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A COMPARISON OF PSYCHOTOMIMETIC DRUG EFFECTS ON RAT BRAIN NOREPINEPHRINE METABOLISM[1]

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ABSTRACT

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The effects of LSD, psilocybin, mescaline, amphetamine and cold water swimming stress on the metabolism of ^{3}H-norepinephrine in rat brain were determined. Graded doses (130–1300 μg/kg) of LSD showed no specific effects on brain catecholamine metabolism, suggesting that this drug had little direct activity on brain noradrenergic neurons. Psilocybin (25 mg/kg) had effects similar to those obtained with amphetamine (2 mg/kg), as evidenced by a prominent and sustained elevation in ^{3}H-normetanephrine content. These findings are consistent with an increased release of norepinephrine from central nerve endings. Cold water swim stress, on the other hand, resulted in a profound increase in ^{3}H-deaminated catechol metabolites, suggesting that the intracellular catabolism of norepinephrine was affected specifically. Mescaline (25 mg/kg) had a biphasic effect on brain ^{3}H-norepinephrine metabolism. Shortly after injection, mescaline-treated rats had a metabolite pattern similar to animals subjected to cold water swimming; from 90 minutes to 4 hours after mescaline, however, ^{3}H-normetanephrine levels were elevated markedly. Based on these data, mescaline appears to cause an initial increase in intracellular ^{3}H-norepinephrine metabolism, followed by a period of enhanced release similar to the effects of amphetamine and psilocybin. These data indicate that the psychotomimetic drugs tested share no single common effect on brain norepinephrine metabolism.

Available information on the relationship between biochemical and psychological variables after psychotomimetic drug treatment indicates that altered cerebral 5-hydroxytryptamine (serotonin) function probably is involved in the drug response of various mammalian species (see Aghajanian *et al.*, 1970; Freedman, 1961a;

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Freedman and Giarman, 1962; Freedman *et al.*, 1970; Tilson and Sparber, 1972). Interactions between the psychotomimetics and brain catecholamine containing neuronal systems, although much discussed, have not been extensively investigated (Freedman, 1961b). Barchas and Freedman (1963) first demonstrated that LSD caused differential effects on brain norepinephrine and serotonin content, suggesting that the potent behavioral effects of the drug might be related to imbalance in the activity of brain catecholamine- and serotonin-containing neurons. Indirect evidence for participation of brain catecholamines in the LSD response was obtained by Horita and Hamilton (1969), who observed that inhibition of catecholamine biosynthesis affected a portion of the behavioral response profile of lysergic acid diethylamide (LSD) in the rabbit. The latter finding, although interesting, is tempered by the apparent lack of catecholamine involvement in several of LSD's behavioral effects in rats (Appel *et al.*, 1970; Tilson and Sparber, 1972). Psilocybin and related behaviorally active compounds, like LSD, are structurally similar to serotonin and cause similar effects on cerebral serotonin stores (Freedman, 1963); however, by biochemical criteria, they correlate poorly to activity on catecholamine-containing neuronal systems (see Bebbington and Brimblecombe, 1969; Praag, 1970). The effects of mescaline, a phenylethylamine derivative like the catecholamines, might be expected to have activity on brain norepinephrine- and/or dopamine-containing neurons; however, much of the relevant data either has been inferential (Bebbington and Brimblecombe, 1969, Tonge and Leonard, 1972) or negative (Tilson and Sparber, 1972).

The present study compares the effects of LSD, psilocybin and mescaline to those of cold-water swim stress and amphetamine on rat brain ^{3}H-norepinephrine metabolism and catecholamine synthesis. Data obtained suggest that there are large differences among the psychotomimetic drugs regarding their apparent relationship to cerebral catecholamine metabolism.

Methods

Experimental subjects were male Sprague-Dawley rats weighing 160 to 250 g. Animals were housed in groups of four to six per cage in an environmentally controlled room for a minimum of 5 days prior to experimentation. Food and water were available *ad libitum* until the start of the injection procedures.

All drug solutions were prepared immediately prior to the time of injection. LSD tartrate (doses indicated in the text), psilocybin phosphate (25 mg/kg) and mescaline (25 mg/kg) were dissolved in 0.9% saline and injected intraperitoneally. Animals subjected to the cold-water swimming stress were placed into large containers filled with water (15°C) either 90 minutes (norepinephrine metabolism studies) or 40 minutes (catecholamine synthesis studies) after receiving the appropriate radiochemical. Rats remained in the water for a maximum of 20 minutes, but were removed prior to that time if they became exhausted and were unable to stay on the surface.

Norepinephrine metabolism studies. Subjects were anesthetized lightly with ether and injected intracisternally with 8.3 μc of DL-norepinephrine-7-^{3}H (New England Nuclear Corporation, Boston, Mass.; 6.88–8.76 c/mmol). The radioactive catecholamine was diluted with Merle's solution to the appropriate concentration; injection volume was 25 μl. Cold-water swim stress, drug or saline (0.9%) injections occurred 90 minutes after the intracisternal injection.

Norepinephrine-^{3}H and its metabolites in whole brain were estimated by the method of Schanberg *et al.* (1967). Aliquots of fractions containing norepinephrine, deaminated catecholamines, normetanephrine, and deaminated-O-methylated metabolites were counted in a Packard liquid scintillation spectrometer. Count data were corrected for quenching, but not for metabolite recovery, and expressed as disintegrations per minute of metabolite per gram of brain. Endogenous norepinephrine content was measured according to the method described by Anton and Sayre (1962).

Because of the number of individual experiments performed, all radioactivity data within a given experiment were re-expressed as percentages of saline control activity for individual metabolic fractions at each time of sacrifice after drug injection (or 20-minute swim period). An analysis of variance was performed for each block of converted data on each metabolite fraction at common time points across all experiments to ascertain the validity of the two-tailed t tests performed (unpaired; adjusted for groups of unequal variance). Significant differences obtained by t test but not by analysis of variance are designated appropriately in the text and figures.

Catecholamine synthesis studies. Rats were anesthetized lightly with ether. Eighty microcuries of L-tyrosine-3,5-^{3}H (Schwarz BioResearch, Inc., Orangeburg, N.Y.; 20 c/mmol) in 0.9% saline were injected rapidly into the external jugular vein in a volume of 200 μl. Drug or control (saline) injec-

tions were given immediately thereafter, and animals were returned to their home cages until sacrificed 1 hour later. Subjects subjected to swim stress were placed into cold water 40 minutes after the tyrosine injection. An additional group of control subjects in the cold-water stress experiment was sacrificed at the time of entry into the water to account for any possible differences in the levels of ^{3}H-catecholamines resulting from early sacrifice. The 40-minute and 1-hour control groups were identical and data from the two control groups in the swim-stress experiment were pooled in analysis of the results.

Radiolabeled catecholamines formed from ^{3}H-tyrosine were isolated on Biorex-70 columns by the method of Barchas *et al.* (1972). Aliquots from the Biorex-70 eluate were taken for estimation of endogenous norepinephrine and dopamine, and the remainder was adjusted to pH 4.5 with 0.3 N NaOH and passed over a Dowex 50W-X8 column (200-400 mesh, H^+ form, 4 × 35 mm). Norepinephrine was separated from dopamine as described by Stolk (1973). Aliquots of the Dowex eluates (for radioactive catecholamines) and of the Biorex effluent (for radioactive tyrosine) were assayed in a Nuclear-Chicago liquid scintillation spectrometer. Recovery of norepinephrine and dopamine from Biorex-70 was 92 and 91%, respectively; cumulative recovery from Biorex-70 and Dowex 50 was 70 to 72% for norepinephrine, and from 60 to 66% for dopamine (recovery constant within any given experiment). Separation of norepinephrine from dopamine on the Dowex 50 column was nearly quantitative, with less than 5% cross-contamination. As in the norepinephrine metabolism experiments, data were corrected for quenching but not for absolute recovery.

Results

Norepinephrine Metabolism

Effects of LSD. Alterations in the metabolism of intracisternally injected ^{3}H-norepinephrine and in endogenous brain norepinephrine content (whole brain) induced by a 1300 μg/kg LSD injection are summarized in figure 1 and table 1, respectively. The major effect of this dose of LSD is to reduce the levels of ^{3}H-norepinephrine isolated from brain. Significant reductions in the labeled catecholamine were obtained by 20 minutes after the injection, and were sustained over the 6-hour postinjection period. Endogenous norepinephrine content was reduced to about the same extent as labeled norepinephrine at 20, 90 and 120 minutes after the injection, but had returned to control levels 4 hours after LSD.

The metabolites of intracisternally injected ^{3}H-norepinephrine tended to be uniformly at or above control metabolite levels during the 2-hour period after LSD. When compared to the reduction in ^{3}H-norepinephrine content over this same time period, it is apparent that catecholamine metabolism is enhanced in general; there was no differentiation in the pattern of ^{3}H-norepinephrine metabolites observed, suggesting that O methylation and deamination both were increased slightly. By 4 hours after 1300 μg/kg (

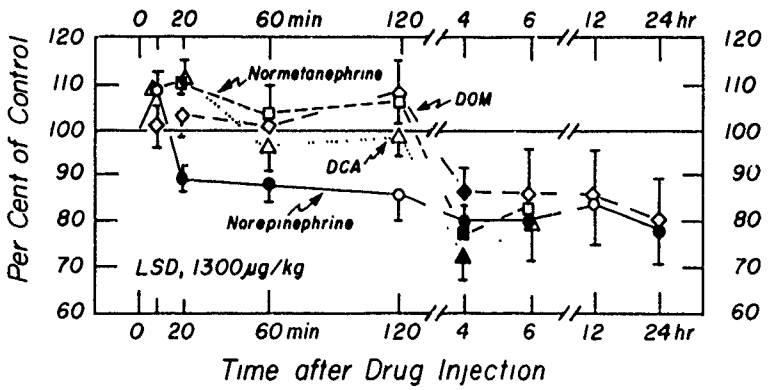

FIG. 1. Effect of 1300 μg/kg of LSD on ^{3}H-norepinephrine metabolism in rat brain. ^{3}H-norepinephrine was injected intracisternally 90 minutes prior to LSD; rats were killed at the indicated times after the LSD injection. Values represent the mean metabolite level, expressed as a percentage of the level obtained in control animals (100%), ± S.E.M. for groups of at least 12 rats. Symbol identification: ○, ^{3}H-norepinephrine; □, ^{3}H-NMN; △, ^{3}H-DCA; ◇, ^{3}H-DOM. Representative absolute metabolite radioactivity in control rats 60 minutes after i.p. saline injection: ^{3}H-norepinephrine, 325 nc/g; ^{3}H-NMN, 18.2 nc/g; ^{3}H-DCA, 10.5 nc/g; ^{3}H-DOM, 336 nc/g. Solid symbols denote a significant difference ($P < .05$) from controls both by analysis of variance (see "Methods") and *t* test, whereas semi-solid symbols indicate that a significant difference ($P < .05$) from controls was found by *t* test only.

TABLE 1

Endogenous norepinephrine content in rat whole brain after treatment with various psychoactive drugs or exposure to cold-water swim

Treatment	30 Min[a]	90 Min	120 Min	240 Min
Control	100.9 ± 1.5 (27)[b]	100.0 ± 2.2 (19)	100.0 ± 2.6 (16)	100.0 ± 1.9 (24)
LSD				
260 g/kg	88.4 ± 4.2[c] (5)			
1300 g/kg	89.3 ± 4.2[c] (14)	92.5 ± 2.6[c] (14)	90.1 ± 3.9[c] (12)	96.6 ± 3.8 (13)
Psilocybin, 25 mg/kg	82.2 ± 3.0[c] (6)	79.1 ± 3.4[c] (5)	76.8 ± 4.1[c] (6)	80.8 ± 3.0[c] (6)
Mescaline, 25 mg/kg	91.3 ± 2.3[c] (5)			
Cold-water swim	91.7 ± 2.5[c] (6)			104.3 ± 1.9 (6)

[a] Minutes after treatment (or after exposure to swim stress).
[b] Number of determinations. All values represent mean ± S.E.M.
[c] Denotes a significant difference ($P < .05$) from control value.

LSD, the levels of ^{3}H-norepinephrine and its metabolites were comparable, all being reduced approximately 20% from control values. A dose-response curve for LSD (260–1300 μg/kg) on labeled norepinephrine metabolism revealed that the 1300 μg/kg dose was the only one causing consistent alterations in catecholamine degradation.

Psilocybin. In contrast to the relatively mild alterations caused by LSD, 25 mg/kg of psilocybin caused dramatic changes both on endogenous brain norepinephrine content (table 1) and on metabolism of ^{3}H-norepinephrine in whole brain (fig. 2). Endogenous amine content was reduced by as much as 24% during the 4-hour period after drug administration. Labeled norepinephrine content generally followed the reduction in endogenous catecholamine levels. The most prominent effect of psilocybin was on ^{3}H-normetanephrine (^{3}H-NMN) levels (fig. 2), which were increased over 2-fold 1 hour after drug injection. ^{3}H-NMN levels remained elevated significantly for 4 hours, indicating the duration of action for 25 mg/kg of psilocybin on brain norepinephrine metabolism. The ^{3}H-deaminated catechol metabolites fraction (^{3}H-DCA) showed a less dramatic spike 1-hour after psilocybin but otherwise were unaffected. Modest increases in the major metabolic fraction, comprised of ^{3}H-deammated-O-methylated products and their conjugates (^{3}H-DOM), coincided with the duration of elevated ^{3}H-NMN levels.

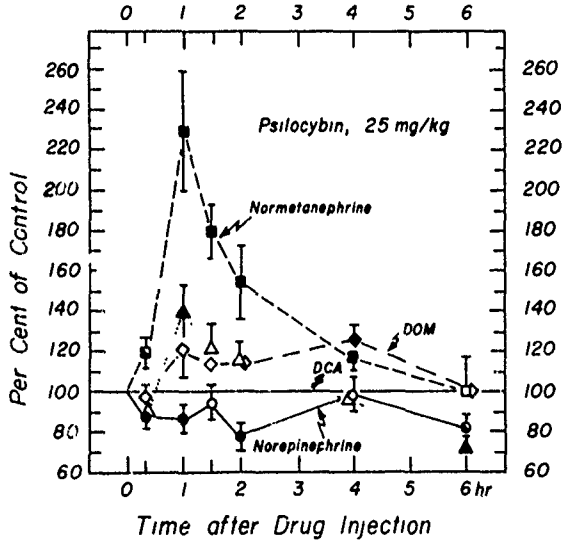

FIG. 2. Effect of 25 mg/kg of psilocybin on ^{3}H-norepinephrine metabolism in rat brain. ^{3}H-norepinephrine was injected intracisternally 90 minutes prior to psilocybin; rats were killed at the indicated times after the psilocybin injection. Values represent the mean metabolite level, expressed as a percentage of the level obtained in control animals (100%), ± S.E.M. for groups of at least 5 rats. Symbol identification: ○, ^{3}H-norepinephrine; □, ^{3}H-NMN; △, ^{3}H-DCA; ◇, ^{3}H-DOM. Representative absolute metabolite radioactivity in control rats 90 minutes after i.p. saline injection: ^{3}H-norepinephrine, 247 nc/g; ^{3}H-NMN, 17.9 nc/g; ^{3}H-DCA, 5.2 nc/g; ^{3}H-DOM, 311 nc/g. Solid symbols denote a significant difference ($P < .05$) from controls both by analysis of variance (see "Methods") and t test, whereas semi-solid symbols indicate that a significant difference ($P < .05$) from controls was found by t test only.

Mescaline. The pattern of ^{3}H-norepinephrine metabolism after the injection of 25 mg/kg of mescaline, indicated in figure 3, is quite different from those obtained after LSD or psilocybin. ^{3}H-DCA content 20 minutes after mescaline is elevated by 40%, but declines rapidly thereafter to near control levels. In contrast, ^{3}H-NMN levels, normal shortly after drug

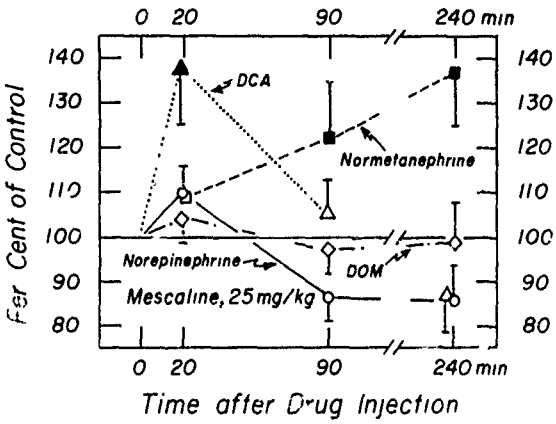

Fig. 3. Effect of 25 mg/kg of mescaline on ^{3}H-norepinephrine metabolism in rat brain. ^{3}H-norepinephrine was injected intracisternally 90 minutes prior to mescaline; rats were sacrificed at the indicated times after the mescaline injection. Values represent the mean metabolite level, expressed as a percentage of the level obtained in control animals (100%), ± S.E.M. for groups of at least five rats. Symbol identification: ○, ^{3}H-norepinephrine; □, ^{3}H-NMN; △, ^{3}H-DCA; ◇, ^{3}H-DOM. Representative absolute metabolite radioactivity in control rats 90 minutes after i.p. saline injection: ^{3}H-norepinephrine, 276 nc/g; ^{3}H-NMN, 21.1 nc/g; ^{3}H-DCA, 15.7 nc/g; ^{3}H-DOM, 354 nc/g. Solid symbols denote a significant difference ($P < .05$) from controls both by analysis of variance (see "Methods") and t test, whereas semi-solid symbols indicate that a significant difference ($P < .05$) from controls was found by t test only.

treatment, increase progressively and are approximately 40% higher than controls at 4 hours. There were no significant changes in either the ^{3}H-norepinephrine or ^{3}H-DOM fractions at any time after mescaline, although estimates of endogenous norepinephrine content revealed a small but significant decline 20 minutes after injection (table 1).

Cold-water swim stress. Rats forced to swim in 15°C water for a maximum of 20 minutes revealed a significant increase in all metabolic fractions except ^{3}H-NMN immediately following the stress (fig. 4). Endogenous norepinephrine concentration, on the other hand, was decreased 8% at this time after swimming, indicating that norepinephrine specific activity increased by 13% over controls. There was a large and prolonged elevation of the ^{3}H-DCA fraction obtained 1.5 and 4 hours after termination of the stress, which was accompanied by a smaller increase in ^{3}H-DOM. Labeled norepinephrine, ^{3}H-NMN and endogenous norepinephrine levels were normal during this time period.

Amphetamine. The effects of D-amphetamine on ^{3}H-norepinephrine metabolism were used as a reference point in evaluating the effects of the psychotomimetic drugs employed in the experiments described above. D-Amphetamine sulfate (2 mg/kg i.p.) injected 2 hours after the intracisternal injection of ^{3}H-norepinephrine results in a prominent increase in ^{3}H-NMN levels (75% greater than control content) but no alteration in other metabolic fractions; these data are in close agreement with more detailed analyses of the temporal and dose-related effects of amphetamine on brain norepinephrine metabolism (Cook and Schanberg, 1970; Scheel-Kruger, 1971; Tilson and Sparber, 1972; Taylor and Sulser, 1973).

Catecholamine Synthesis

The effects of LSD (1300 μg/kg), psilocybin and cold-water swimming stress on formation of norepinephrine and dopamine from ^{3}H-tyrosine are summarized in table 2. Endogenous norepi-

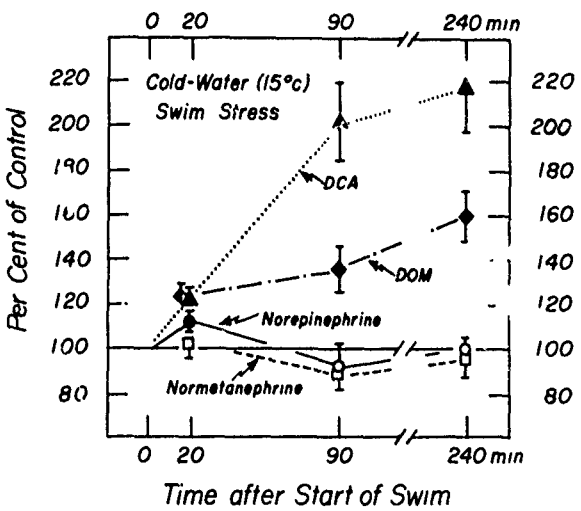

Fig. 4. Effect of cold-water (15°C) swim stress on ^{3}H-norepinephrine metabolism in rat brain. ^{3}H-norepinephrine was injected intracisternally 90 minutes prior to placement of rats into the water; rats were sacrificed at the indicated times after placement into the water. Total time spent in the water was 20 minutes maximum, with exhausted rats being removed prior to that time if necessary. Values represent the mean metabolite levels, expressed as a percentage of the level obtained in control animals (100%), ± S.E.M., for groups of at least six rats. Symbol identification: ○, ^{3}H-norepinephrine; □, ^{3}H-NMN; △, ^{3}H-DCA; ◇, ^{3}H-DOM. Representative absolute metabolite radioactivity in control subjects 90 minutes after start of swim study: ^{3}H-norepinephrine 304 nc/g; ^{3}H-NMN, 16.0 nc/g; ^{3}H-DCA, 6.8 nc/g; ^{3}H-DOM, 296 nc/g. Solid symbols denote a significant difference ($P < .05$) from controls both by analysis of variance (see "Methods") and t test.

TABLE 2

Effects of LSD, psilocybin and cold-water swim stress on the synthesis of catecholamines from ^{3}H-tyrosine in brain

Group	N	Dopamine		Norepinephrine	
		μg/g brain	*dpm/μg amine*	*μg/g brain*	*dpm/μg amine*
Control	6	0.575 ± 0.024[a]	1564 ± 194	0.334 ± 0.012	938 ± 74
LSD	6	0.690 ± 0.029[b]	1790 ± 112	0.332 ± 0.009	1172 ± 40[b]
Control	5	0.974 ± 0.026	710 ± 36	0.488 ± 0.029	1130 ± 52
Psilocybin	5	0.862 ± 0.049	1118 ± 123[b]	0.389 ± 0.019[b]	1648 ± 357[b]
Control	12	0.954 ± 0.033	1196 ± 67	0.349 ± 0.016	1336 ± 85
Swimming	6	0.873 ± 0.040	1459 ± 105[b]	0.331 ± 0.009	1875 ± 165[b]

[a] Mean values ± S.E.M.

[b] Denotes a significant difference ($P < .05$) from respective control group. Doses of psychotomimetic drugs were as follows: LSD, 1300 μg/kg, psilocybin, 25 mg/kg, both injected i.p. ^{3}H-tyrosine was injected into the external jugular vein immediately prior to drug injections. Animals exposed to cold-water swim stress were placed into tanks of 15°C water 40 minutes after receiving the tyrosine injection. All subjects were sacrificed 1 hour after tyrosine injection.

nephrine content in the three experimental groups is in close agreement with the data shown in table 2. All three treatments resulted in a significant elevation in norepinephrine specific activity, with psilocybin and cold-water swimming groups both causing approximately 50% increases, and LSD a 20% increase, in norepinephrine formation. Only LSD caused a significant alteration in endogenous dopamine levels and failed to increase dopamine specific activity. Tyrosine concentrations in all experimental groups were not significantly different from control values in any of the experiments.

Discussion

The differences between LSD, mescaline and psilocybin on brain norepinephrine metabolism are readily apparent from the present study. LSD was observed to cause modest reductions in endogenous and tritiated norepinephrine levels, but no specific alterations in norepinephrine metabolism, despite the use of high drug dosages (table 1; fig. 1). Psilocybin decreased endogenous and labeled norepinephrine content in brain, and caused a marked increase in labeled ^{3}H-NMN levels (table 1; fig. 2), effects similar to those obtained after amphetamine treatment; psilocybin caused a transient increase in deaminative metabolism during the peak elevation in ^{3}H-NMN levels. Mescaline, which had minimal effects on endogenous or ^{3}H-norepinephrine, caused a biphasic change in catecholamine metabolism (fig. 3); this was characterized by an initial increase in deaminative metabolism, similar to the sustained changes obtained after cold-water swim stress (fig. 4), followed by a delayed elevation in ^{3}H-NMN content, resembling that observed after psilocybin or amphetamine treatment. These metabolic differences imply that the three psychotomimetic drugs tested interact with brain noradrenergic systems in fundamentally different ways, in contrast to the similar effects of psilocybin, mescaline and LSD on serotonin metabolism (Freedman *et al.*, 1970; Tilson and Sparber, 1972).

The initial finding of Barchas and Freedman (1963), corroborated by this (table 1) and other investigations (Tonge and Leonard, 1969a, b), suggested a correlation between brain norepinephrine and behavioral responding. Further evidence for implicating cerebral norepinephrine metabolism in the response to LSD was provided by Horita and Hamilton (1969), who demonstrated that pretreatment of rabbits with α-methyltyrosine eliminated or attenuated the postulated central hyperexcitability and the peripheral sympathetic stimulation to LSD without affecting the hyperthermic response. However, direct assessment of brain catecholamine metabolism in the present study, through use of intracisternally injected ^{3}H-norepinephrine, revealed only minor alterations, and those ob-

served occurred only after high doses of LSD. This lack of a specific alteration in norepinephrine metabolism leads to the conclusion that any effect of LSD on cerebral norepinephrine metabolism probably is secondary to the direct action(s) of the drug, *i.e.*, hyperthermia or peripheral sympathetic stimulation. In this respect, it is perhaps significant that the stimulation of norepinephrine formation from ^{3}H-tyrosine (table 2), although significant, is quantitatively much less than the alterations obtained after psilocybin or cold-water swim stress. The indirect nature of LSD's effect on brain norepinephrine suggested here is supported by metabolic evidence in previous reports. Tonge and Leonard (1969b) detected no alterations in endogenous brain NMN content after LSD treatment. Similarly, Tilson and Sparber (1972) observed no changes in the release of ^{3}H-norepinephrine, ^{3}H-NMN or ^{3}H-deaminated-O-methylated products and their conjugates (^{3}H-DOM) during the peak period of behavioral activity change due to LSD. Thus, available data indicate that central noradrenergic systems probably are not directly related to the effects of LSD, at least in the rat.

Psilocybin injection resulted in a prompt and sustained (4-hour) elevation in ^{3}H-NMN levels, accompanied by consistent reductions in both endogenous and ^{3}H-norepinephrine (table 1; fig. 2); other metabolite fractions generally were not altered significantly during the 4-hour period after drug treatment (exceptions: ^{3}H-deaminated catechol metabolites at 1 hour and ^{3}H-DOM at 4 hours). Brain norepinephrine formation increased by 50% shortly after psilocybin treatment. Since alterations in NMN levels generally are thought to parallel changes in norepinephrine release from presynaptic nerve terminals (Schildkraut *et al.*, 1967), these data suggest that psilocybin selectively enhances the release, as well as the synthesis, of brain norepinephrine.

A comparison of the effects of psilocybin and amphetamine on brain ^{3}H-norepinephrine metabolism reveals a marked similarity between the two drugs. Carr and Moore (1969), Wise and Stein (1970) and Tilson and Sparber (1972) all have demonstrated a correlation between amphetamine-induced stimulation of norepinephrine release, and NMN formation, and the behavioral effects of the drug. Despite the biochemical similarities between amphetamine and psilocybin and the comparable behavioral effects observed in at least one test system (Uyeno, 1969), notable differences exist between these two psychoactive drugs with respect to serotonin metabolism. Thus, psilocybin treatment causes an elevation in serotonin content (Freedman, 1963) and a reduction in the levels of 5-hydroxyindoleacetic acid (5-HIAA; Freedman *et al.*, 1970; Tonge and Leonard, 1969a) and inhibits the binding of serotonin to synaptosomes (Marchbanks, 1967), all of which are effects of psilocybin shared with LSD; additionally, these two drugs exhibit cross-tolerance behaviorally (Appel and Freedman, 1968). Amphetamine, on the other hand, causes both increases and decreases of serotonin content in mouse brain, depending upon dosage (Smith, 1965), and increases rat brain 5-HIAA levels (Tagliamonte *et al.*, 1971). In view of the similarities between psilocybin and LSD (but not amphetamine) on serotonin metabolism on the one hand, and between psilocybin and amphetamine (but not LSD) on norepinephrine metabolism on the other hand, it is difficult to ascribe functional significance to either of the effects of psilocybin on biogenic amine metabolism at the present time.

The response of ^{3}H-norepinephrine metabolism to mescaline is the most complex pattern observed in the present study. The initial (40-minute) metabolic pattern reveals a prominent increase in deaminated catechol products, with neither ^{3}H-norepinephrine nor the remaining labeled metabolite fractions being affected significantly (fig. 3). This change is indicative of an increase in deaminative catabolism of norepinephrine intracellularly, since monamine oxidase activity is localized to mitochondria; Tonge and Leonard (1969b) postulated a comparable effect on the basis of reductions in endogenous NMN concentration after mescaline. It is interesting to note that cold water swimming results in a similar alteration of brain ^{3}H-norepinephrine metabolism, although slower in onset and longer in duration than after mescaline (fig. 4). Whereas the effect of cold water swimming on brain ^{3}H-norepinephrine metabolism may well be directly related to marked reductions in body temperature (Stone, 1970), such is not the case after mescaline. In terms of neurotransmitter availability at receptor sites, changes in intracellular catecholamine metabolism, as seen for mescaline and cold-water swim stress, may be of

equal importance as those generally ascribed to norepinephrine release and extracellular NMN formation. The mechanisms regulating enhanced intra- *vs.* extracellular catecholamine catabolism are important topics for future consideration.

Following the apparent increase in intracellular ^{3}H-norepinephrine degradation shortly after mescaline injection, the pattern of catecholamine metabolism changes to one indistinguishable from that obtained with either psilocybin (fig. 2) or amphetamine; thus, the initial period of accelerated intraneuronal degradation is followed by one reflecting enhanced release of norepinephrine. Although mescaline and amphetamine (apart from structural similarities) share common behavioral activity at doses employed in the present study (see Uyeno and Mitoma, 1969; Sparber and Tilson, 1972), prominent dissimilarities between these compounds also exist, particularly with respect to effects on serotonergic systems (*cf.* Tagliamonte *et al.*, 1971, Tilson and Sparber, 1972). The similarities and differences between amphetamine and mescaline merit more detailed comparison with respect to dose parameters, time course and species.

Differentiation of potential subclasses among psychotomimetic drugs has proved difficult, whether attempted on physiological, pharmacological or psychological grounds. One major categorization is between "anticholinergic" and "sympathomimetic" compounds (the terminology is that used by Bebbington and Brimblecombe, 1969; similar subclasses are described in other sources: *viz.* Murphree, 1971). Giarman and Freedman (1965) have discussed potential subclassification of the "sympathomimetic" psychotomimetic drugs. The indolealkylamine hallucinogens (LSD, psilocybin, dimethyltryptamine) can be differentiated from the phenylethylamine compounds (mescaline, 2,5-dimethoxy-α-4-dimethylphenylethylamine) by their effects on brain serotonin metabolism. The indolealkylamine derivatives increase serotonin content and decrease 5-HIAA levels, whereas phenylethylamine derivatives increase both serotonin and 5-HIAA concentrations in brain (Freedman *et al.*, 1970). The indolealkylamine and phenylethylamine derivatives also can be differentiated from each other by behavioral cross-tolerance studies (Appel and Freedman, 1968). However, data from the present study reveal prominent differences with respect to effects on norepinephrine metabolism between three "sympathomimetic" hallucinogens that cannot be accounted for by molecular structure (*i.e.*, indolealkyl- or phenylethylamine nucleus). While this points more to the heterogeneity of these compounds than to a shared action on central noradrenergic neurons, it is readily apparent that an effect on brain biogenic amine metabolism (be it serotonin and/or norepinephrine) is a major characteristic of drugs possessing "psychotomimetic" activity. Although the documented effects of these compounds lead to no single distinguishing neurochemical mechanism, the initial hypothesis of Barchas and Freedman (1963) relating psychotomimetic activity to an imbalance between central noradrenergic and serotonergic function remains viable. Alternatively, the notable differences in biochemical effects of the psychotomimetic drugs are valid bases for concluding that individual compounds derive their psychotomimetic activity from characteristic and peculiar mechanisms.

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