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CHAPTER 23

Metabolic Effects of Psychoactive Drugs

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The advent and widespread use of psychotomimetic and psychotherapeutic drugs, while of indisputable value, pose certain questions as to their effects on several somatic and metabolic functions—growth in children, resistance to infection, production of antibodies, etc. Furthermore, there is a great need for investigations aimed toward an elucidation of the action of these drugs at the biochemical, cellular, and molecular levels. With this in view, we have attempted to study the metabolic effects of some psychoactive drugs. We have previously reported [1] the metabolic effects of lysergic acid diethylamide (LSD). In the present study, results of the administration of 2-bromolysergic acid analogue (BOL), phenylisopropyl hydrazine (JB 516 or Catron), and chlorpromazine are presented.

MATERIALS AND METHODS

For purposes of convenience and reproducibility of results, the albino rat was chosen as the experimental animal. Adult rats of our stock colony, which were originally of the Wistar strain, were used. A total of 16 rats were used for the studies on LSD, while 12 were used for each of the other drugs. The values for each group were averaged (Table I, II, and III). The rats were placed in metabolism cages in advance of the actual experiment to acclimatize them to the cage.

The amount of food consumed was estimated by carefully weighing the food placed in the food cups and the residue at the end of every 24-hour period. The technique of paired feeding was not used because of (1) possible metabolic changes in the control animals and (2) the difference between the experimental

TABLE I

Metabolic Effects of LSD and BOL in Rats
(mean values)

Metabolic Entity	LSD			BOL		
	Control	Experimental	% Change	Control	Experimental	% Change
Food intake (g)	19.26	16.26	-15.6	14.8	15.8	6.7
Water intake (ml)	34.4	33.2	- 3.5	—	—	—
Weight of feces (% food intake)	22.0	22.8	3.6	20.0	20.0	0.0
Urinary N (mg/day)	422	348	-17.5	443	453	2.2
Urea N (% urinary N)	72.4	61.2	-15.5	75.4	79.7	5.7
Urinary inorganic phosphate (μM/day)	535	487	- 9.0	544	530	-2.6
Total urinary keto acid (μM/day)	68.1	56.0	-17.8	58.2	64.2	10.3
Keto acid/g food intake	4.0	3.28	-18.8	3.97	4.1	2.8
Creatinine (O.D.* units)	35.8	32.2	-10.0	34.1	35.6	4.4
Total Bratton-Marshall amines (O.D. units)	48.7	41.2	-15.4	34.2	42.6	24.6
Diazotized sulfanilic acid positive substances (O.D. units)	76.5	64.0	-16.3	73.6	77.8	5.7
Phenolic substances/g food intake (O.D. units)	1.08	1.22	13.0	—	—	—
5-hydroxyindole acetic acid (O.D. units)	29.5	46.5	57.6	—	—	—

*Optical Density.

TABLE II

Metabolic Effects of JB 516 and Chlorpromazine
(dose 40 mg/kg)

Metabolic Entity	JB 516			Chlorpromazine		
	Control	Experimental	% Change	Control	Experimental	% Change
Food intake (g)	15.2	3.4	-77.6	13.9	1.4	-89.9
Creatinine mg/day	21.2	9.6	-54.4	21.6	7.2	-66.7
Weight of feces (g)	3.8	0.9	-76.3	3.36	0.71	-78.8
Total urinary N*	20.8	17.9	-14.1	20.4	20.0	- 2.0
Urea N (% urinary N)	64.4	60.2	- 6.5	—	—	—
Total phenolics*	8.5	9.9	16.6	7.6	8.2	7.9
Diazotized sulfanilic acid positive substances*	4.0	2.9	-27.5	4.4	2.4	-45.4
Nitrosonaphtol-positive substances*	0.165	0.157	- 4.8	0.138	0.231	67.4
Bratton-Marshall total amines*	0.41	0.35	-14.6	0.39	0.33	-15.4
Ninhydrin-positive substances (calculated as glutamic acid*)	48.8	69.8	43.0	46.0	59.8	30.0
Urea*	30.7	23.1	-24.7	29.5	27.5	-67.7
Keto acid*	3.58	2.90	-19.0	3.09	2.27	-26.5
Inorganic phosphate*	32.0	70.9	121.6	32.0	46.9	46.6

*Excretion of substance calculated per mg of creatinine excreted in the urine.

TABLE III

Metabolic Effects of JB 516 and Chlorpromazine
(dose 10 mg/kg)

Metabolic Entity	JB 516			Chlorpromazine		
	Control	Experimental	% Change	Control	Experimental	% Change
Food intake (g)	15.15	3.14	-79.3	15.21	13.59	-10.65
Weight of feces (g)	3.19	1.73	-45.76	3.59	3.37	- 6.12
Creatinine (mg)	21.3	14.45	-32.15	22.2	21.6	- 2.70
Urea N (mg)	319	176	-44.8	331	315	- 4.8
Urea N*	15.15	12.4	-18.1	15.2	14.8	- 2.6
Bratton-Marshall total amines	10.45	6.68	-36.1	12.21	11.0	- 9.9
Bratton-Marshall amines*	0.496	0.471	- 5.0	0.553	0.513	- 7.2
Inorganic phosphate (μM/day)	723.7	579.5	-19.2	737	831	12.7
Inorganic phosphate*	33.9	40.9	20.6	33.4	38.3	14.7
Keto acid*	4.26	3.22	-24.4	4.10	4.08	- 0.5
Ammonia*	3.59	3.24	- 9.7	3.56	3.47	- 2.5
Urinary N*	30.9	15.2	-50.8	—	—	—
Ninhydrin-positive substances*	89.0 89.0	87.6 87.6	- 1.6 - 1.6	73.7 73.7	89.0 89.0	20.8 20.8
Diazotized sulfanilic acid positive substances*	4.15	2.68	-35.4	3.76	3.19	-15.1
Nitrosonaphthol-positive substances*	0.12	0.09	-25.0	0.13	0.10	-23.1

*Excretion of substance calculated per mg of urinary creatinine.

and control animals was quite large in some of the experiments (Table II). Urine and feces were carefully collected according to a standardized procedure of rinsing the cages by the same person. The procedure employed for washing was the same from day to day with respect to the amount of water used to wash the cages and with respect to rinsing the cages and other operational details.

Urine, while being collected, was preserved from microbial decomposition by the use of 3 ml of hydrochloric acid. The urine and feces were collected for two days without administration of any drug. These specimens served as controls. After the two days, each rat received the drug each day by the intraperitoneal route. The amounts used were as follows: LSD 500 μg per animal. BOL 500 μg per animal, JB 516 40 mg/kg in one set of experiments and 10 mg/kg in another set, and chlorpromazine 40 mg/kg in one set and, 10 mg/kg in another set of experiments. After the administration of the drug, urine and feces were collected exactly as before for two more days. The collections for each day were kept and analyzed separately.

The feces were dried in a steam oven. The urines were made up to volume and analyzed for total urinary nitrogen and ammonia according to standard procedures using Kjeldahl digestion and Nessler's reagent methods. Inorganic phosphate was estimated according to Fiske and Subba Row [2] and total keto acids according to Friedman and Haugen [3]. Creatinine was estimated by reacting it with picric acid followed by an alkali [4]. Urea was estimated gravimetrically by precipitating as the xanthydrol derivative. Total amines were estimated by the Bratton-Marshall test [5]. Phenolic substances were estimated with the Folin phenol reagent after the addition of the alkaline copper solution (reagent C) of Lowry et al. [6]. The nitrosonaphthol-positive substances were estimated according to the procedure described by Udenfriend and his associates [7]. The diazotized sulfanilic acid positive substances [8] and 5-hydroxyindole acetic acid were assayed according to methods described in the literature [9]. For purposes of calculation, the individual data for each rat were first calculated and then were divided by the number of rats to compute the average.

RESULTS

The values presented in Tables I, II, and III represent the average for the animals in each group. The effects of LSD on

the intact rat include piloerection, rigidity of the limbs, increased sensitivity to stimuli, a crawling-like gait, etc. However, this condition disappears in two to three hours, and the rat begins to behave normally. On the other hand, the administration of BOL does not produce any of these symptoms. Furthermore, in the two-day experiment period we did not notice any increased tolerance to LSD. This is probably owing to the short experimental period.

While LSD and BOL did not decrease the food intake of the rat drastically, chlorpromazine at a level of 40 mg/kg and JB 516 even at 10 mg/kg have done so. This effect of JB 516 is interesting in view of the enhanced activity of the animal after the administration of JB 516. This effect is probably comparable to the action of amphetamine, which is structurally related to JB 516. We have shown the similarity of action of amphetamine and JB 516 on liver alcohol dehydrogenase [10]. A striking difference between the action of LSD on the one hand and of JB 516 and chlorpromazine on the other is that the effect of LSD lasts only a few hours. So, in the 24-hour metabolic experiment the animal is under the acute influence of LSD for only a few hours, while the effects of JB 516 and of chlorpromazine are longer lasting.

The urinary creatinine level is supposed to fall in diseases affecting the muscular system. In the present experiment the decrease in the urinary creatinine after the administration of both JB 516 and chlorpromazine (Table II) is marked in spite of the fact that one drug causes sedation and the other excitation with increased movements. At the lower dose of chlorpromazine (Table III) and in the experiments with LSD and BOL (Table I) the effect of the drug on the excretion of creatinine is not marked.

In view of the extreme decrease in food intake following JB 516 and chlorpromazine, all values in Table II and some in Table III have been expressed as amounts excreted per milligram of urinary creatinine. Actually, in the experiment cited in Table II, the urinary nitrogen was higher in many cases after the administration of the drug than the nitrogen ingested in the food. This shows catabolism of the tissue nitrogen after a higher dose of JB 516 and chlorpromazine. However, the relative amounts of urea excreted are affected by LSD and by JB 516 only. We have previously discussed the effect of LSD on urea excretion [1]. In view of the inhibitory effect of JB 516 on the oxidation of ethyl alcohol and vitamin A alcohol by liver alcohol dehydrogenase [10], it is

plausible to postulate altered functioning of the liver and changes in the metabolism of visual pigments subsequent to the administration of JB 516.

Another interesting metabolic aspect is the excretion of inorganic phosphate. LSD, as shown in Table I, decreases total urinary inorganic phosphate output. Chlorpromazine enhances this output (Table III). JB 516 decreases the total amount of urinary phosphate. But if expressed as micromoles per milligram creatinine, the effect of chlorpromazine at lower levels diminishes while JB 516 actually enhances the amount (Table III). Thus, there seems to be a relation between behavioral aspects as related to activity of the animal and the excretion of creatinine and phosphate.

Keto acid excretion is decreased by LSD, JB 516, and chlorpromazine, a finding suggesting that this aspect may not have a direct bearing on the action of the drug. However, as in some other estimations, in the present study determination of the total level of a group of compounds (for example, amines, keto acids, amino acids) may tell us only a part of the story. Experiments on the determination of the urinary levels of individual compounds, like noradrenalin or indole acetic acid, are in progress. An interesting result in this connection is the increased excretion of 5-hydroxyindole acetic acid after the administration of LSD to the rat (Table I). This may indicate increased metabolism of 5-hydroxytryptamine in the LSD-treated rat and corroborates our investigations on the effect of psychoactive drugs on the levels of serotonin in different parts of the brain and body (Table IV). The experimental details of the study presented in Table IV have been presented elsewhere [8]. The question whether the effect of LSD in mobilizing serotonin is specific to serotonin only or whether LSD increases the levels of other neurohormones, like noradrenalin and acetylcholine, is being further investigated.

The excretion of nitrosonaphthol-positive substances increases much more after chlorpromazine than after JB 516 (Table II). The results cited in Table III show that while chlorpromazine does not affect the excretion of Bratton-Marshall positive amines significantly, JB 516 causes an appreciable decrease. But, if expressed on the creatinine basis, this decrease diminishes to a large extent. This may suggest a positive correlation (direct proportionality) in the excretion of creatinine and these amines. On the other hand, JB 516 caused a decrease (Table III) in the urinary inorganic phosphate from 723.7 μM to 579.5 μM. When

TABLE IV

Effect of Some Psychoactive Drugs on Serotonin Levels in the Rabbit (per cent change over control)

Organ Tissue	Effect of		
	LSD	BOL	Chlorpromazine
Liver	50.6	28.7	3.4
Lung	43.1	37.3	17.6
Kidney	71.2	100.0	5.8
Spleen	30.8	- 8.9	25.3
Heart	188.1	-28.4	-50.7
Brain			
Cerebrum	-6.25	-37.5	-54.2
Cerebellum	38.7	- 4.8	- 4.8
Stem	38.7	- 2.8	-27.4
Rest of brain	28.8	-21.2	-38.5

expressed on the basis of creatinine, these values become 33.9 and 40.9 respectively. This may denote a negative correlation between the excretion of creatinine and inorganic phosphate. Since creatine and phosphate (as phosphocreatine and adenosine triphosphate) are intimately involved in muscular activity and since animals receiving chlorpromazine and JB 516 differ greatly in their motor activity, the effect of these drugs on enzymes involved in muscular activity should be of interest.

DISCUSSION

The metabolism of phosphate seems to be related in more than one way with the effects of LSD. This may, as mentioned earlier, have a bearing on the hallucinogenic action of LSD or may simply be a reflection of the stress created in recipient animals. We have also investigated the effect of LSD, BOL, insulin, and glucagon on

rabbit serum inorganic phosphate content. For this purpose, blood was drawn from a rabbit by means of a heart puncture, and the rabbit was then administered the drug by the intravenous route. After an hour, blood was drawn from the animal by the same method. This way, each experimental animal served as its own control. Details of this experiment will be published elsewhere. However, the results concerning the phosphate levels are presented in Table V.

TABLE V

Effect of Insulin, LSD and BOL on Rabbit Serum Inorganic Phosphate (values expressed as change over control)

Drug	No. Animals	% Change
Insulin	6	-24.4
LSD	6	64.3
BOL	3	3.7

TABLE VI

Blood Inorganic Phosphate Content in Schizophrenic Children (mean values)

	Schizophrenic			Nonschizophrenic			
Test	No. Cases	Average	S.D.*	No. Cases	Average	S.D.*	P†
Plasma inorganic phosphate (μM/ml)	78	0.27	0.30	29	0.16	0.15	0.01
RBC inorganic phosphate (μM/g hemoglobin)	80	5.15	4.28	26	2.8	1.34	less than 0.01

*Standard deviation.
†Significance.

It may be seen that insulin decreased the amount of inorganic phosphate, while LSD increased it. The action of insulin may be due to increased esterification of inorganic phosphate to form glucose-6-phosphate and possibly further production of high-energy phosphate compounds. It has been reported by Abood and his co-workers [12] that LSD uncoupled oxidative phosphorylation. This action of LSD may explain the increased levels of inorganic phosphate in the serum of rabbits administered LSD. It is of interest to note that BOL did not show a similar effect (cf. Table V).

It is possible that the effect of LSD may be related to its psychotomimetic action in so far as the inorganic phosphate content of both serum and erythrocyte hemolyzates is elevated in childhood schizophrenia, as shown in Table VI. The differences between the schizophrenic population and the control hospitalized children are statistically significant. Thus, it is possible that one of the biochemical malfunctions both in psychosis and in psychotomimetic action may be related to the metabolism of phosphate and dependent exergonic processes of the organism.

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