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Structure Activity Relations of some Indolealkylamines in Comparison to Phenethylamines on Motor Activity and Acquisition of Avoidance Behavior

Michael R. Vasko*, Michael P. Lutz, and Edward F. Domino

Michigan Neuropsychopharmacology Research Program, Department of Pharmacology, University of Michingan, Ann Arbor, Michigan and Lafayette Clinic, Detroit, Michigan

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Abstract. The structure-activity relationships (SAR) of various known hallucinogenic and nonhallucinogenic indolealkylamine and phenethylamine derivatives were compared on two different behaviors: mouse locomotor activity and acquisition of one-way avoidance behavior in the rat. Certain parallels were observed between the two classes of compounds. α-Methyl substituted derivatives of the indoles and phenethylamines increased dramatically psychomotor stimulant effects. Acquisition of one-way avoidance behavior was reduced by the more potent hallucinogens and psychomotor stimulants of both classes. Pargyline pretreatment enhanced the psychomotor stimulant effects of all of the compounds tested except 5-hydroxytryptamine (5-HT), *d*-amphetamine, mescaline and lysergic acid diethylamide (LSD-25).

Key words: Indolealkylamines — Phenethylamines — Locomotor Activity — Hallucinogens — One-Way Avoidance Behavior — Monoamine Oxidase Inhibitor — LSD-25.

Interest in indolealkylamine and phenethylamine derivatives has steadily increased since 5-hydroxytryptamine (5-HT) and norepinephrine (NE) were first shown to be present in the central nervous system (Vogt, 1954; Amin *et al.*, 1954). Furthermore, tryptamine derivatives like N,N-dimethyl-5-hydroxytryptamine (bufotenin), N,N-dimethyltryptamine (DMT), and 5-methoxydimethyltryptamine (5-MeoDMT), and phenethylamine derivatives like mescaline have been studied for possible hallucinogenic effects (Sai-Hálász *et al.*, 1958; Hawkins and Fabing, 1956; Holmstedt and Lindgren, 1967; Buchanan, 1929; Stocking, 1940; Rinkel, 1957). These compounds have also been postulated to play a role in mental disorders (Pollin *et al.*, 1961; Woolley, 1962) in relation to adrenergic and serotonergic neurons.

We were interested in studying the effects of indole derivatives on simple animal behaviors, prior to judicious studies in humans. We have

* Predoctoral fellow in the Department of Pharmacology, University of Michigan.

used the model of the structure activity relations (SAR) of phenethylamines in the hope of uncovering some similarities. This manuscript describes some of the relations observed comparing various compounds on these behavioral endpoints in rodents.

Materials and Methods

Materials. All drugs were given i.p. Dosage was calculated as base and the agent dissolved in 0.9% NaCl. Saline and pargyline controls were run in both behaviors. Volumes injected never exceeded 1.0 ml and usually were less than 0.5 ml. The indoles, 5-methoxytryptamine, 5-methoxy N,N-dimethyltryptamine, N-methyltryptamine and 5-hydroxy N,N-dimethyltryptamine were obtained from the Aldrich Chemical Company. α-Methyltryptamine succinate was obtained from Dr. D. McCarthy of Parke Davis and Company. Trytamine was obtained from Calbiochem and N,N-dimethyltryptamine from the Regis Chemical Company. The 5-hydroxytryptamine creatinine sulfate was obtained from British Drug Houses Ltd. The α-methyl N-methyltryptamine (SKF-7024-B) was obtained from Smith, Kline and French. Phenethylamine was obtained from the Aldrich Chemical Company. The *d*-amphetamine sulfate was obtained from Calbiochem. Pargyline was obtained from Dr. A. Dren of Abbott Laboratories. The LSD-25 was obtained from Dr. M. Braude, Executive Secretary, FDA-NIMH Drug Abuse Advisory Committee, Center for Studies of Narcotic and Drug Abuse, National Institute of Mental Health.

Mouse Locomotor Activity. Subjects were naive albino male mice from Spartan Farms, weighing 25—45 g. The animals had free access to food and water until weighed for the experiment. They were then injected i.p. and either run immediately for 2 h or isolated in a plastic box for a variable period of time depending upon the drug injected and then run. The mice were kept on a circadian rhythm schedule 12 h light (8.00 a.m. to 8.00 p.m.) and 12 h dark (8.00 p.m. to 8.00 a.m.). They were run only in the daylight hours. The animals were used for only one session and then discarded.

The apparatus used to measure locomotor activity was an Electronic Motility Meter (FC 40) with forty photocells and an overhead light source. Two such units were put into a single isolation box (inside dimensions: 60 × 91 cm) one above the other. With this method only the animal's horizontal movements were recorded. The temperature inside the box was 23°C, but the temperature immediately above the photocells sometimes reached 28°C. External noise was reduced by a white noise generator connected to a speaker inside the box. Two 7 watt overhead lights were used to avoid further excesses in heat. Animals were run one per transparent box. The transparent box used for the session had numerous air vents and was covered with a metal screen, thus increasing further the air circulation. Animals were placed in the container after injection, and the box placed above the photocells immediately prior to the beginning of a session. No animal was placed in the isolation chamber until immediately prior to the session. Each session was 120 min long.

Animals were given an i.p. injection of drug just prior to the beginning of the session. The only exceptions to this were when the two α-methyl indoles were employed. Due to their delayed onset of action (Murphree, 1961), the animals were run thirty min after i.p. injection. Pargyline, a monoamine oxidase (MAO) inhibitor, as a pretreatment, was given i.p. in a dose of 150 mg/kg 2 h prior to the start of the session.

Acquisition of One-Way Avoidance Behavior. Naive albino male Holtzman rats weighing 270—440 g were tested in a one-way shock avoidance apparatus (Tenen,

1965, Newman *et al.*, 1972). They had free access to food and water until just prior to the session. Animals were on a 12.30 a.m. to 7.30 a.m. dark and 7.30 a.m. to 12.30 a.m. light cycle. Sessions consisted of fifty trials as described previously (Newman *et al.*, 1972). Drugs were given i.p. just prior to the session, except for two α-methyl indoles as described above. Only naive animals were used. Results were calculated as percent of avoidance. The actual mean number of avoidances can be obtained by dividing the percent avoidance by 2. The sequence of a session consisted of a light stimulus for 5 sec, a shock to the foot pads for 5 sec, then a 30 sec rest period. If the animal jumped on the platform in the first 5 sec, it was termed an avoidance response. If it jumped on the platform during the shock, it was termed an escape response.

Results

Locomotor Activity. As can be seen in Figs. 1 and 2, most of the indole derivatives studied did not cause any significant increase in mouse locomotor activity. The major exceptions were the two α-methyl indoles which produced a marked increase in locomotor activity in doses of 10 to 32 mg/kg. The increases in activity were dose-related. These agents appeared to be unusual among the indoles tested.

The results with the indoles are to be compared with various phenethylamines and LDS-25 as shown in Fig. 3. Phenethylamine, like tryptamine, had no significant effects on locomotor activity, but its α-methyl derivative, *d*-amphetamine, had marked effects, as is well known.

When the mice were pretreated with pargyline (150 mg/kg i.p. 2 h before) dramatic increases in locomotor activity were seen with most of the agents tested. Pargyline caused an increase in the maximum response and also a shift to the left in their dose response curves. The only indole not potentiated by pargyline pretreatment on motor activity was 5-HT. Of the phenethylamine derivatives tested only phenethylamine showed a significant potentiation of motor activity with pargyline pretreatment, as shown in Fig. 3. The locomotor effects of the hallucinogenic derivatives LSD-25 and mescaline as well as the psychomotor stimulant *d*-amphetamine were not potentiated by pargyline.

The quantitative increases in motor activity before and after pargyline were related to the chemical structure of the compounds tested. Of the tryptamine derivatives studied tryptamine itself appeared to be the least potent, followed by 5-methoxytryptamine, dimethyl-tryptamine, 5-methoxydimethyltryptamine. The most potent were α-methyl and α-methyl-N-methyl tryptamine. Of the phenethylamine derivatives tested only *d*-amphetamine showed a marked increase in motor activity. After pargyline pretreatment only phenethylamine showed a marked enhancement of motor activity. Pargyline by itself did not have any significant effect in increasing locomotor activity in the dose given for the 2 h sessions after pretreatment.

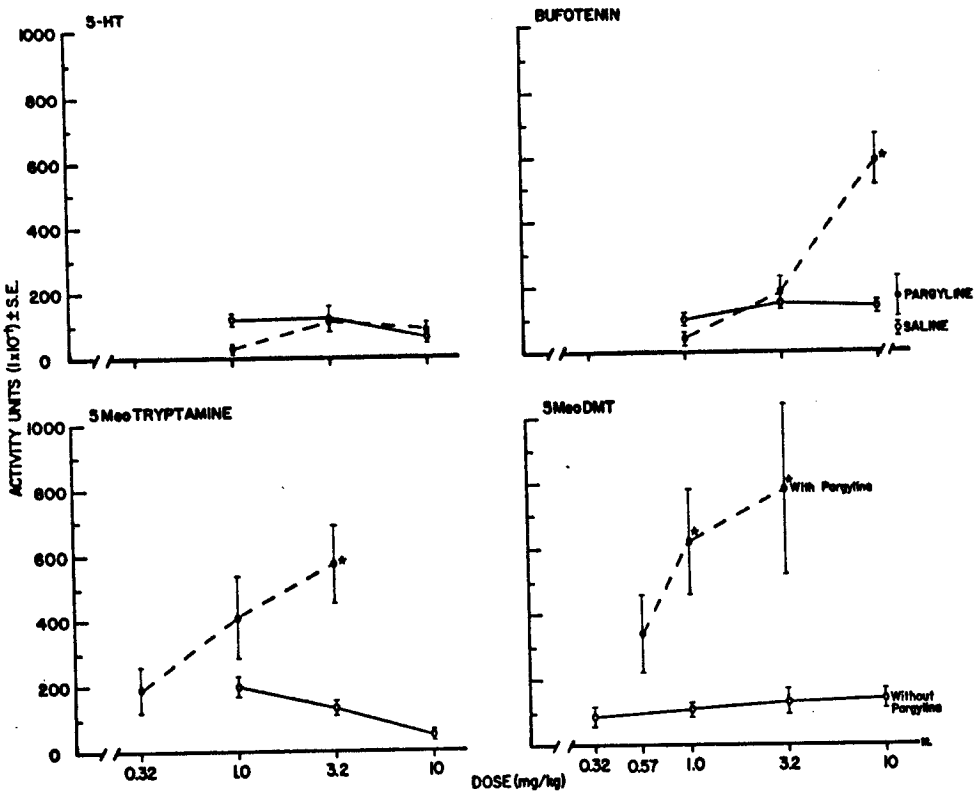

Fig. 1. Effects of various 5-hydroxytryptamine derivatives on mouse locomotor activity with and without pargyline pretreatment. Mean motor activity ± S.E./120 min is given on the ordinant and log dose on the abscissa. Each point represents the mean ± S.E. of 6 mice run individually. Pargyline was given in a dose of 150 mg/kg i.p. 120 min prior to the test agent which was also given i.p. In this and all other figures the * indicates a P value of < 0.05 group comparison with and without pargyline pretreatment

Acquisition of One-Way Avoidance Behavior. This behavior showed very clearly the SAR of the compounds tested. Tryptamine alone and N-methyltryptamine had little or no effect on acquisition behavior when compared with saline controls (Table 1). The same results were seen with phenethylamine. α-Methyl N-methyltryptamine had an intermediate depressant effect between tryptamine and DMT. α-methyltryptamine showed very strong effects in suppressing this behavior (Table 1). Both 5-HT and bufotenin showed very little effect. The addition of a 5-methoxy group to tryptamine and dimethyltryptamine caused

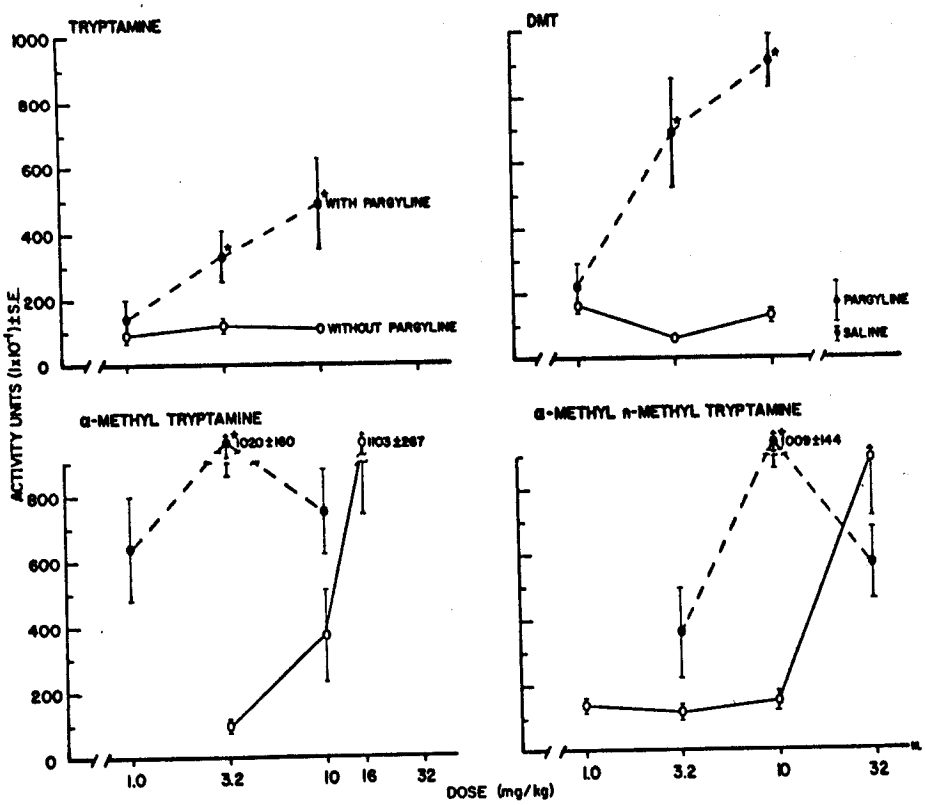

Fig. 2. Effects of various tryptamine derivatives on mouse locomotor activity with and without pargyline pretreatment. For all indole derivatives except α-methyltryptamine and α-methyl N-methyltryptamine the drug was administered i.p. and locomotor activity measured immediately for the next 120 min. In the case of the α-methyltryptamines the pretreatment time was 1/2 h in view of the delayed onset of action of *alpha* substituted derivatives

further behavioral toxicity as manifested by an even greater decrease in acquisition.

The effects of the phenethylamine derivatives on acquisition are also summarized in Table 1. As observed before, the α-methyl derivative, *d*-amphetamine, had a potent suppressant effect. In an analogous manner to the indoles, phenethylamine had very little depressant effect, while its α-methyl derivative, *d*-amphetamine, was a potent inhibitor of avoidance acquisition. LSD-25, a known hallucinogen in man, was the most effective in depressing this behavior.

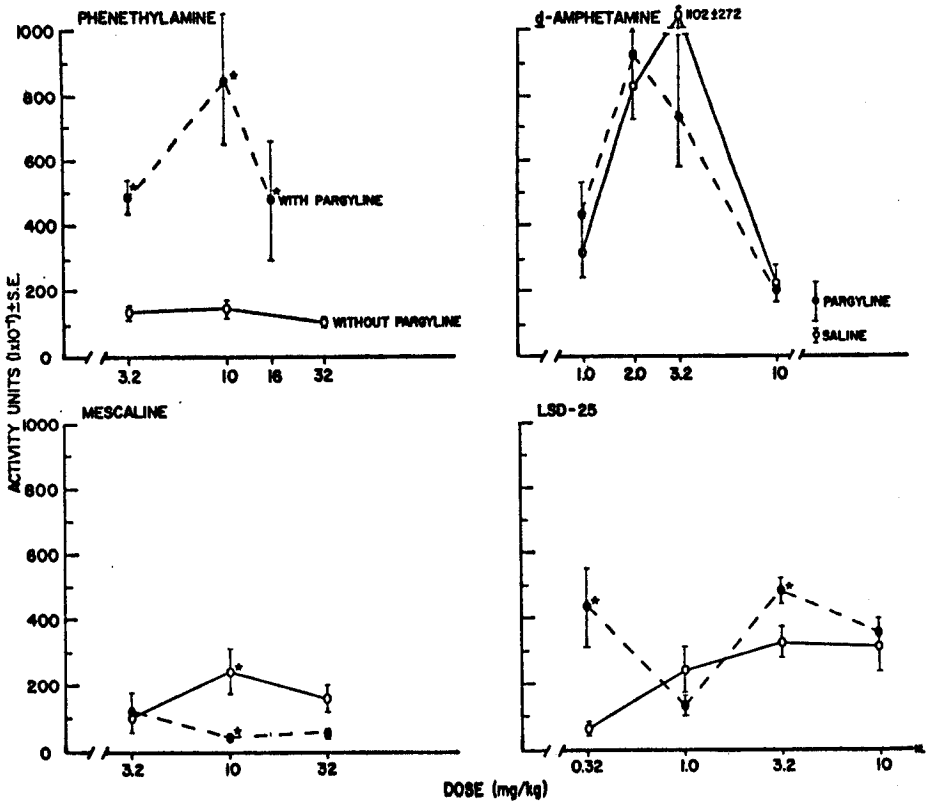

Fig. 3. Effects of various phenethylamine derivatives and LSD-25 on mouse locomotor activity with and without pargyline. Pargyline was given in a dose of 150 mg/kg i.p. 120 min prior to the test agent which was also given i.p.

Discussion

One major criticism of the use of mouse locomotor activity and rat jump box avoidance behavior is that these methods are nonspecific. A large number of drugs will affect both behaviors. More specific behaviors indicative of a hallucinogenic effect include the wing splay of the baby chick (Mandell *et al.*, 1971) and head bobbing in mice (Siegal and Jarvik, 1972). However, the value of the present methods lies in their simplicity and objectivity.

Although the behavioral methods used in this study are rather nonspecific, they show clearly a great separation of the various derivatives of the two classes of compounds tested. There are many similarities between tryptamine and phenethylamine and their α-methyl derivatives.

Table 1. Effects of various indolealkylamine and phenethylamine derivatives on the acquisition of one way avoidance behavior

Drug	Dose mg/kg i.p.	*N*	% Avoidance ± S.E.	*P* Value compared to saline
Saline	—	8	88.3 ± 2.1	—
Tryptamine	1.0	6	79.3 ± 5.2	N.S.
	3.2	6	90.0 ± 1.1	N.S.
	10.0	6	79.0 ± 2.7	< 0.05
N-methyltryptamine	3.2	6	86.3 ± 1.2	N.S.
	10.0	6	87.0 ± 1.9	N.S.
α-methyltryptamine	1.0	6	71.0 ± 8.9	N.S.
	3.2	6	44.0 ± 11.3	< 0.01
	10.0	6	14.3 ± 5.3	< 0.001
α-Methyl N-methyltryptamine	3.2	6	85.0 ± 1.7	N.S.
	10.0	6	73.6 ± 4.2	< 0.05
	32.0	6	21.0 ± 3.4	< 0.001
Dimethyltryptamine	1.0	6	88.3 ± 1.2	N.S.
	3.2	6	81.3 ± 5.0	N.S.
	10.0	6	50.5 ± 2.9	< 0.001
5-Hydroxytryptamine	3.2	6	80.6 ± 3.4	N.S.
	10.0	6	84.0 ± 4.9	N.S.
5-Methoxytryptamine	1.0	6	83.3 ± 4.8	N.S.
	3.2	6	83.0 ± 4.2	N.S.
	10.0	6	67.3 ± 6.7	< 0.05
Bufotenin	1.0	6	84.7 ± 1.4	N.S.
	3.2	5	79.6 ± 2.1	< 0.05
	10.0	6	78.3 ± 2.6	< 0.05
5-Methoxydimethyltryptamine	1.0	6	76.0 ± 5.8	N.S.
	3.2	6	74.3 ± 5.9	N.S.
	10.0	6	37.7 ± 11.4	< 0.01
Phenethylamine	1.0	6	85.6 ± 2.5	N.S.
	3.2	6	88.3 ± 1.2	N.S.
	10.0	6	90.3 ± 1.4	N.S.
d-Amphetamine	1.0	6	83.7 ± 4.0	N.S.
	3.2	6	64.3 ± 13.0	N.S.
	10.0	6	30.7 ± 14.8	< 0.01
LSD-25	0.3	6	76.7 ± 2.3	< 0.02
	1.0	6	51.0 ± 12.0	< 0.02
	3.2	6	35.7 ± 16.1	< 0.02

It has long been postulated that animal locomotor activity is a suitable model of CNS psychomotor stimulation in man. Of all of the indole derivatives with known hallucinogenic properties in man which we tested, only the α-methyl indoles had any significant effect on locomotor

activity. DMT, 5-MeoDMT, bufotenin and tryptamine (Figs. 1 and 2) did not affect locomotor activity. Neither did the hallucinogens LSD-25 or mescaline (Fig. 3).

In like manner, phenethylamine in the doses tested did not increase locomotor activity. Its α-methyl derivative, *d*-amphetamine, did. These similarities between the two α-methyl analogs suggest that these compounds are active because they are not metabolized by MAO (Blaschko, 1952). It is possible that they have direct receptor agonist actions. However, the fact that pargyline shifted the dose-effect curve of the α-methyl tryptamines to the left also suggests that they may act indirectly by releasing brain amines. Other indole amines tested increased motor activity as well, but only after MAO was inhibited. It should be noted that there is some evidence to support a possible tryptaminergic receptor in the brain (Vane, 1961).

α-Methyltryptamine had a delayed onset of action which cannot be explained as delayed uptake (Murphree, 1961). Perhaps α-methyltryptamine has an indirect effect in causing the release of 5-HT, the same way that α-methylphenethylamine (*d*-amphetamine) affects norepinephrine. Other evidence that supports this notion is that pargyline potentiated the effect of α-methyltryptamine. Since this agent is not oxidized by MAO, it may be releasing some substance that is biotransformed. Although there was a slight shift to the left in the dose effect curve to *d*-amphetamine after pargyline pretreatment, it was not statistically significant. In contrast, Smith (1965) was able to show a shift in *d*-amphetamine dose response curve for locomotor activity with iproniazid pretreatment. Further studies are obviously indicated because the substrate specificities of iproniazid and pargyline as MAO inhibitors may vary.

After pargyline pretreatment, locomotor activity was enhanced by the potent hallucinogenic indoles 5-MeoDMT and DMT more than by 5-methoxy-tryptamine and tryptamine. Bufotenin had almost no locomotor stimulant effects after pargyline and 5-HT had none, presumably because these agents do not readily penetrate the blood-brain barrier. Structural alterations which are known to increase hallucinogenic activity also increased mouse locomotor activity after MAO inhibition. A similar SAR was seen for the phenethylamine derivatives. Those agents known to cause the most central nervous stimulation in man also produced the greatest increase in mouse locomotor activity (Fig. 3). After pargyline, phenethylamine also showed an increase in motor activity. Presumably, it is normally metabolized so rapidly it has no significant activity, but if the biotransformation is reduced its activity resembles *d*-amphetamine.

The hallucinogenic phenethylamine, mescaline, as well as LSD (Fig. 3) do not show the increase in locomotor activity after pargyline that was seen with the indoles.

The SAR of the indole derivatives was also similar using acquisition of rat jump box behavior as an endpoint. The more potent hallucinogenic indoles depressed acquisition of avoidance behavior more than the non-hallucinogens. These results agree with the structure-activity relationship study using established conditioned avoidance behavior (Gessner, 1962). Likewise, the more potent psychomotor stimulants like *d*-amphetamine depress this behavior more than poor stimulants like phenethylamine.

The fact that pargyline pretreatment enhances the locomoter effects of most of the drugs studied suggests that these compounds may either act directly prior to being metabolized by MAO and/or they release brain biogenic amines. Perhaps some of the indole compounds may act directly on receptor site (DMT) but others like α-methoxytryptamine may act directly and/or indirectly. Studies on brain levels of neurotransmitter substances, especially NE, DA and 5-HT and their metabolites may lead to knowledge on the mechanism of action of the observed behavioral endpoints.

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Dr. Edward F. Domino
Pharmacology Laboratory
The Lafayette Clinic
951 East Lafayette
Detroit, Michigan 48207
U.S.A.