.1	36.8
Rn. M.	M	19	127	120	77	84	14	16	36.7	37.2
D. H.	M	19	100	120	72	78	22	20	36.6	36.9
M. G.	F	18	129	120	88	94	16	10	37.5	36.7
Mean	—	24	117	—	78	91	17	18	36.9	36.9
Standard error	—	±2	±5	—	±3	±7	±1	±1	±0.1	±0.1
p*	—	—	—	—	<0.1	>0.05	>0.4		>0.6	
Nine Schizophrenic Patients										
V. S.	F	41	108	100	76	96	20	22	36.9	—
T. H.	M	36	95	120	92	92	22	20	36.3	36.9
R. T.	M	22	82	120	60	84	16	12	36.6	—
P. L.	M	33	82	120	104	105	14	15	37.0	37.0
J. W.	M	33	128	120	92	82	8	14	37.0	37.0
W. H.	M	27	113	120	76	78	19	26	36.8	37.3
W. C.	M	34	76	120	101	87	27	23	37.0	36.9
B. G.	M	31	112	120	102	119	32	24	36.6	38.2
D. L.	M	27	80	120	94	102	20	21	37.0	37.3
Mean	—	32	97	—	89	94	20	20	36.8	37.2
Standard error	—	±2	±6	—	±5	±5	±2	±2	±0.1	±0.2
p*	—	—	—	—	>0.2		>0.9		>0.1	

I: control.
II: during period of LSD-25 effect.
* Determined by the method of paired comparison.

creases in mean arterial blood pressure (MABP) were produced by the drug rising from 86 to 91 mm. Hg ($p < 0.05$) in the former and from 90 to 97 mm. Hg ($p \sim 0.02$) in the latter. Mean internal jugular venous pressure (MJVP) was unaffected in the normal subjects but in the schizophrenic patients was raised significantly from 7 to 9 mm. Hg ($p \sim 0.02$) by the drug. The effects of LSD-25 on the various cerebral circulatory and metabolic functions studied, for example, cerebral blood flow (CBF), vascular resistance (CVR), oxygen consumption (CMR_{O_2}), glucose utilization (CMR_G), arteriovenous oxygen and glucose differences [$(A\text{-}V)_{O_2}$ and $(A\text{-}V)_G$, respectively], and R.Q. were remarkable only for the absence of any statistically significant changes.

TABLE 2

EFFECTS OF LYSERGIC ACID DIETHYLAMIDE ON CEREBRAL CIRCULATION AND METABOLISM

Subject	MABP in mm. Hg		MJVP in mm. Hg		CBF in cc./100gm./min.		CVR in $\frac{\text{mm. Hg}}{\text{cc./100gm./min.}}$		$(A\text{-}V)_{O_2}$ in vol. %		CMR_{O_2} in cc./100gm./min.		$(A\text{-}V)_G$ in mg.%		CMR_G in mg./100gm./min.		O_2/G in mM/mM		Cerebral R.Q.	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II
Thirteen Normal Subjects																				
M. G. L.	87	83	2	2	73	83	1.2	1.0	6.46	5.97	4.7	4.9	—	—	—	—	—	—	0.97	0.94
W. W.	92	96	8	—	78	65	1.1	—	6.99	6.58	5.4	4.3	—	—	—	—	—	—	0.99	0.95
Rb. M.	80	86	—	—	81	71	—	—	5.67	5.56	4.6	3.9	—	—	—	—	—	—	0.92	0.90
A. R.	78	82	4	6	63	61	1.2	1.2	6.53	6.32	4.1	3.9	—	—	—	—	—	—	0.85	0.97
J. K.	76	75	4	6	66	55	1.1	1.3	4.79	4.22	3.1	2.3	5.4	4.8	3.5	2.7	7.1	7.0	0.99	1.02
D. B.	93	97	7	7	53	47	1.6	1.9	7.65	7.05	4.0	3.3	7.3	8.7	3.9	4.1	8.4	6.5	0.93	1.03
M. L.	92	95	8	6	58	64	1.4	1.4	6.75	6.99	3.9	4.5	6.3	8.3	3.7	5.3	6.8	8.6	0.90	0.95
L. N.	90	94	3	2	67	62	1.3	1.5	5.57	6.30	3.7	3.9	8.6	8.7	5.7	5.4	5.2	5.8	0.84	0.95
H. H.	85	109	8	5	54	43	1.4	2.4	6.09	9.99	3.3	4.3	12.8	14.6	7.0	6.2	3.8	5.5	0.91	0.99
C. S.	81	96	7	9	64	87	1.2	1.0	5.36	4.91	3.4	4.3	9.8	8.5	6.3	7.4	4.4	4.6	1.02	0.93
Rn. M.	98	105	7	7	—	—	—	—	5.42	5.26	—	—	10.0	6.2	—	—	4.4	6.8	0.87	0.81
D. H.	87	86	5	5	75	93	1.1	0.9	3.63	3.23	2.7	3.0	—	—	—	—	—	—	1.16	1.32
M. G.	78	77	5	10	72	88	1.0	0.8	5.37	5.51	3.9	4.8	11.9	—	8.6	—	3.6	—	0.95	0.98
Mean	85.9	90.8	5.7	5.9	67.0	68.2	1.24	1.34	5.87	5.99	3.90	3.95	9.0	8.5	5.5	5.2	5.5	6.4	0.95	0.98
Standard error	±1.9	±2.9	±0.6	±0.8	±2.6	±4.7	±0.05	±0.16	±0.29	±0.45	±0.22	±0.22	±0.9	±1.2	±0.7	±0.7	±0.6	±0.5	±0.02	±0.03
p^*	<0.05		>0.5		~0.9		>0.4		>0.7		>0.8		>0.9		~0.7		~0.3		>0.1	
Nine Schizophrenic Patients																				
V. S.	93	99	7	9	68	65	1.3	1.4	5.92	6.54	4.0	4.3	—	—	—	—	—	—	0.97	0.88
T H.	86	95	5	8	86	96	0.9	0.9	4.73	3.95	4.0	3.8	7.7	5.9	6.6	5.7	4.9	5.4	0.91	1.28
R. T.	88	110	12	13	75	75	1.0	1.3	5.68	5.92	4.2	4.4	5.1	7.7	3.8	5.8	9.0	6.2	1.01	1.01
P. L.	90	91	8	8	68	51	1.2	1.6	5.32	7.40	3.6	3.8	5.0	13.0	3.4	6.6	8.5	4.7	0.90	0.92
J. W.	85	91	7	8	75	79	1.0	1.1	6.68	5.39	5.0	4.3	9.0	9.7	6.8	7.7	5.9	4.5	1.09	0.88
W. H.	85	90	6	6	86	80	0.9	1.1	5.03	4.37	4.3	3.5	—	—	—	—	—	—	0.94	1.04
W. C.	91	89	9	10	66	69	1.3	1.1	5.95	5.47	3.9	3.8	8.7	8.6	5.7	5.9	5.5	5.1	0.95	0.90
B. G.	99	109	4	7	52	—	1.8	—	6.09	6.29	3.2	—	10.7	10.1	5.5	—	4.6	5.0	0.90	0.99
D. L.	97	99	9	9	72	87	1.2	1.0	4.78	4.52	3.4	3.9	7.9	9.2	5.7	8.0	4.9	4.0	0.90	1.06
Mean	90.4	97.0	7.4	8.7	72.0	75.2	1.18	1.19	5.58	5.54	3.96	3.98	7.7	9.2	5.4	6.6	6.2	5.0	0.95	1.00
Standard error	±1.7	±2.7	±0.8	±0.7	±3.5	±4.9	±0.09	±0.08	±0.22	±0.38	±0.18	±0.11	±0.8	±0.8	±0.5	±0.4	±0.7	±0.3	±0.02	±0.04
p^*	~0.02		~0.02		>0.8		~0.3		>0.9		>0.6		>0.2		<0.1 > 0.05		<0.1 > 0.05		>0.4	

I: control.
II: during period of LSD-25 effect.
* Determined by the method of paired comparison.

TABLE 3

EFFECTS OF LYSERGIC ACID DIETHYLAMIDE ON BLOOD CONSTITUENTS

Subject	Art. hemoglobin concentration in grams %		Blood O_2 content in volumes %				Blood CO_2 content in volumes %				Blood glucose concentration in mgs. %				Blood pH				Blood CO_2 tension in mm. Hg				Blood O_2 saturation in percentage			
			Arterial		Int. Jugular		Arterial		Int. Jugular		Arterial		Int. Jugular		Arterial		Int. Jugular		Arterial		Int. Jugular		Arterial		Int. Jugular	
	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II	I	II
Thirteen Normal Subjects																										
M. G. L.	16.49	16.25	20.66	20.81	14.20	14.84	45.63	45.38	51.91	50.96	—	—	—	—	7.35	7.35	7.33	7.29	44	44	52	54	92.5	93.2	69.1	65.1
W. W.	14.07	15.09	18.75	20.12	11.76	13.54	47.94	46.58	54.68	52.83	—	—	—	—	7.41	7.39	7.36	7.36	40	42	50	49	96.7	96.4	62.9	66.5
Rb. M.	15.18	15.63	19.14	19.15	13.47	13.59	48.26	46.28	53.45	51.27	—	—	—	—	7.42	7.40	7.40	7.33	40	40	46	50	96.8	93.6	72.2	70.9
A. R.	14.68	15.17	19.50	20.10	12.97	13.78	49.74	48.57	55.30	54.69	—	—	—	—	7.42	7.44	7.37	7.40	41	38	49	47	96.3	96.1	66.5	69.1
J. K.	13.57	13.98	18.12	17.68	13.33	13.46	46.26	45.91	51.01	50.22	84.5	74.4	79.1	69.6	7.43	7.39	7.35	7.35	37	40	47	47	98.0	95.7	70.3	72.5
D. B.	15.09	15.63	20.65	21.20	13.00	14.15	41.34	38.04	48.46	45.27	107.8	109.7	100.5	101.0	7.47	7.46	7.41	7.43	35	30	41	37	98.1	98.5	63.8	67.3
M. L.	13.49	14.35	18.08	18.42	11.33	11.43	49.55	47.97	55.64	53.58	82.3	86.3	76.0	78.0	7.38	7.37	7.35	7.34	44	43	51	51	99.1	97.6	63.0	60.4
L. N.	12.38	13.49	16.91	17.72	11.34	11.42	46.85	44.70	51.53	50.66	98.7	99.3	66.7	64.2	7.43	7.42	7.40	7.35	37	37	42	46	98.7	99.3	66.7	64.2
H. H.	15.63	16.70	20.46	22.16	14.39	12.17	48.89	30.02	54.44	39.94	93.7	129.4	80.9	114.8	7.45	7.54	7.37	7.45	39	20	50	51	98.4	99.8	67.9	54.4
C. S.	12.46	13.66	16.68	17.72	11.32	12.81	45.97	46.13	51.46	50.69	96.8	92.7	87.0	84.2	7.39	7.35	7.34	7.31	39	43	48	50	99.8	99.8	65.7	70.3
Rn. M.	14.89	15.63	19.70	20.49	14.28	15.23	46.96	45.28	51.67	49.55	89.5	91.0	79.5	84.8	7.39	7.37	7.36	7.34	40	41	48	49	99.0	98.8	70.5	72.2
D. H.	13.37	13.12	17.53	17.47	13.90	14.24	45.06	44.56	49.28	44.81	—	—	—	—	7.38	7.38	7.35	7.33	40	39	45	47	99.0	97.9	77.0	77.6
M. G.	12.91	12.91	17.03	17.14	11.66	11.63	46.31	45.20	51.43	50.59	101.0	94.9	89.1	—	7.39	7.40	7.34	7.35	40	38	48	47	98.0	97.0	66.7	65.1
Mean	14.17	14.74	18.71	19.25	12.84	13.25	46.83	44.20	52.34	49.62	94.3	97.2	82.4	85.2	7.41	7.40	7.36	7.36	39.7	38.1	47.5	48.1	97.7	97.2	67.9	67.4
Standard error	±0.35	±0.34	±0.40	±0.46	±0.34	±0.35	±0.62	±1.37	±0.62	±1.12	± 3.0	±5.8	±3.5	±6.7	±0.01	±0.01	±0.01	±0.01	±0.7	±1.8	±0.9	±1.1	±0.5	±0.6	±1.1	±1.6
p*	<0.01		<0.01		>0.1		<0.1 > 0.05		<0.02		>0.5		~0.5		>0.6		>0.4		>0.3		>0.3		>0.1		~0.7	
Nine Schizophrenic Patients																										
V. S.	11.25	13.37	17.00	18.10	11.08	11.56	46.40	44.02	52.15	49.79	—	—	—	—	7.48	7.48	7.46	7.43	32	32	37	39	96.9	94.9	66.2	66.3
T. H.	13.66	14.35	18.15	18.76	13.42	14.81	47.32	46.30	51.63	51.37	72.7	75.8	65.0	69.9	7.38	7.37	7.32	7.34	42	42	51	54	97.2	95.5	70.0	73.9
R. T	14.77	16.25	19.79	21.50	14.11	15.58	49.38	46.38	55.13	52.33	83.7	83.4	78.6	75.7	7.36	7.40	7.30	7.34	46	41	57	51	97.4	98.8	67.3	70.3
P. L.	14.77	15.18	19.05	19.42	13.73	12.02	43.15	36.61	47.96	43.44	173.0	155.0	168.0	142.0	7.49	7.46	7.34	7.42	32	28	44	36	98.4	97.9	68.8	58.2
J. W.	14.35	14.48	18.29	18.40	11.61	13.01	42.70	44.58	49.98	49.31	101.0	97.7	92.0	88.0	7.41	7.38	7.33	7.34	36	40	49	48	98.0	97.5	59.6	66.8
W. H.	13.28	13.57	18.01	17.88	12.98	13.51	48.27	48.94	52.01	53.48	—	—	—	—	7.41	7.41	7.37	7.37	40	39	46	48	98.0	97.6	69.0	72.6
W. C.	13.20	13.57	17.75	17.20	11.80	11.73	48.86	46.67	54.50	51.58	87.7	98.3	79.0	89.7	7.37	7.37	7.32	7.31	43	42	54	52	99.4	97.2	71.5	71.1
B. G.	15.65	16.49	20.14	21.53	14.05	15.24	42.68	36.31	48.19	42.56	96.6	119.0	85.9	108.9	7.40	7.38	7.34	7.33	38	34	47	43	97.8	98.0	67.3	67.6
D. L.	13.57	14.15	18.50	18.52	13.72	14.00	48.02	46.19	52.32	50.98	91.5	94.6	83.6	85.4	7.37	7.37	7.33	7.32	43	42	51	51	97.9	97.7	71.9	72.7
Mean	13.83	14.60	18.52	19.03	12.94	13.50	46.31	44.00	51.54	49.43	100.9	103.4	93.2	94.2	7.41	7.40	7.35	7.36	39.1	37.8	48.4	46.9	97.9	97.2	68.0	68.8
Standard error	±0.42	±0.38	±0.33	±0.51	±0.38	±0.51	±0.91	±1.50	±0.83	±1.29	±12.7	±10.0	±12.9	±9.2	±0.02	±0.01	±0.02	±0.01	±1.7	±1.7	±2.0	±2.1	±0.2	±0.4	±1.2	±1.6
p*	<0.01		<0.1 > 0.05		>0.1		<0.05		~0.02		>0.6		>0.8		>0.4		>0.3		>0.1		>0.1		>0.1		>0.6	

I: control.
II: during period of LSD-25 effect.
* Determined by the method of paired comparison.

Arterial hemoglobin concentration was significantly elevated by LSD-25 in both normal subjects and schizophrenic patients, rising from mean control values of 14.17 and 13.83 gm. per cent to mean experimental values of 14.74 and 14.60 gm. per cent, respectively ($p < 0.01$ in both groups). As a consequence of the hemoconcentration, mean arterial oxygen content rose from 18.71 to 19.25 vol. per cent ($p < 0.01$) in the normal group, but in the schizophrenic patients the increase to 19.03 vol. per cent during the LSD-25 action from a control value of 18.52 vol. per cent only approached statistical significance ($p < 0.1 > 0.05$). The slight increases in oxygen content observed in the internal jugular venous blood were not statistically significant. Arterial carbon dioxide content was reduced in normal subjects by LSD-25 from a mean control value of 46.83 vol. per cent to 44.20 vol. per cent, a change barely lacking statistical significance ($p < 0.1 > 0.05$). Internal jugular venous carbon dioxide content was reduced significantly from 52.34 to 49.62 vol. per cent ($p < 0.02$). In the schizophrenic patients LSD-25 caused a fall in both arterial and cerebral venous carbon dioxide contents, the former decreasing from 46.31 to 44.00 vol. per cent ($p < 0.05$) and the latter from 51.54 to 49.43 vol. per cent ($p \sim 0.02$). It is likely that the tendency for carbon dioxide contents of the arterial and cerebral venous bloods to fall during LSD-25 action was the result of hyperventilation. The fact that the decreases in carbon dioxide tensions in the same bloods were not statistically significant probably reflects only the greater precision of the method for measuring blood carbon dioxide content as compared with that for calculating blood carbon dioxide tension. In both the arterial and internal jugular venous bloods of both the normal subjects and the schizophrenic patients, glucose concentration, *p*H, and the percentage of oxygen saturation of hemoglobin remained unchanged by LSD-25.

Discussion

Perhaps the most obvious and striking feature of the results reported here is the remarkable paucity of effects of LSD-25 on the cerebral circulatory and metabolic functions studied. Indeed, except for the minimal increases in arterial hemoglobin concentration and mean arterial blood pressure and a marked dilatation of the pupils, there is little in the results of these physiological studies to indicate any activity on the part of the drug. This is equally true for both the normal and schizophrenic groups. On the other hand, the results of the psychological and psychiatric evaluations of the drug action clearly demonstrated the characteristic responses ascribed to LSD-25. It is, therefore, necessary to conclude that the disturbances in psychological and mental functions produced by lysergic acid are unrelated to any changes in the cerebral circulation or those aspects of the metabolism that are reflected in the rates of oxygen and glucose utilization by the brain as a whole.

These results concerning the effects of LSD-25 on the *in vivo* cerebral metabolism are in contrast with some of those obtained in studies on cerebral tissue *in vitro*. For example, Mayer-Gross, McAdam, and Walker[9] have reported that in guinea pig brain brei, lysergic acid produced a stimulation of oxygen consumption associated with a decreased utilization of hexosemonophosphate.

Grenell[10] has observed a similar stimulation of oxygen consumption by LSD-25 in cortical homogenates but one associated with a decrease in the recoverable adenosinetriphosphate. On the other hand, Lewis and McIlwain[11] have observed slight depressions in oxygen consumption produced by LSD-25 in cortical slices of guinea pig brain, and the inhibitory effect of the drug was enhanced by electrical stimulation of the tissue slices. Geronimus and his co-workers[12] have also observed an inhibitory effect of lysergic acid on brain oxygen consumption *in vitro*. In view of these contradictory findings *in vitro*, which are in disagreement not only with our *in vivo* findings but also among themselves, it is difficult to evaluate their significance. Indeed, in an organ such as the brain in which the normal function of the cellular elements depends to so great an extent on the normal interaction of those elements, particularly as regards the processes affected by LSD-25, any effects observed *in vitro* that are in disagreement with those *in vivo* must be seriously questioned before attaching any great functional significance to them.

It is possible that the action of lysergic acid is associated with changes in cerebral circulation or metabolism, but in areas representing so small a fraction of the total brain that the effects are obscured in measurements in the brain as a whole. Alternatively, it may be that in a heterogeneous organ like the brain, many of whose parts are functionally inversely or reciprocally related, changes in metabolic activity in some areas are balanced by inverse changes in other areas so that the net metabolic rate of the brain remains unchanged. These possibilities await further evaluation by methods that measure blood flow and metabolism in localized areas of the brain *in vivo*.

The psychotomimetic state produced by lysergic acid must now be added to a growing list of conditions in which gross alterations in mental and psychological functions are not related to any significant changes in cerebral circulation or metabolic rate. Thus a similar lack of changes in the latter functions has been observed in schizophrenia,[21] during the performance of mental arithmetic,[22] and during the action of the tranquilizing drug, chlorpromazine.[23, 24] Also, although there is a slight but significant rise in cerebral blood flow, no change in cerebral metabolic rate occurs during natural sleep.[25] On the basis of the results obtained in studies such as these, it has become increasingly obvious that the cerebral processes underlying many mental and psychological functions are too subtle to reflect their changes in the over-all circulation and metabolism of the brain.

The only truly positive physiological changes observed in the present study were a marked mydriasis, a slight increase in mean arterial blood pressure, and a mild hemoconcentration. Whether the hemoconcentration represents an absolute increase in circulating hemoglobin mobilized from stored pools of red cells or is the result of a relative increase in hemoglobin concentration because of a loss of plasma volume remains undetermined. In any case, a similar combination of changes has been found to occur during the infusion of *l*-norepinephrine in man.[26] This similarity of effects between LSD-25 and *l*-norepinephrine may be of interest in view of the suggestion by Rinkel and his associates[27] that the action of lysergic acid may be related to its interference somewhere in the adrenalin cycle. Although it must be pointed out that the

elevated blood pressure and the hemoconcentration could both be explained by the increased motor activity that our subjects and patients exhibited under the influence of LSD-25, these findings are not inconsistent with the concept that LSD-25 exerts its effect through some involvement in the epinephrine system.

Summary

(1) Studies of the cerebral circulation and metabolism during a control period and during the height of action of intravenously administered LSD-25 were performed in 13 normal or nonpsychotic subjects and 9 schizophrenic patients.

(2) Despite the occurrence of the characteristic psychological and mental effects of LSD-25, there were no changes produced by the drug in cerebral blood flow, vascular resistance, oxygen and glucose utilization, or R.Q. in either the nonpsychotic or schizophrenic subjects.

(3) Except for mydriasis, a slight elevation in mean arterial blood pressure, and a moderate increase in arterial hemoglobin concentration, the latter associated with a comparable rise in blood-oxygen content, LSD-25 did not produce any changes of significance in the various physiological functions and blood chemical constituents studied in both groups of subjects.

Acknowledgments

The authors express their appreciation to Robert Butler for his valuable aid in the selection and management of the schizophrenic patients and to June Gans, Mary Sultzer, Gladys Ellis, and Carolyn Smith for their technical assistance.

References

1. STOLL, W. A. 1947. Lysergsäure-diäthylamid, ein Phantasticum aus der Mutterkorngruppe. Schweiz. Arch. Neurol. Psychiat. **60:** 279.
2. RINKEL, M., H. J. DESHON, R. W. HYDE & H. C. SOLOMON. 1952. Experimental schizophrenia-like symptoms. Am. J. Psychiat. **108:** 572.
3. HOCH, P. H., J. P. CATTELL & H. H. PENNES. 1952. Effects of mescaline and lysergic acid (d-LSD-25). Am. J. Psychiat. **108:** 579.
4. GADDUM, J. H. 1954. Drugs antagonistic to 5-hydroxytryptamine. Ciba Foundation Symposium on Hypertension. :75. Little, Brown & Co. Boston, Mass.
5. WOOLLEY, D. W. & E. SHAW. 1954. A biochemical and pharmacological suggestion about certain mental disorders. Proc. Natl. Acad. Sci. **40:** 228.
6. GADDUM, J. H. 1953. Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine. J. Physiol. **121:** 15P.
7. AMIN, A. H. T., B. B. CRAWFORD & J. H. GADDUM. 1953. The distribution of 5-hydroxytryptamine and substance P in the central nervous system. Proc. 19th Intern. Physiol. Congr. :165. Montreal, Canada.
8. MAYER-GROSS, W., W. MCADAM & J. W. WALKER. 1951. Psychological and biochemical effects of lysergic acid diethylamide. Nature. **168:** 827.
9. MAYER-GROSS, W., W. MCADAM & J. W. WALKER. 1953. Further observations on the effects of lysergic acid diethylamide. J. Mental Sci. **99:** 804.
10. GRENELL, R. G. Personal communication.
11. LEWIS, J. L. & H. MCILWAIN. 1954. The action of some ergot derivatives, mescaline and dibenamine on the metabolism of separated mammalian tissues. Biochem. J. **57:** 680.
12. GERONIMUS, L. H., H. A. ABRAMSON, L. T. INGRAHAM & B. SKLAVOFSKY. 1954–1955. Effects of LSD-25. :36. Ann. Rept. Biol. Lab. Cold Spring Harbor. New York, N. Y.
13. KETY, S. S. & C. F. SCHMIDT. 1948. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure, and normal values. J. Clin. Invest. **27:** 476.

14. Abramson, H. A., M. E. Jarvik, M. R. Kaufman, C. Kornetsky, A. Levine & M. Wagner. 1955. Lysergic acid diethylamide (LSD-25). I. Physiological and perceptual responses. J. Psychol. **39:** 3.
15. Van Slyke, D. D. & J. M. Neill. 1924. The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. **61:** 523.
16. Evelyn, K. A. & H. T. Malloy. 1938. Microdetermination of oxyhemoglobin, methemoglobin, and sulfhemoglobin in a single sample of blood. J. Biol. Chem. **126:** 655.
17. Nelson, N. 1944. A photometric adaptation of the Somogyi method for the determination of glucose. J. Biol. Chem. **153:** 375.
18. Rosenthal, T. B. 1948. The effect of temperature on *p*H of blood and plasma *in vitro*. J. Biol. Chem. **173:** 25.
19. Wyeth, J., P. Ecker & B. D. Polis. 1954. Spectrophotometric determination of blood oxygen saturation. Report No. NADC-MA-5408, Aviation Medical Acceleration Laboratory, U. S. Naval Air Development Center, Johnsville, Pa.
20. Peters, J. A. & D. D. Van Slyke. 1932. Quantitative Clinical Chemistry. II. Methods. Williams & Wilkins. Baltimore, Md.
21. Kety, S. S., R. B. Woodford, M. H. Harmel, F. A. Freyhan, K. E. Appel & C. F. Schmidt. 1948. Cerebral blood flow and metabolism in schizophrenia. The effects of barbiturate semi-narcosis, insulin coma, and electroshock. Am. J. Psychiat. **104:** 765.
22. Sokoloff, L., R. Mangold, R. L. Wechsler, C. Kennedy & S. S. Kety. 1955. The effect of mental arithmetic on cerebral circulation and metabolism. J. Clin. Invest. **34:** 1101.
23. Morris, G., R. Pontius, R. Herschberger & J. H. Moyer. 1955. Cerebral hemodynamics following administration of chlorpromazine. Federation Proc. **14:** 371.
24. Fazekas, J. F., S. N. Albert & R. W. Alman. 1955. Influence of chlorpromazine and alcohol on cerebral hemodynamics and metabolism. Am. J. Med. Sci. **230:** 128.
25. Mangold, R., L. Sokoloff, E. Conner, J. Kleinerman, P. O. G. Therman & S. S. Kety. 1955. The effects of sleep and lack of sleep on the cerebral circulation and metabolism of normal young men. J. Clin. Invest. **34:** 1092.
26. King, B. D., L. Sokoloff & R. L. Wechsler. 1952. The effects of *l*-epinephrine and *l*-norepinephrine upon cerebral circulation and metabolism in man. J. Clin. Invest. **31:** 273.
27. Rinkel, M., R. W. Hyde & H. C. Solomon. 1954. Experimental psychiatry. III. A chemical concept of psychosis. Diseases of Nervous System. **15:** 3.