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THE INFLUENCE OF HALLUCINOGENIC DRUGS UPON *IN VIVO* BRAIN LEVELS OF ADENINE NUCLEOTIDES, PHOSPHOCREATINE AND INORGANIC PHOSPHATE IN THE RAT

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The ability to cause visions, hallucinations, disorders of sensory perception and of the thought processes together with behavioural and emotional changes is shared by compounds of differing chemical structures with a broad spectrum of peripheral pharmacological actions (Jacobsen, 1963). They include the indole derivatives, lysergide (lysergic acid diethylamide; LSD) and lysergic acid monoethylamide (Rothlin, 1957), bufotenine (Fabing & Hawkins, 1956) and psilocybin (Hofmann, Heim, Brack & Kobel, 1958; Weidmann, Taeschler & Konzett, 1958; Hollister, 1961); the derivatives of phenethylamine, mescaline (Buchanan, 1929; Stockings, 1940; Mayer-Gross, 1951; Rinkel, 1957; Deniker, 1957) and 3,4,5-trimethoxy-α-methylphenethylamine (3,4,5-trimethoxyamphetamine) (Shulgin, Bunnell & Sargent, 1961); a series of piperid-3-yl benzilates (Abood, Ostfeld & Biel, 1959) and Ditran (a mixture of 30% 1-ethylpiperid-3-yl α-cyclopentyl-α-phenylglycollate hydrochloride and 70% 1-ethylpyrrolidin-2-ylmethyl α-cyclopentyl-α-phenylglycollate hydrochloride) (Hollister, Prusmack, Paulsen & Rosenquist, 1960; Finkelstein, 1961), which have atropinic activity. Hyoscine, cocaine and atropine itself, all of which possess hallucinogenic properties, may also be included.

The subjective effects in man vary from drug to drug; evidence of a common mechanism of action in the central nervous system is lacking and it has not been established that their peripheral actions are related to their hallucinogenic properties. Amphetamine-like drugs and other types of antidepressives which cause behavioural stimulation in the rat have been shown by Lewis & Van Petten (1962, 1963) to raise brain levels of adenosine triphosphate (ATP) and the ATP/ADP ratio; at the same time they lower brain levels of adenosine diphosphate (ADP). These effects have prompted us to investigate the properties of a further group of behavioural stimulants which are hallucinogenic in man.

METHODS

The drugs used and their doses are shown in Table 1. (±)-3,4-Dihydroxyphenylalanine (dopa) and (±)-5-hydroxytryptophan were dissolved in 0.9% w/v saline using the minimum quantity of 0.1 N-hydro-

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chloric acid. Other drugs were dissolved in 0.9% w/v saline and sterilized by filtration. Matching control solutions were used throughout. Drug administration was by intraperitoneal injection.

Male Wistar rats weighing from 70 to 100 g were used in groups of three of equal body weight. One member of each group received the control solution, and the others the drug solutions. The order of treatment was randomized using three of the five possible latin-square designs (Lewis & Van Petten, 1962). After injection each rat was placed in a small cylindrical cage (Lewis & Van Petten, 1962; Kaul, Lewis & Livingstone, 1965) until the end of the experimental period of 0.5, 1.5 or 3 hr. Killing, dissection, extraction and assay for adenine nucleotides, phosphocreatine and inorganic phosphate were as described by Lewis & Van Petten (1962). The results were evaluated by the appropriate analysis of variance.

RESULTS

The results are summarized in Table 1. No attempt was made to estimate quantitatively the degrees of behavioural stimulation shown. The control animals were observed to settle down quickly in the cages and remained inactive, usually dozing or asleep. Animals given dopa or 5-hydroxytryptophan showed no signs of stimulation or unusual activity. Animals treated with lysergide, mescaline and psilocybin were very excited at all doses and time intervals used. At 5 and 10 mg/kg, hyoscine also caused great excitement but at 1.5 hr and with 1 or 2 mg/kg (series 20) the animals appeared normal. Lysergide, mescaline and the higher doses of hyoscine appeared to be the most potent. With lysergide the animals turned continuously, washed themselves repeatedly and at times gnawed the cages. The bufotenine-treated rats were very excited at 0.5 hr, less so at 1.5 hr, while animals treated with JB 329 were excited at 0.5 and 1.5 hr but almost normal at 3 hr.

Dopa and 5-hydroxytryptophan had no significant effects upon the ATP level or the ATP/ADP ratio. Adenosine monophosphate (AMP) was raised significantly by dopa (25 mg/kg) and 5-hydroxytryptophan (20 mg/kg); dopa (25 mg/kg) also raised phosphocreatine. Lysergide lowered ADP, raised the ATP/ADP ratio and increased ATP at all dose levels and times. Phosphocreatine rose at 0.5 and 1.5 hr at both doses used (series 10 and 11) but there was no significant effect at 3 hr, despite significant increases in the ATP/ADP ratio and in ATP, and a significant fall in ADP at this time (series 12). Bufotenine raised the ATP/ADP ratio and lowered ADP at 0.5 and 1.5 hr (series 8 and 9). At 1.5 hr, 5 mg/kg had no significant effect on ATP (series 9). Phosphocreatine rose at 0.5 hr (series 8) but not at 1.5 hr (series 9). The pattern elicited by psilocybin (series 5, 6 and 7) was similar to that due to bufotenine. Phosphocreatine rose significantly only at 0.5 hr (series 5). Apart from the 0.05 mg/kg dose at 3 hr (series 7), the ATP/ADP ratio and ATP level rose in all instances. Bufotenine and psilocybin appeared to have shorter, less intense actions than lysergide.

Mescaline significantly raised phosphocreatine levels at 1.5 hr only (series 3). ADP levels fell at 0.5 and 1.5 hr (series 2 and 3) and, except in series 4 (15 mg/kg at 3 hr), the ATP/ADP ratio rose. ATP rose only at 1.5 hr (series 3) and 0.5 hr (15 mg/kg, series 2). Phosphocreatine levels were not changed significantly by atropine, but at 0.5 hr doses of both 2.5 and 5 mg/kg of this compound lowered ADP, and 5 mg/kg caused a significant rise in ATP (series 21). Hyoscine had more marked effects. Higher doses raised phosphocreatine levels (series 16, 17 and 18) and, at all time intervals investigated, ADP levels fell; ATP levels and the ATP/ADP ratio rose significantly. With the lower doses there were no significant changes in phosphocreatine levels but at 0.5 hr (series 19) the ADP level fell and ATP and the ATP/ADP ratio rose significantly; the effect had disappeared at 1.5 hr

(series 20). When JB 329 (1-ethylpiperid-3-yl α-cyclopentyl-α-phenylglycollate hydrochloride) was used, phosphocreatine rose at 0.5 and 1.5 hr (series 13 and 14); ADP fell at all time intervals. ATP and the ATP/ADP ratio rose at 0.5 and 1.5 hr (series 13 and 14) and total adenine nucleotides rose at 0.5 and 1.5 hr but fell at 3 hr (series 15). At this time there was no significant effect on ATP or the ATP/ADP ratio but AMP was reduced (series 15).

Cocaine (series 1) raised both ATP and the ATP/ADP ratio but at the dose level used behavioural stimulation was absent.

A change in the inorganic phosphate concentration occurred only once, namely 0.5 hr after hyoscine (5 mg/kg); the concentration rose from 4.78 ± 0.40 to 6.46 ± 0.39 μmoles/g of frozen brain (means and standard errors; $P < 0.05$; series 16). In all other instances the inorganic phosphate content remained the same.

DISCUSSION

There appears to be some correlation between the ability of the drugs investigated to cause behavioural stimulation in the rat and to raise brain levels of phosphocreatine and ATP and the ATP/ADP ratio. In these respects they resemble the amphetamine-like compounds and other antidepressives investigated by Lewis & Van Petten (1962, 1963). Drug-induced convulsions and electro-shock seizures usually lower both phosphocreatine and ATP (Stone, Webster & Gurdjian, 1945; Gurdjian, Webster & Stone, 1947; Klein & Olsen, 1947; Shapot, 1957), but raised concentrations of carbon dioxide in the inspired gases prevent the fall in phosphocreatine perhaps due to an improved cerebral blood flow and raised oxygen tension (Bain & Klein, 1949). Falls in phosphocreatine and ATP during convulsions may thus be due to a failure of synthetic mechanisms secondary to cerebral hypoxia (Bain & Klein, 1949). An effect of this kind would also follow from the observation that blockade of electron transport by anoxia or inhibitors of cellular respiration lowers ATP levels in brain mitochondria (Balázs, Magyar & Richter, 1964). Dawson & Richter (1950) found, however, that although electrical stimulation of the rat brain lowered phosphocreatine levels the onset of convulsions was not marked by changes in level of phosphocreatine or ATP. Falls in phosphocreatine and ATP also follow the use of convulsant doses of metabolic inhibitors (Dawson & Peters, 1955; Pscheidt, Benitez, Kirschner & Stone, 1954), tumbling in the Noble-Collip drum (Le Page, 1946), fear of an electro-shock (Sytinsky, 1956) and persistent teasing (Shapot, 1957), but Dawson & Richter (1950) found that exciting rats by rotation in a beaker caused brain phosphocreatine to rise.

The increases in phosphocreatine levels observed may be due to increased synthesis secondary to an improved cerebral blood flow. This would be reflected in the increased ATP levels recorded. In behaviourally alert animals, decreased phosphocreatine or ATP utilization seems unlikely. The rise in ATP levels may also be due to a considerably increased electron transfer rate in the reaction $NAD \rightleftharpoons NADH_2$ which is essential for ATP synthesis. This is indicated by recent observations of Lewis & Pollock (1965) using dexamphetamine.

The majority of compounds tested have peripheral sympathomimetic actions or possess atropinic activity which may produce sympathetic predominance. The drug effects could therefore be initiated by an increase in cardiac output and a raised peripheral resistance.

TABLE 1

IN VIVO EFFECTS OF PSYCHOTOMIMETIC DRUGS ON THE ADENINE NUCLEOTIDE AND PHOSPHOCREATINE CONCENTRATIONS IN THE RAT BRAIN

Values are means and standard errors. * $0{\cdot}05>P>0{\cdot}01$; † $0{\cdot}01>P>0{\cdot}001$; ‡ $P>0{\cdot}001$; ** Missing value calculated. 5HTP=5-Hydroxytryptophan. JB 329 is 1-ethylpiperid-3-yl α-cyclopentyl-α-phenylglycollate hydrochloride. Times are from the injection of drug

Series	Treatment	Dose (mg/kg)	Time (hr)	Concentration (μmoles/g of frozen brain) of					ATP/ADP ratio
				Phosphocreatine	AMP	ADP	ATP	AMP+ADP+ATP	
1	Control	—	1·5	2·57±0·08	0·89±0·06	0·74±0·02	2·25±0·03	3·89±0·08	3·03±0·09
	Cocaine	15	1·5	2·52±0·08	0·85±0·05	0·69±0·01	†2·51±0·06	4·04±0·11	†3·66±0·12
	Cocaine	30	1·5	2·51±0·07	0·83±0·03	0·68±0·02	†2·54±0·06	4·06±0·05	†3·75±0·19
2	Control	—	0·5	2·71±0·10	0·91±0·05	0·77±0·03	2·13±0·05	3·82±0·10	2·77±0·08
	Mescaline	15	0·5	3·06±0·10	*0·77±0·05	‡0·61±0·02	*2·56±0·06	3·94±0·09	‡4·25±0·19
	Mescaline	50	0·5	2·93±0·16	*0·75±0·06	‡0·54±0·02	2·37±0·15	3·77±0·21	‡4·56±0·26
3	Control	—	1·5	2·76±0·10	0·94±0·04	0·83±0·04	2·14±0·05	3·91±0·08	2·64±0·15
	Mescaline	15	1·5	‡3·10±0·11	0·82±0·06	†0·59±0·03	‡2·74±0·14	4·15±0·17	‡4·66±0·29
	Mescaline	50	1·5	‡3·20±0·15	*0·70±0·03	†0·55±0·02	‡2·68±0·07	3·93±0·10	‡4·88±0·17
4	Control	—	3	3·14±0·14	0·90±0·03	0·80±0·01	2·30±0·04	4·00±0·05	2·87±0·05
	Mescaline	15	3	2·90±0·16	0·88±0·06	0·77±0·02	2·28±0·04	3·94±0·06	2·98±0·12
	Mescaline	50	3	3·08±0·12	0·82±0·05	†0·66±0·02	2·38±0·05	3·86±0·09	‡3·67±0·15
5	Control	—	0·5	2·68±0·04	0·89±0·03	0·79±0·01	2·22±0·04	3·90±0·07	2·78±0·04
	Psilocybin	0·05	0·5	*3·18±0·25	0·81±0·03	‡0·64±0·02	‡2·53±0·04	3·97±0·04	‡3·99±0·13
	Psilocybin	0·1	0·5	*3·17±0·13	*0·77±0·08	‡0·59±0·02	‡2·69±0·09	4·06±0·09	‡4·59±0·18
6	Control	—	1·5	2·76±0·12	0·90±0·04	0·79±0·02	2·16±0·03	3·85±0·07	2·75±0·04
	Psilocybin	0·05	1·5	2·68±0·14	0·84±0·04	‡0·64±0·02	‡2·47±0·03	3·96±0·07	‡3·86±0·08
	Psilocybin	0·1	1·5	2·92±0·12	0·77±0·04	‡0·57±0·02	‡2·65±0·01	3·99±0·11	‡4·67±0·18
7	Control	—	3	2·87±0·06	0·97±0·07	0·76±0·01	2·20±0·04	3·94±0·10	2·89±0·05
	Psilocybin	0·05	3	3·02±0·18	0·86±0·05	0·73±0·01	2·21±0·05	3·81±0·06	3·02±0·08
	Psilocybin	0·1	3	3·25±0·13	0·82±0·05	‡0·63±0·02	†2·43±0·06	3·87±0·10	‡3·89±0·15
8	Control	—	0·5	2·67±0·10	0·97±0·04	0·77±0·01	2·11±0·06	3·85±0·09	2·73±0·08
	Bufotenine	5	0·5	*2·90±0·11	0·85±0·06	‡0·57±0·02	†2·40±0·09	3·83±0·10	‡4·19±0·19
	Bufotenine	10	0·5	*2·95±0·09	0·79±0·04	‡0·53±0·01	†2·59±0·08	3·92±0·13	‡4·89±0·14
9	Control	—	**1·5	2·78±0·04	0·96±0·06	0·74±0·02	2·09±0·04	3·69±0·18	2·91±0·13
	Bufotenine	5	1·5	2·97±0·04	0·92±0·05	*0·62±0·03	2·25±0·11	3·78±0·16	‡3·69±0·19
	Bufotenine	10	1·5	3·11±0·10	0·86±0·06	*0·58±0·03	*2·62±0·07	4·07±0·10	‡4·62±0·27
10	Control	—	0·5	2·82±0·09	0·88±0·02	0·84±0·02	2·17±0·04	3·89±0·05	2·61±0·09
	Lysergide	0·05	0·5	*3·28±0·10	0·84±0·02	‡0·59±0·01	‡2·74±0·10	4·17±0·09	‡4·63±0·19
	Lysergide	0·1	0·5	*3·22±0·13	0·81±0·02	‡0·51±0·02	‡2·83±0·06	4·15±0·08	‡5·62±0·15
11	Control	—	1·5	2·92±0·04	0·93±0·04	0·85±0·02	2·25±0·06	4·04±0·07	2·62±0·07
	Lysergide	0·05	1·5	*3·18±0·11	0·90±0·04	‡0·64±0·02	‡2·75±0·08	*4·29±0·12	‡4·35±0·17
	Lysergide	0·1	1·5	*3·22±0·05	0·87±0·03	‡0·57±0·02	‡2·92±0·08	*4·36±0·07	‡5·19±0·21

TABLD 1—*continued.*

Series	Treatment	Dose (mg/kg)	Time (hr)	Concentration (μmoles/g of frozen brain) of Phosphocreatine	AMP	ADP	ATP	AMP+ADP+ATP	ATP/ADP ratio
12	Control	—	3	2·93±0·04	0·90±0·04	0·89±0·02	2·31±0·05	4·10±0·08	2·59±0·07
	Lysergide	0·05	3	3·12±0·10	0·90±0·02	‡0·72±0·02	*2·58±0·09	4·21±0·11	‡3·62±0·12
	Lysergide	0·1	3	3·19±0·08	0·81±0·02	‡0·67±0·02	*2·63±0·04	4·10±0·06	‡3·96±0·13
13	Control	—	0·5	2·93±0·07	0·89±0·07	0·84±0·02	2·29±0·02	4·02±0·06	2·85±0·08
	JB 329	0·05	0·5	†3·33±0·06	0·80±0·04	‡0·64±0·02	‡2·68±0·08	*4·12±0·10	‡4·24±0·18
	JB 329	0·1	0·5	†3·29±0·10	0·87±0·03	‡0·58±0·02	‡2·84±0·08	*4·29±0·10	‡4·90±0·23
14	Control	—	1·5	2·81±0·07	0·88±0·04	0·85±0·02	2·29±0·08	4·02±0·10	2·70±0·13
	JB 329	0·05	1·5	*3·10±0·08	0·91±0·05	‡0·68±0·02	‡2·67±0·09	*4·27±0·12	‡3·91±0·14
	JB 329	0·1	1·5	*3·14±0·11	0·88±0·02	‡0·67±0·02	‡2·82±0·09	*4·38±0·09	‡4·23±0·20
15	Control	—	3	2·82±0·08	0·92±0·04	0·79±0·03	2·29±0·06	4·01±0·10	3·03±0·11
	JB 329	0·05	3	2·86±0·10	‡0·81±0·03	†0·72±0·03	2·20±0·05	*3·73±0·07	3·08±0·13
	JB 329	0·1	3	2·85±0·08	‡0·81±0·03	†0·70±0·02	2·29±0·07	*3·80±0·10	3·27±0·10
16	Control	—	0·5	2·82±0·05	0·83±0·03	0·80±0·02	2·34±0·04	3·97±0·07	2·94±0·07
	Hyoscine	5	0·5	†3·17±0·06	0·81±0·02	‡0·64±0·02	*2·67±0·04	4·12±0·06	‡4·18±0·12
	Hyoscine	10	0·5	†3·15±0·06	0·80±0·03	‡0·61±0·02	*2·70±0·07	4·12±0·10	‡4·45±0·15
17	Control	—	1·5	2·77±0·07	0·74±0·01	0·77±0·02	2·11±0·07	3·63±0·07	2·73±0·09
	Hyoscine	5	1·5	*3·00±0·07	*0·69±0·02	‡0·58±0·02	‡2·53±0·04	*3·81±0·05	‡4·37±0·15
	Hyoscine	10	1·5	*3·01±0·03	0·76±0·02	‡0·59±0·03	‡2·58±0·07	*3·93±0·06	‡4·38±0·25
18	Control	—	3	2·81±0·04	0·83±0·03	0·78±0·02	2·43±0·08	4·04±0·10	3·13±0·09
	Hyoscine	5	3	*3·07±0·06	0·80±0·02	†0·67±0·01	‡2·68±0·07	4·15±0·07	‡4·01±0·13
	Hyoscine	10	3	*3·03±0·10	0·77±0·02	†0·66±0·03	‡2·74±0·07	4·19±0·09	‡4·18±0·20
19	Control	—	0·5	2·91±0·02	0·81±0·03	0·78±0·02	2·23±0·02	3·82±0·03	2·86±0·07
	Hyoscine	1	0·5	3·04±0·06	0·78±0·01	‡0·69±0·02	†2·43±0·06	3·89±0·08	‡3·58±0·16
	Hyoscine	2	0·5	2·93±0·05	0·78±0·02	‡0·62±0·02	†2·54±0·07	3·94±0·08	‡4·08±0·16
20	Control	—	1·5	2·85±0·06	0·82±0·03	0·78±0·03	2·21±0·07	3·82±0·07	2·85±0·13
	Hyoscine	1	**1·5	2·83±0·06	0·76±0·04	0·74±0·01	2·25±0·09	3·75±0·11	3·04±0·16
	Hyoscine	2	1·5	2·93±0·04	0·78±0·02	0·72±0·02	2·27±0·07	3·77±0·09	3·16±0·13
21	Control	—	0·5	2·82±0·13	0·90±0·02	0·79±0·03	2·35±0·05	4·03±0·08	2·99±0·08
	Atropine	2·5	0·5	2·95±0·10	†0·84±0·03	†0·68±0·01	2·47±0·05	3·99±0·06	†3·63±0·11
	Atropine	5	0·5	2·90±0·09	†0·78±0·03	†0·66±0·02	*2·55±0·12	4·00±0·15	†3·87±0·20
22	Control	—	1·5	2·78±0·05	0·82±0·03	0·75±0·01	2·12±0·04	3·68±0·08	2·93±0·04
	Atropine	2·5	1·5	2·85±0·07	0·82±0·03	0·78±0·01	2·10±0·04	3·70±0·06	2·71±0·07
	Atropine	5	1·5	2·76±0·03	0·80±0·02	0·75±0·02	2·10±0·04	3·63±0·04	2·80±0·11
23	Control	—	1·5	2·47±0·08	0·81±0·05	0·76±0·02	2·22±0·09	3·79±0·11	2·91±0·15
	5HTP	20	1·5	2·59±0·06	*0·95±0·05	0·76±0·02	2·29±0·09	4·00±0·11	3·06±0·18
	Dopa	25	1·5	*2·68±0·06	*0·91±0·03	0·78±0·02	2·18±0·06	3·87±0·06	2·81±0·14
24	Control	—	1·5	2·76±0·04	0·92±0·05	0·78±0·01	2·22±0·04	3·93±0·07	2·84±0·08
	Dopa	80	1·5	2·65±0·03	0·89±0·03	0·81±0·02	2·17±0·05	3·87±0·04	2·69±0·11

The ineffectiveness of dopa and 5-hydroxytryptophan does not suggest an effect due to mimicry of, or increased sensitivity to, noradrenaline or 5-hydroxytryptamine in brain.

It is doubtful whether the effects of hallucinogenic drugs upon behaviour in the rat can be compared legitimately with their actions in man. In man, despite quantitative and perhaps qualitative differences in their subjective effects, the hallucinogens appear to cause mental changes by an action upon those regions of the temporal lobes described by Penfield (1959) as the interpretive cortex. The raised levels of labile phosphates may increase the rate of transmitter synthesis or increase electrical activity by an action on mechanisms regulating the flux of ions across cell membranes. These effects may increase neuronal activity in regions of the brain and this may explain the hallucinations, dream-like states and other phenomena following the use of hallucinogens and which can also be induced by electrical stimulation of the temporal lobes (Penfield, 1959).

SUMMARY

1. The effects upon rat brain levels of adenine nucleotides, phosphocreatine and inorganic phosphate of injecting lysergide, psilocybin, mescaline, bufotenine, JB 329, hyoscine, atropine, cocaine, dopa and 5-hydroxytryptophan have been studied.

2. With the exceptions of dopa and 5-hydroxytryptophan, all drugs raised ATP levels and the ATP/ADP ratio, and, except for 5-hydroxytryptophan, atropine and cocaine, the phosphocreatine levels.

3. Only hyoscine caused a significant rise in the inorganic phosphate concentrations. The other drugs did not change the phosphate content.

4. There appears to be some relationship between the ability to cause behavioural stimulation in the rat and to produce increased levels of labile energy-yielding phosphates in brain tissue.

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