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Relative Potency of Amphetamine Derivatives and N,N-Dimethyltryptamines*

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Abstract. The relative potency of amphetamine derivatives and N,N-dimethyltryptamine (DMT) derivatives was evaluated in rats trained to swim through an underwater tube in order to escape at the other and of the tank. All of the compounds tested significantly increased the starting latency. The time of peak effect of 2,5-dimethoxy-4-ethyl-amphetamine (DOET), 2,5-dimethoxy-4-methyl-amphetamine (DOM), and 6-hydroxy-DMT was estimated at 40 min after the intraperitoneal injection and that of DMT, 4-methoxy-DMT, and psilocybin was 20 min. Dose-response curves showed that the increase in the latency was dose-dependent. The descending rank order of potency of the compounds, according to the median effective dose (ED_{50}), was: DOET, psilocybin, DOM, DMT, 4-methoxy-DMT, and 6-hydroxy-DMT.

Key-Words: Amphetamine Derivatives — N,N-Dimethyltryptamines — Relative Potency.

Previous work with psychotropic compounds has shown that amphetamine derivatives: 2,5-dimethoxy-4-ethyl-amphetamine (DOET) and 2,5-dimethoxy-4-methyl-amphetamine (DOM) were significantly more potent than N,N-dimethyltryptamine (DMT) and its derivatives: 4-methoxy-dimethyltryptamine (4-methoxy-DMT) and 6-hydroxy-dimethyltryptamine (6-hydroxy-DMT), in the disruption of the size discrimination performance of the squirrel monkey motivated by a grape reward (Uyeno, 1969). Furthermore, it was found that 6-hydroxy-DMT was significantly less potent than DMT, indicating that 6-hydroxylation reduces the potency of DMT in the disruption of the previously learned response.

In the present experiment the relative effects of the same compounds and O-phosphoryl-4-hydroxy-ω-DMT (psilocybin) on the underwater swimming performance of rats were investigated.

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Methods

The apparatus consisted of a sheet metal tank (3.66 m by 0.40 m by 0.15 m) with four parallel channels (Uyeno, 1968). Each channel was 3.47 m long, and consisted of a translucent red plastic tube with the diameter of 9 cm. At one end of the channels a detachable 39 cm by 17 cm by 16 cm start box with four compartments was placed in the tank. At the other end, the channels led to the goal box containing four compartments into which the animals escaped. The channels were completely submerged in 23° C water.

The subjects were 190 male rats of the Long-Evans strain, each weighing between 180—200 g. They were housed individually and fed *ad libitum*. By a series of pretraining trials, they were adapted to swimming underwater. A trial was initiated by placing one animal in each of the four compartments of the start box, submerging the start box, and lifting the common guillotine door to allow each animal to swim into its respective tube. Lifting the door automatically started a set of four latency timers. The starting latency of an animal's response was the time which elapsed from the moment the start door was opened until the animal swam past the first photocell, located 17 cm from the start door. Swimming time was recorded as the time to swim from the first photocell to the second photo-cell at the escape exit. On the first pretraining trial the rats were forced to swim underwater through tubes, 1.32 m long in order to escape. On the second and third trials they swam the distance of 2.1 m and 3.47 m, respectively. After the pretraining trials they were given a series of training trials (with an inter-trial interval of approximately 1 h) with the full length channel. They were given eight trials per day until they reached a criterion of three successive latency scores of 1.5 sec or less. On the basis of the mean latency scores of the three criterion trials, the animals were assigned to a control (0.9% saline) group and 18 experimental groups (three experimental groups/compound), with 10 animals per group.

On the day after reaching the criterion they were given test trials at 1, 10, 20, 40, 60, 90, and 120 min after an intraperitoneal injection. The compounds and doses evaluated are shown in Table 1. A standard volume of 2.5 ml/kg of saline or drug-saline solution was administered to each control or experimental animal, respectively.

Results and Discussion

On the test trials, a starting latency of 1.6 sec or longer was considered as an increase with respect to the pre-drug criterion of 1.5 sec. All of the compounds increased the mean starting latency. Generally, the mean latencies of the animals injected with DOET or DOM, were greater than

the mean latencies of the animals, injected with one of the N,N-dimethyltryptamines. The high doses of DOET and DOM increased the swimming times of some animals, but the high doses of other compounds did not. None of the compounds decreased the mean latency nor the mean swimming time. Since the starting latency was a more sensitive measure than the swimming time, the former was used to determine the time of peak effect of the compounds and to plot dose-response curves. For each dose level the percentage of animals that showed an increase in latency at each post-injection time, is shown in Table 1. With regard to the animals administered DMT, 4-methoxy-DMT, or psilocybin, the percentage of animals that showed an increase in latency was highest on the trial given 20 min after the injection. Therefore, the time of peak effect of these compounds was considered to be 20 min after the injection. The time of peak effect of DOM, of DOET, and of 6-hydroxy-DMT was 40 min after the injection.

The dose-response curves were plotted in the following manner. For each dose level of each compound the total number of animals that showed an increase in starting latency at the time of peak effect was obtained. The difference between this score and the control score was

Table 1. *Percentage of animals that showed an increase in starting latency*

Compound	Dose		Post-injection time (min)						
	mg/kg	μmoles/kg	1	10	20	40	60	90	120
DOM	1	4.1	10	30	30	30	10	10	0
	2	8.2	10	20	50	60	60	30	30
	4	16.3	10	60	60	70	50	30	20
DOET	1	3.9	10	20	50	50	50	20	30
	2	7.7	10	40	80	80	40	50	30
	4	15.4	30	50	90	90	70	60	30
DMT	1.6	8.3	10	10	20	10	10	20	0
	3.1	16.6	10	30	50	10	20	20	10
	6.3	33.2	10	50	80	50	40	20	10
4-Methoxy-DMT	1.6	7.2	10	20	30	20	20	10	0
	3.1	14.3	10	30	40	20	20	10	0
	6.3	28.7	20	50	70	20	10	0	0
6-Hydroxy-DMT	5	20.8	10	10	30	40	20	20	0
	10	41.6	20	30	30	50	30	30	0
	20	83.2	20	30	40	70	50	30	10
Psilocybin	1.3	4.4	0	10	30	30	10	10	0
	2.5	8.8	20	30	60	40	40	10	0
	5.0	17.6	10	50	90	50	60	30	0
Saline	—	—	0	0	10	0	10	0	0

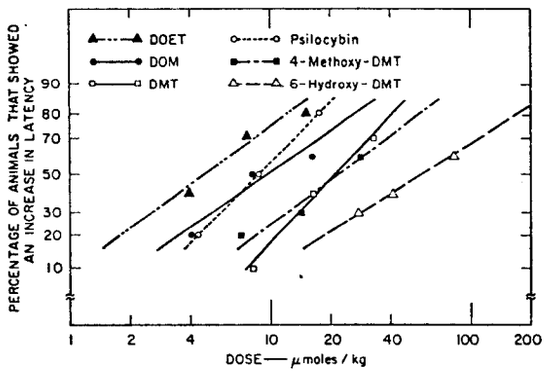


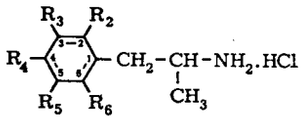
Fig. 1. Dose-response curves: effect of the compounds on the starting latency

considered to be a behavioral measure of the drug effect. These difference scores were expressed as percentages of the total number of experimental animals in each dose level, and plotted against dose on logarithmic probability paper (Fig. 1). The dose-response curves show that the effect of the compounds on starting latency was a function of dose. The median effective dose (ED_{50}) is defined as a dose at which 50% of the animals showed an increase in latency. The ED_{50} calculated according to the method of Litchfield and Wilcoxon (1949) are given in Tables 2 and 3.

The relative potency of the compounds (as measured by an increase in starting latency) was computed by derivation of potency ratios according to the method of Litchfield and Wilcoxon (1949). The potency ratio between two compounds was calculated by dividing the ED_{50} of the less potent one (i. e., the one with the larger ED_{50}) by the ED_{50} of the other. The compounds are arranged in descending order of potency in the first column of Table 4, and in the top row of the table from left to right. The amphetamine derivatives (DOET and DOM) were significantly more potent than DMT derivatives except psilocybin (the phosphoric acid ester of 4-hydroxy-dimethyltryptamine), which was as potent as DOM. 6-hydroxy-DMT was significantly the least potent of all.

Table 2 illustrates the structure-activity relation of amphetamine and its derivatives. The three amphetamine derivatives retain the carbon chain and the two methoxy substituents at position 2 and 5. They differ structurally only in the substituent located at position 4. DOET with the ethyl substituent and DOM with the methyl substituent in position 4 are significantly more effective in increasing the starting latency than is 2,4,5-trimethoxyamphetamine (TMA-2) with the methoxy substituent (Uyeno, 1968).

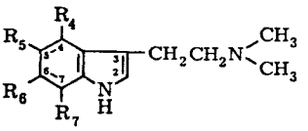
Table 2. *Structure and activity of amphetamine derivatives*



Compound	R_2	R_3	R_4	R_5	R_6	Latency test ED_{50} µmoles/kg	Hallucinogenic properties
d-Amphetamine[a]	H	H	H	H	H	36.5	No
DOET[b]	CH_3O	H	CH_3CH_2	CH_3O	H	4.7	Yes
DOM[c]	CH_3O	H	CH_3	CH_3O	H	9.5	Yes
TMA-2[a]	CH_3O	H	CH_3O	CH_3O	H	15.0	Yes

[a] Uyeno, 1968. — [b] Shulgin *et al.*, 1969. — [c] Snyder *et al.*, 1967.

Table 3. *Structure and activity of N,N-dimethyltryptamine and its derivatives*



Compound	R_4	R_5	R_6	R_7	Latency test ED_{50} µmoles/kg	Hallucinogenic properties
Psilocybin	H_2PO_3 | O	H	H	H	8.7	yes[a]
DMT	H	H	H	H	20.1	yes[b]
4-Methoxy-DMT	CH_3O	H	H	H	22.0	—
6-Hydroxy-DMT	H	H	OH	H	57.0	questionable[c]

[a] Isbell, 1959. — [b] Szara, 1957. — [c] Rosenberg *et al.*, 1963.

Table 3 shows the structural formulae of the four N,N-dimethyltryptamine derivatives that retain the side chain and differ structurally only in the substituents located in position 4 and 6. Psilocybin, with the 0-phosphoryl-hydroxy group at position 4, is significantly most effective. 6-hydroxy-DMT with the hydroxy group at position 6 is least effective.

The results indicating that the amphetamine derivatives are significantly more potent than 4-methoxy-DMT and 6-hydroxy-DMT in disrupting the starting performance of the rats, support the previous study

Table 4. *Relative potencies of the compounds*

Compound	Variable	DOET	Psilocybin	DOM	TMA-2	DMT	4-Methoxy-DMT	6-Hydroxy-DMT
LSD-25[a]	P.R.[b]	2.5	4.6	5.0	7.9	10.6	11.6	30.0
	Sig.[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	C.L.[d]	(1.2—5.1)	(2.9—7.4)	(2.6—9.7)	(4.3—14.5)	(6.2—18.1)	(6.3—21.4)	(14.9—60.3)
DOET	P.R.		1.9	2.0	3.2	4.3	4.7	12.1
	Sig.		No	No	Yes	Yes	Yes	Yes
	C.L.				(1.3— 7.8)	(1.8— 9.9)	(1.9—11.4)	(4.7—31.3)
Psilocybin	P.R.			1.1	1.7	2.3	2.5	6.6
	Sig.			No	No	Yes	Yes	Yes
	C.L.					(1.2— 4.3)	(1.3— 5.1)	(3.0—14.2)
DOM	P.R.				1.6	2.1	2.3	6.0
	Sig.				No	No	Yes	Yes
	C.L.						(1.0— 5.3)	(2.5—14.7)
TMA-2[a]	P.R.					1.3	1.5	3.8
	Sig.					No	No	Yes
	C.L.							(1.6— 9.0)
DMT	P.R.						1.1	2.8
	Sig.						No	Yes
	C.L.							(1.3— 6.4)
4-Methoxy-DMT	P.R.							2.6
	Sig.							Yes
	C.L.							(1.1— 6.1)

[a] Uyeno, 1968.

[b] Potency ratio $= \frac{\text{ED}_{50} \text{ of compound in the top row}}{\text{ED}_{50} \text{ of compound in the first column}}$.

[c] Significant at the 5% level.

[d] 95% confidence limits.

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conducted with squirrel monkeys (Uyeno, 1969). The increase in the starting latency was due to the hesitation to emerge from the startbox when the door was raised. The delay seems to indicate that the compounds disrupted the perception (Schwartz and Cheney, 1965) of the starting stimulus; i. e., the opening of the door. The finding that DOM is significantly less effective than lysergic acid diethylamide (LSD-25) (Uyeno, 1968) in disrupting the performance of the rats, is consistent with the data of Snyder *et al.* (1967). Furthermore, the finding that 6-hydroxy-DMT is significantly less potent than DMT, is in accord with that of Rosenberg *et al.* (1963), and that of Taborsky *et al.* (1966) who reported that 6-hydroxy-5-methoxy-DMT is significantly less potent than non-hydroxylated 5-methoxy-DMT in decreasing the bar-pressing performance of food-deprived rats. These results indicate that 6-hydroxylation reduces the potency of DMT.

4-Methoxy-DMT	P.R.	2.6
	Sig.	Yes
	C.L.	(1.1 — 6.1)

[a] Uyeno, 1968.
[b] Potency ratio $= \frac{ED_{50} \text{ of compound in the top row}}{ED_{50} \text{ of compound in the first column}}$.
[c] Significant at the 5% level.
[d] 95% confidence limits.

References

Isbell, H.: Comparisons of the reactions induced by psilocybin and LSD-25 in man. Psychopharmacologia (Berl.) **1**, 29—38 (1959).

Litchfield, J. T., Jr., Wilcoxon, F.: A simplified method of evaluating dose-effect experiments. J. Pharmacol. exp. Ther. **96**, 99—113 (1949).

Rosenberg, D. E., Isbell, H., Miner, E. J.: Comparison of a placebo, N-dimethyltryptamine, and 6-hydroxy-N-dimethyltryptamine, and 6-hydroxy-N-dimethyltryptamine in man. Psychopharmacologia (Berl.) **4**, 39—42 (1963).

Schwartz, A. S., Cheney, C.: Retinal effects of high doses of LSD in the cat. Exp. Neurol. **13**, 273—282 (1965).

Shulgin, A. T.: Psychotomimetic Amphetamines: methoxy 3,4-dialkoxy-amphetamines. Experientia (Basel) **20**, 366—367 (1964).

— Sargent, T., Naranjo, C.: Structure-Activity Relationships of One-Ring Psychotomimetics. Nature (Lond.) **221**, 537—541 (1969).

Snyder, S. H., Faillace, L., Hollister, L.: 2,5-Dimethoxy-4-methylamphetamine (STP): A new hallucinogenic drug. Science **158**, 669—670 (1967).

Szara, S.: The comparison of the psychotic effect of tryptamine derivates with the effects of mescaline and LSD-25 in self experiments. In: Psychotropic Drugs. S. Garattini and V. Ghetti, *eds.*, pp. 460—467. Amsterdam: Elsevier 1957.

Taborsky, R. G., Delvigs, P., Page, I. H.: 6-Hydroxylation: effect on the psychotropic potency of tryptamines. Science **153**, 1018—1020 (1966).

Uyeno, E. T.: Hallucinogenic compounds and swimming response. J. Pharmacol. exp. Ther. **159**, 216—221 (1968).

— Alteration of a learned response of the squirrel monkey by hallucinogens. Int. J. Neuropharmacol. **8**, 245—253 (1969).

— Otis, L. S., Mitoma, C.: Behavioral evaluation of hallucinogenic trimethoxyamphetamines in squirrel monkeys (*Saimiri sciureus*). Commun. Behav. Biol., Part A **1**, 83—90 (1968).

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