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# HALLUCINOGENS AS DISCRIMINATIVE STIMULI: A COMPARISON OF 4-OMe DMT and 5-OMe DMT WITH THEIR METHYLTHIO COUNTERPARTS

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## Summary

Rats, trained to discriminate 1.5 mg/kg of the hallucinogenic agent 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) from saline in a two-lever drug discrimination task, were challenged with various doses of the 4-methoxy, 4-methylthio and 5-methylthio derivatives of DMT. The 5-OMe DMT cue was found to generalize to all three of these agents; the order of potency is 5-OMe > 5-SMe > 4-OMe > 4-SMe DMT.

With respect to hallucinogenic activity, one of the most potent tryptamine derivatives studied to date is 5-methoxy-N,N-dimethyltryptamine (5-OMe DMT) (1). We have previously found that 5-OMe DMT serves as a discriminative stimulus in rats, when paired with saline (2,3). Tests of generalization (transfer), using such a paradigm, afford a useful method for assessing the behavioral effects of other related agents. For example, the 5-OMe DMT cue has been shown to generalize to the interoceptive cues produced by LSD and various ring-substituted derivatives of N,N-dimethyltryptamine (DMT) (2,3), suggesting that these agents are capable of producing effects in animals similar to those produced by the training drug.

Two novel derivatives of DMT have recently been prepared, 4-methylthio-and 5-methylthio-DMT (4-SMe and 5-SMe DMT, respectively). Because of the close structural similarity between these new compounds and 4-OMe DMT and 5-OMe DMT, it was of interest to compare the behavioral effects of all four compounds in animals. The aim of the current study was to determine if the 5-OMe DMT cue would generalize with the effects produced by 4-SMe- and 5-SMe DMT.

## Methods

Eighteen male Sprague-Dawley rats were trained to discriminate 5-OMe DMT hydrogen oxalate (1.5 mg/kg) from saline (1 mL/kg) in a two-lever operant task, as we have previously described in detail (2,3). Briefly, administration of saline or 5-OMe DMT, 15 min prior to a variable 15-second (VI-15) schedule of reinforcement, served as the discriminative cue for the correct (reinforced) lever. Occasional periods (2.5 min) of non-reinforcement were used to assess the degree of stimulus control over behavior exerted by saline and by 5-OMe DMT, and to evaluate the new compounds. Drugs: The synthesis of the methylthio com-

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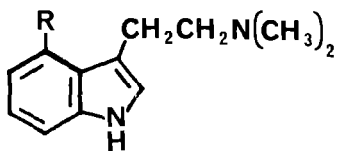
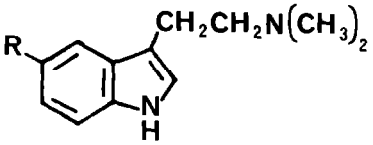
TABLE I
Data for Generalization of 5-OMe DMT to 4-OMe DMT, 4-SMe DMT and 5-SMe DMT




4-OMe DMT R = $OCH_3$

4-SMe DMT R = $SCH_3$




5-OMe DMT R = $OCH_3$

5-SMe DMT R = $SCH_3$

| Drug | Dose (mg/kg) | N | % 5-OMe DMT-Correct Responses[a] (±SEM) | ED50 (mg/kg)[b] | Responses/min[a] (±SEM) |
|---|---|---|---|---|---|
| 4-OMe DMT | 0.5 | 6 | 20% ( 4.9) | | 12.8 (4.4) |
| | 1.0 | 6 | 61% ( 6.1) | | 13.3 (5.0) |
| | 2.0 | 6 | 70% ( 7.3) | | 22.3 (2.9) |
| | 4.0 | 6 | 83% ( 3.6) | 1.07(0.48-2.41) | 12.7 (1.5) |
| 4-SMe DMT[c] | 1.0 | 3 | 0% | | 16.7 (3.2) |
| | 2.0 | 3 | 30% (10.4) | | 12.5 (1.9) |
| | 3.0 | 3 | 30% ( 3.1) | | 13.4 (4.6) |
| | 4.0 | 3 | 60% ( 9.4) | | 17.2 (4.9) |
| | 4.3 | 3 | 72% ( 8.9) | | 10.1 (3.6) |
| | 4.5 | 6 | 90% ( 3.1) | | 6.5 (1.5) |
| | 5.0 | 3 | [e] | 3.10(2.24-4.29) | |
| 5-SMe DMT[c] | 0.5 | 3 | 36% ( 2.9) | | 15.5 (2.3) |
| | 0.75 | 3 | 47% ( 8.7) | | 12.2 (1.4) |
| | 0.85 | 3 | 72% (10.2) | | 17.3 (4.6) |
| | 1.00 | 6 | 89% ( 4.1) | 0.64(0.46-0.90) | 16.2 (2.1) |
| 5-OMe DMT | 1.5 | 18 | 86% ( 2.3) | 0.40[d] | 16.2 (1.8) |
| Saline(mL/kg) | 1.0 | 18 | 18% ( 5.2) | | 13.3 (1.9) |

[a]Data obtained during 2.5 min non-reinforced lever-responding test periods. [b]With 95% confidence limits. [c]Tested in three animals/dose level. Dose which resulted in generalization was administered to a second group of three animals; results reflect combined data for all six animals at that dose level. [d]An $ED_{50}$ was not determined for 5-OMe DMT in this group of animals; however, we have previously published an $ED_{50}$ of 0.40 mg/kg in animals trained to discriminate 1.5 mg/kg 5-OMe DMT from saline, and an $ED_{50}$ of 0.42 mg/kg in animals trained to discriminate 1.0 mg/kg 5-OMe DMT from saline (2). [e]Disruption. (No responding.)

pounds have been reported (4); for the purpose of this study, both compounds were converted to their hydrogen oxalate (HOx) salts. Microanalytical data for the salts, calculated for $C_{13}H_{18}N_2S \cdot C_2H_2O_4$, are: C:55.53, H:6.21, N:8.63%; found, for 4-SMe DMT HOx (mp 155° softens, 170°dec) C:55.68, H:6.26, N:8.58% and for 5-SMe DMT HOx (mp 184-186°) C:55.57, H:6.23, N:8.62%. All solutions were prepared fresh daily in saline. $ED_{50}$ values were calculated on the basis of the weights of the salts.

## Results and Discussion

As in our previous reports, animals trained to discriminate 5-OMe DMT from saline consistently responded 85-96% on the 5-OMe DMT-appropriate lever when administered 1.5 mg/kg of 5-OMe DMT, while responding on the same lever was never more than 23% following injection of saline. As reported earlier (3), the 5-OMe DMT cue generalizes to 4-OMe DMT; generalization was also observed, in a dose-related manner, to both 4-SMe DMT and 5-SMe DMT (Table 1). Response rates under drug or non-drug conditions were similar.

It is well established that hallucinogenic/psychotomimetic agents (5), in general, and 5-OMe DMT, in particular, can serve as discriminative stimuli in animals. Although it can not necessarily be concluded that those agents to which hallucinogenic agents generalize are themselves hallucinogenic (6,7), generalization in such a paradigm suggests a hallucinogenic potential. 5-OMe DMT is a potent hallucinogen; 4-OMe DMT, though not yet studied in man, has been shown to be behaviorally-active in animal studies (8). The results of this study support the latter findings in that the 5-OMe DMT cue generalizes to 4-OMe DMT. Furthermore, because the 5-OMe DMT cue also generalizes to both methylthio compounds, it may be inferred that all four compounds apparently produce similar interoceptive cues in rats. With respect to the potency of these DMT analogs, 5-OMe > 5-SMe > 4-OMe > 4-SMe. Thus, the thiomethyl derivatives are slightly less active than their corresponding methyl ethers.

## Acknowledgements

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