Effects in normal man of α-methyltryptamine and α-ethyltryptamine

DL-α-Methyltryptamine methyl sulfate in oral doses of 20 mg. and DL-α-ethyltryptamine acetate in oral doses of 150 mg. were compared objectively and subjectively in a group of trained, normal human volunteers. Blood pressure, pulse rate, pupil diameter, oral temperature, and grip strength were recorded hourly. Subjective effects were recorded 3 and 24 hours after administration of the drugs.

A significant decrease in heart rate occurred 2 hours after α-ethyltryptamine. Significant rises in systolic and diastolic blood pressure occurred 3 hours after α-methyltryptamine. There also were significant increases in pupil diameter after each drug.

The subjective effects were similar in many respects, but there were important differences. The onset of action was rapid for α-ethyltryptamine and slow for α-methyltryptamine; duration of action was longer for the latter than for the former. The most common effect, reported by 8 of the 11 subjects taking α-ethyltryptamine, was a feeling of being elated or intoxicated. The most common effects reported by those who took α-methyltryptamine were nervous tension and restlessness not unlike those produced by 50 to 60 μg of lysergic acid diethylamide.

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Tryptamine and 5-hydroxytryptamine are two metabolic amines formed in the body by decarboxylation. A study of the DL-α-methyl and DL-α-ethyl congeners of tryptamine has shown each of these to be active monamine oxidase inhibitors in vitro. Recent investigations at The Upjohn Company* and by Greig, Walk, and Gibbons[2] indicate that the inhibiting actions of the two derivatives do not differ greatly.

Pharmacologic properties

α-Methyltryptamine. Oral LD_{50} in the rat is given by Sandoz, Inc.,† as 138 ± 25 mg. per kilogram (weight, age, and strain not

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†A. Cerletti: Via personal communication from R. Bircher, September, 1959.

Table I. *Number of subjects who reported each effect of α-methyltryptamine and α-ethyltryptamine 24 hours after administration*

Effect	α-Methyltryptamine methyl sulfate, 20 mg. (12 subjects total)	α-Ethyltryptamine acetate, 150 mg. (11 subjects total)
Visual flashes	1	2
Blurred vision	3	3
Exhilaration and/or intoxication	3	8
Dizziness	3	2
Muscle cramps or tightness	4	3
Numbness	2	1
Nervous tension	7	2
Afternoon lethargy or sedation	1	5
Restlessness, inability to relax in afternoon	7	0
Headache	3	2
Analgesia	2	0
Loss of appetite and/or slight nausea	5	6
Hangover	4	4
Lysergic acid diethylamide simulation	1	0
Similar to lysergic acid diethylamide	7	1
Lysergic acid diethylamide plus something more	1	1

specified); the same source indicates mydriasis and pressor effect in the cat with rapid tachyphylaxia. However, The Upjohn Company* finds LD_{50} in the rat to be 22.4 ± 4.4 mg. per kilogram.

α-Ethyltryptamine. Oral LD_{50} in the rat is 48 ± 11 mg. per kilogram (The Upjohn Company*), and intraperitoneal LD_{50} in the mouse is 72.5 ± 16 mg. per kilogram. The compound is nontoxic at 10 mg. per kilogram per day orally for 4 weeks in rats and at a dosage of 3 mg. per kilogram per day orally for 21 days in dogs; intravenous injection produces a slight pressor effect in the dog. The relative toxicities of the α-ethyltryptamine and α-methyltryptamine, therefore, are not entirely clear at present, but they are evidently of the same order of magnitude.

Methods

Selection of subjects. As in similar studies,[1] the subjects were inmates of the U. S. Penitentiary, Atlanta, who volunteered for the study. After careful screening, the subjects were introduced to the pharmacologic effects of D-lysergic acid diethylamide. During a 4-week period, successive oral doses of 25, 50, 75, and 100 μg were administered at 1 week intervals. In this way, each subject became fully familiar with the effects of the drug both qualitatively and quantitatively.[1] They also were trained to know that only an unbiased opinion about their subjective effects was wanted and that their status on the project was not dependent on giving "right answers." Each experimental procedure included active and inert blanks, and the subjects were also given doses of lysergic acid diethylamide from time to time. This was intended to help them keep in mind their scales of subjective effects so that they would be, insofar as possible, neither "placebo reactors" nor unduly skeptical. It served at least to keep them alert at all times to the question of whether they received an active drug or a blank. For participating, each man was given $3 for each week on the project and 3 days' "good time," i.e., credit toward conditional release, for each month on the project. In all, there were 16 subjects.

Assay of new compounds. It is our usual policy to begin the testing of a new compound with a trivial dose in 1 individual only. This is gradually increased until a

*Alan B. Varley: Personal communication, April, 1961.

Table II. *Representative 24 hour reports*

Time	*Subjects' description of effects*
Subject K: α-methyltryptamine, 20 mg. oral dose	
8:00 A.M.	Reported to project after good night's sleep
8:30	Received drug
11:30	For first 3 hours, no effects; thought I'd had a blank
12:30 P.M.	Becoming physically uncomfortable, muscles tense, nervous, irritable, stomach slightly unsettled
2:30	Very restless; can't sleep; must be LSD, but this delayed reaction is something new to me; lots of nervous tension, stiff neck, blurry vision, loss of depth perception; would equate this to 50 γ LSD-25 in case LSD was not given
5:00	Excessive dilation of pupils about 8 mm., but no resulting distortion or fuzziness
8:00	Judgment impaired to some extent, probably through sheer fatigue; I feel completely washed out and spent physically
Next day	If LSD, then strong dosage, since effects never completely receded before going to sleep (midnight); the next morning considerably "hung over," feeling run down, and mentally sluggish
Subject H: α-ethyltryptamine, 150 mg. oral dose	
8:30 A.M.	Received drug, ate no breakfast
9:00	Felt the drug right away, felt dizzy, intoxicated; things are picking up
9:30	At first check felt fine, stimulated; thought my eyes were going out of focus, but they settled down
10:30	Still riding high; can't figure if I'm nervous and tense or just intoxicated
11:30	Ate no lunch, feel good, thought the doctor had already left; talking a lot, in fact at one time wouldn't answer anyone in plain English, had to spout gibberish at them
12:30 P.M.	Still talking gibberish, but starting to come down off my high
1:30	Lethargy is starting to set in
3:00	Drowsy, stomach feels jittery; would like to sleep
8:00	Throat is sore from talking too much, slight headache
11:00	Going to be *tired* and let down
Next day	Awoke feeling fair, little used up; throat feels very tired

predetermined level is reached or until effects are noticed. DL-α-Ethyltryptamine acetate was given orally in an initial dose of 30 mg. This was increased in increments of 15 mg. at weekly intervals to a level of 150 mg. At this dose, the drug effects were definite. Following a Latin square design with crossovers, 11 subjects received this dosage, the remainder receiving in all instances only lactose placebos. The drug was given at 8:30 A.M. after baseline observations of blood pressure, pulse rate, oral temperature, and grip strength had been made. These measurements were repeated at hourly intervals after medication. At the end of the test period, the subjects were asked nondirectively to describe the effects of the medication. The physician who made the inquiries did not know at the time what the subjects had been given. The subjects also made 24 hour reports after administration. The same procedure was followed for the testing of DL-α-methyltryptamine methyl sulfate (IT-290), except that the first dose was 10 mg. and the largest dose 20 mg. Twelve subjects received the 20 mg. dose of active compound in this study.

Results

Subjective observations. Table I shows the range of subjective effects produced by the two compounds as abstracted from the 24 hour reports. As reported by our subjects, the onset of action of α-methyltryptamine is slow after oral administration, becoming noticeable only after 3 to 4 hours. The duration of action was long, usually 12 to 24 hours, with 2 subjects reporting a duration of 2 days. Ten of the 12 reported unpleasant feelings: nervous tension, irrita-

bility, restlessness, and inability to relax and sleep during the afternoon. Visual effects were not pronounced, but 3 reported difficulty in focusing, 1 a few flashes of light. Two subjects, 1 who arrived for the experiment with a headache, the other with a headache and a toothache, reported an analgesic effect lasting about 3 hours. In general, the subjects did not like the drug, expressed feelings of discomfort, and likened the effects to a long-lasting lysergic acid diethylamide-like compound.

α-Ethyltryptamine, on the other hand, was characterized by a more rapid onset of action (30 to 90 minutes). Eight of the 11 subjects reported feelings of intoxication. Two stated that they felt "stimulated." One reported no effect other than feeling "hot and itchy." Five noted an afternoon lethargy, letdown, or sedation. Only 1 reported that he slept poorly, and that because of a headache. Four reported a hangover the next day. But for the most part the effects were short (2 to 6 hours) or moderate (6 to 12 hours) in duration. Six subjects reported loss of appetite and/or slight nausea. Muscle effects consisted of cramps or tenseness and weakness or numbness. Three reported visual disturbances; these consisted of blurred vision or a few flashes of light. Only 2 equated the drug to something like lysergic acid diethylamide. The most prominent effect, therefore, of 150 mg. of α-ethyltryptamine is a feeling of intoxication accompanied by loss of appetite. This intoxicated or elated feeling lasts 4 to 5 hours and gives way to lethargy, sedation, or a letdown feeling.

Table II gives two representative 24 hour reports in full.

Objective observations. Table III shows mean blood pressures, heart rates, and, in the case of α-ethyltryptamine only, grip strengths, as recorded at hourly intervals.

α-Methyltryptamine produced an increase in systolic and diastolic blood pressure 3 hours after administration. α-Ethyltryptamine caused slowing of the heart rate at 2 hours, with return to control value at 3 hours. The matched controls, who received only blanks during the same experimental periods, showed no significant changes in any of the variables.

It is to be noted that delayed physiologic actions may have been missed, since recordings were not made later than 3 hours after dosage.

Pupil diameter data were set in a matrix of "larger than," "same as," or "smaller than" control values. The chi square test yielded the following results: for α-methyltryptamine 4.58, which with $df=3$ gives $P < 0.05$; for α-ethyltryptamine 17.41, which with $df=3$ gives $P < 0.01$. In both cases, the pupil diameters were increased.

Discussion

These results strongly suggest that monamine oxidase inhibition as determined in vitro or even in vivo is not a reliable indicator that a compound will have useful drug action. It might seem that inhibition

Table III. *Physiologic observations after dosage with α-methyltryptamine and α-ethyltryptamine*

Compound	*Observation*	*Time*			
		Control	*1 hr.*	*2 hr.*	*3 hr.*
α-Methyltryptamine	Systolic blood pressure (mean mm. Hg)	118.7	118.8	118.9	124.4°
	Diastolic blood pressure (mean mm. Hg)	70.6	71.8	74.6	76.7°
	Heart rate (per minute)	80.0	78.3	80.7	84.4
α-Ethyltryptamine	Systolic blood pressure	117.7	113.2	119.1	120.9
	Diastolic blood pressure	70.5	69.1	70.9	70.9
	Heart rate	77.0	73.0	69.0°	75.0
	Grip strength (Kg.)	48.0	49.0	46.0	45.0

°Differs from control, $P < 0.05$.

of the enzyme that destroys some amines in part should result in gradually developing central nervous system stimulation because of an inferred build-up of epinephrine and norepinephrine in the central nervous system. However, these two compounds, and probably others with monamine oxidase inhibitory activity, have variable stimulant, depressant, or confusional effects in man.

α-Methyltryptamine and α-ethyltryptamine, since they are structurally very similar and are monamine oxidase inhibitors in vitro, would be expected to have comparable action when administered orally to human subjects. Many of the effects listed by the subjects are similar, but the differences are more striking. α-Methyltryptamine produces a delayed effect in man after an oral dose of 15 mg., while α-ethyltryptamine produces an immediate feeling of intoxication when given in an oral dose of 150 mg. and the effects have mostly subsided in 5 to 6 hours.

It is apparent from the 24 hour reports that visual effects are similar, consisting of blurred vision or difficulty in focusing and a few flashes of light similar to those with lysergic acid diethylamide. Both drugs produce dilation of the pupils, as does lysergic acid diethylamide. Other subjective effects common to both compounds and reported with approximately equal frequency are muscle cramps or tightness, headache, loss of appetite and/or slight nausea, dizziness, and numbness. Although the duration of action of α-ethyltryptamine is shorter, 4 subjects in each case complained of a hangover the day after the doses were administered.

The main differences reported were feelings of exhilaration or intoxication, apparently not unpleasant with α-ethyltryptamine, and feelings of tenseness, restlessness, and generalized malaise with α-methyltryptamine. α-Methyltryptamine at a dose of 20 mg. was likened to lysergic acid diethylamide by 9 of the 12 subjects, while α-ethyltryptamine at a dose of 150 mg. was likened to it only by 2 subjects, who felt however that the apprehension and visual effects of lysergic acid diethylamide intoxication were lacking.

The delayed action of α-methyltryptamine suggests that a metabolic product rather than the compound itself might be the active agent.

Conclusion

α-Ethyltryptamine appears to be much less potent than α-methyltryptamine. The effects are similar in several respects but differ markedly in others. α-Ethyltryptamine even in large doses is less psychotomimetic, since the subjects who compared it to lysergic acid diethylamide volunteered that it did not produce the apprehension or the same kind of visual effects. Nine of the 12 subjects who received α-methyltryptamine likened its effects to those of D-lysergic acid diethylamide.

Neither of these compounds, under our conditions of testing, is a reliable central nervous system stimulant.

References

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