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# Stimulus Properties of Mescaline and N-Methylated Derivatives: Difference in Peripheral and Direct Central Administration

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*Abstract.* The purpose of this study was to examine the possibility that N-methylated derivatives of mescaline might produce interoceptive stimuli similar to mescaline. Rats were trained in a two-lever operant chamber to discriminate the drugged (mescaline, 25 mg/kg, i.p.) state from the non-drugged state (saline, i.p.). On session days following mescaline administration, only responses on the right lever of the operant chamber were reinforced and on days following saline only responses on the left lever were rewarded. The degree of discrimination between mescaline and saline was determined by the percentage of responding on the state appropriate lever during extinction. Following the acquisition of response control by i.p. mescaline, the subjects were tested for stimulus generalization after i.p. or intraventricular injections of various doses of mescaline, N-methylmescaline (NMM), N,N-dimethylmescaline (DMM), or saline. Intraventricularly administered mescaline exhibited a dose-dependent generalization to the cue produced by systemically injected mescaline, indicating a central nervous system locus of action. NMM demonstrated only saline responses regardless of the dose or route of administration. DMM at a dose of 50 mg/kg, i.p., generated responses characteristic of mescaline, suggesting a similarity in behavioral effects between DMM and mescaline. However, following intraventricular injection of DMM only a transient generalization to the mescaline state resulted. From these results it is concluded that NMM and DMM, two possible metabolites of mescaline, apparently do not play a significant role in the mescaline-induced internal stimuli.

*Key words:* State Dependent Learning — Mescaline — N-Methylmescaline — N,N-Dimethylmescaline — Intraventricular Injection.

## Introduction

Metabolites of mescaline are of particular interest since it has been reported that the behavioral effects of mescaline do not coincide with its maximal concentration in brain (Harley-Mason *et al.*, 1958; Block, 1958). This suggests that the hallucinogenic action of mescaline results from a metabolite of the amine. While a large number of the known halluci-

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nogens possess N,N-dialkyl groups which are required for psychotomimetic properties, little work has been done with N-methylated derivatives of mescaline; although mescaline can be N-methylated by rabbit lung enzyme (Axelrod, 1961, 1962). Furthermore, Browne, Orengo, and Ho (unpublished) observed that for partially purified Bovine brain N-methyl transferase, mescaline was a better substrate than tryptamine, norepinephrine or histamine, implying the possible N-methylation of mescaline by brain.

Some of the behavioral effects of mescaline and its derivatives have been reported by Smythies and his colleagues using the conditioned avoidance response (CAR) (Smythies and Sykes, 1964, 1966; Smythies *et al.*, 1966, 1967a, b). In a shuttlebox mescaline (25 mg/kg) initially depresses or inhibits the number of barrier crossings in the presence of an auditory CS but later induces a prolonged "excitatory" phase similar to the smaller doses of mescaline which caused only excitation (Smythies and Sykes, 1964). This excitatory phase was interpreted as the result of a metabolic degradation product of mescaline. Based on this reasoning, Smythies and Sykes (1966) concluded that the N,N-dimethyl derivative of mescaline (DMM) is not a psychotomimetic agent since DMM abolishes the inhibitory effect of mescaline and augments its excitatory action. However, DMM exhibits a bidirectional cross-tolerance to mescaline (Smythies *et al.*, 1966), suggesting a lack of specificity in the CAR paradigm. Furthermore, Bridger *et al.* (1972) have recently shown that mescaline causes behavioral excitation when rats are subjected to stressful shock (CAR) and inhibition in the absence of shock (passive avoidance).

That mescaline can be used as a discriminative stimulus in the control of operant behavior by producing internal or interoceptive cues has been demonstrated in several paradigms (Hirschhorn and Winter, 1971; Schechter and Rosecrans, 1972a 1973; Winter, 1973). The present study was undertaken to evaluate the possible similarity between the interoceptive stimuli produced by mescaline and N-methylated mescaline analogs. It is hypothesized that if the conclusion of Smythies and Sykes (1966) that N-methylation of mescaline abolishes psychotomimetic activity is correct, a lack of generalization to the mescaline state should be observed following peripheral as well as direct central administration of the N-methylated derivatives of mescaline.

## Methods

*Subjects.* Thirty-five male Sprague-Dawley rats (250—300 g) obtained from Horton Labs (Oakland, California) served as *Ss*. Throughout the study *Ss* were housed individually in home cages with water freely available. Purina Rat Chow was fed after daily experimental sessions and on week-ends in quantities adjusted to maintain *Ss* between 80 and 85% of their expected free-feeding weight based on the suppliers growth chart.

*Behavioral Apparatus.* Five two-lever operant chambers (Scientific Prototype, Model A-100) enclosed in sound attenuating chambers (Scientific Prototype, Model SPC-300) equipped with fans to circulate fresh air were used. The two operant levers (Scientific Prototype, Model PCS-100) separated by 8 cm were mounted on the manipulation approximately 3 cm above the grid floor of the operant chamber. A brass food trey located on the panel between the levers was connected to a pellet dispenser (BRS/Foringer Model PDC) situated behind the panel. Reinforcement consisted of single 45 mg Noyes pellets (Standard Formula). Illumination was provided by a 7-watt house light mounted in the ceiling of the sound attenuated chamber. Behavioral contingencies and data collection were controlled by programming equipment (Grason Stadler 1200 series) located in the same room.

*Cannulae and Cannulation.* Cannulae were constructed from No. 23 gauge syringe needles (Monoject) and contained a No. 31 gauge removable stylet. The cannula barrel with stylet inserted was cut to a length of 3 mm. Cannulation was performed under Pentobarbital sodium anesthesia (40 mg/kg). Stereotaxic placement of the cannula was 2 mm lateral, 0.75 mm posterior from bregma and 3 mm down from the skull (König and Klippel, 1963). Three small stainless steel screws were implanted into the skull equilaterally around the cannula and the cannula was secured with self-curing dental cement. Following surgery the *Ss* were given 150000 U of Penicillin (Crysticillin, Squibb) i.m., and allowed to recover for one week before testing (see below). After completion of the experiments, *Ss* were given an intraventricular injection of methylene blue dye, sacrificed and cannula placement verified.

## *Discrimination Training*

*Pretraining.* On the first day of pretraining *Ss* were placed in the operant chamber with non-contingent delivery of food pellets on a variable interval schedule (VI 60 sec) as well as on a continuous reinforcement (CRF) schedule programmed on both levers. Two additional daily 30-min sessions of only CRF on either lever was given before introducing a differential reinforcement of low response rate (DRL) schedule. Under a DRL schedule the *Ss* must allow a specified amount of time to elapse between one reinforcement and the availability of the next reinforcement. Premature responses re-set the interval timer; while after the specified interval has elapsed the first response will result in reinforcement. Two days on each lever under DRL-5 sec were followed by two days on DRL-10 and two days on DRL-15 sec. DRL-15 sec (unlimited hold) served as the schedule of reinforcement throughout the remainder of the experiment.

*Training and Extinction Testing. Ss* were run in 5 daily sessions per week. Intraperitoneal injections of either 25 mg/kg of mescaline hydrochloride (Sigma) in isotonic saline or saline were given 15 min before the sessions. Injection volumes were 1 ml/kg. The sequence of weekly injections was a counter balanced order of all the possible permutations of drug (D) and saline (S) with the limitation that not more than two consecutive sessions followed either drug or saline. On session days following drug injections only responses made on the right lever were reinforced, while on saline days responses on the left lever were reinforced. Responses on the inappropriate lever re-set the DRL interval timer.

On the fifth day *Ss* were given an extinction test. During the 30 min extinction sessions responses on both levers were cumulatively recorded. The degree of discrimination between mescaline and saline is defined as the percentage of total responses made on the appropriate lever in the absence of reinforcement. The semi-random lever sequence used in this design resulted in an equal number of extinction tests in which the drug state was the same or different from the one imposed on the previous

day. Each subject received three extinction tests following mescaline and three following saline.

### *Generalization Testing*

*Peripherally Administered Mescaline Analogs.* In order to test the degree of generalization to the mescaline state by NMM and DMM, ten *Ss* were given series of four daily 30-min training sessions in the order SDDS where the training drug was mescaline (25 mg/kg), and tested as before during extinction on a fifth day session. On these test days *Ss* were injected i.p. with either mescaline (10, 25 mg/kg), NMM (10, 25, 50 mg/kg), DMM (10, 25, 50 mg/kg), or saline 15 min before the test. The order in which drugs were tested was randomized between subjects and across weekly tests such that no *S* received the same drug twice. All drugs were purchased from Sigma and administered at the various doses as the hydrochloride salt.

*Intraventricularly Administered Drugs.* Twenty-five *Ss* were run in the SDDS sequence of 4 daily training sessions and one extinction test per week. Extinction tests were conducted immediately following an intraventricular injection of 10 µl of saline; mescaline (10—75 µg), NMM (25—200 µg), or DMM (50—400 µg) over a period of 60 sec. Intraventricular injections were made with a 50-µl Hamilton syringe by removing the stylet and inserting a 30-gauge needle cut to protrude 1 mm beyond the tip of the implanted cannula. After injection, the needle was removed and the stylet reinserted. Drugs were administered in a semi-random order. For most drugs tested, responses were cumulatively recorded in 5-min intervals over the 30-min testing session. However, the session was timed from either the first response or after a 60-min delay in the experiment using high doses of mescaline (75 µg) since this dose initially caused complete disruption of responding.

*Statistical Analysis.* Because of the large individual differences in behavior observed following intraventricular injections of mescaline in the present study, non-parametric statistics were chosen. Thus, the data were analyzed by the Mann-Whitney U Test (Siegel, 1956).

## Results

*Acquisition of Discriminative Response Control.* As shown in Fig. 1, 25 mg/kg of mescaline is a very strong discriminative stimulus. The *Ss* made 60% of their responses on the appropriate lever after only four days of training (i.e., the first extinction test). By the second extinction test the discrimination was adequate and the animals were cannulated. Following cannulation the *Ss* maintained their 80% discriminative responding for four consecutive weeks.

*Systemic Generalization Testing.* Fig. 2 illustrates the generalization gradient produced by i.p. injections of mescaline, DMM, NMM, and saline during a 15-min generalization test. Thus, when tested with mescaline at 10 mg/kg, the *Ss* made 55% of their responses on the lever previously paired with mescaline 25 mg/kg. This low dose of mescaline resulted in responding significantly different ($P < 0.005$) from both training conditions (mescaline 25 mg/kg and saline).

The interoceptive stimuli produced by DMM, like mescaline, is dose dependent. At a dose of 50 mg/kg of DMM the *Ss* responded as if they were given mescaline 25 mg/kg. NMM, on the other hand, appears dis-

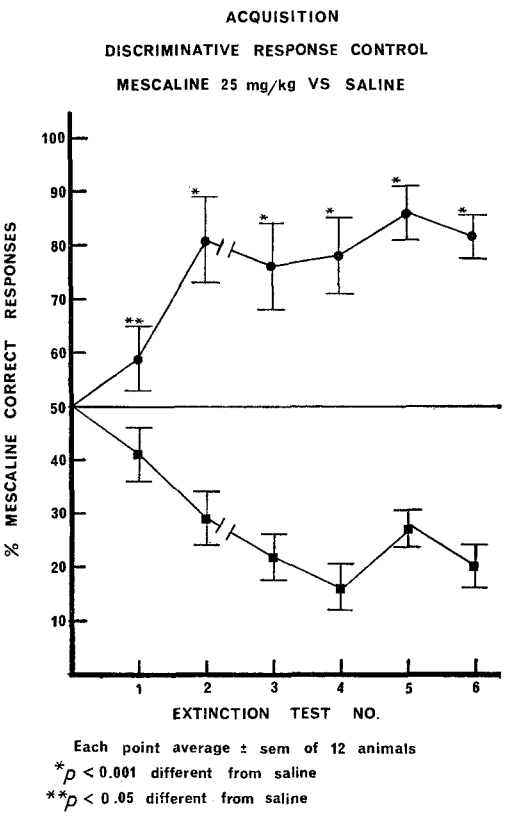


Fig. 1. Values calculated as the number of responses made on the lever paired with mescaline divided by the total responses during a 15-min extinction. Each extinction test represents an intervening interval of four training sessions. Half of the *Ss* were tested following saline (closed squares) and half following mescaline 25 mg/kg (closed circles). *Ss* tested in one condition were tested in the other condition on successively alternating tests

similar to mescaline, since doses up to 50 mg/kg failed to produce responses significantly different from saline. Furthermore, there was no significant difference between the three doses of NMM tested.

*Intraventricular Mescaline.* Fig. 3 A demonstrates that intraventricular injections of the sterile saline vehicle does not affect the animals' ability to make the saline appropriate discrimination. The "drift" in accuracy between 15 and 30 min is characteristic of extinction as is the asymptotic response rate (Fig. 3 B).

The effects observed following intraventricular injections of mescaline were twofold, diminution of response rate and dose-dependent generali-

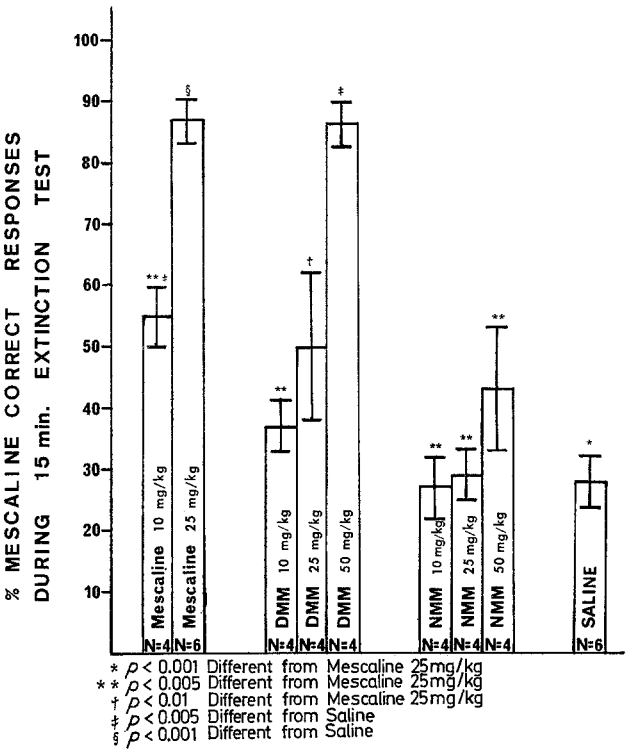


Fig. 2. Generalization gradient produced by i.p. administration of mescaline, DMM, NMM, or saline. Values are the mean ± S.E.M. of the percent of total responses made on the lever previously paired with mescaline 25 mg/kg. *P* values two-tailed Mann-Whitney U test

zation to the stimuli produced by systemically administered mescaline. Fig. 4B demonstrates that intraventricular injection of mescaline at doses from 12.5 to 50 μg resulted in a four-fold reduction in response rate, compared to saline (Fig. 3B). The generalization gradient generated by intraventricular mescaline at these low doses (12.5—50 μg) appears to produce a random response (Fig. 4A). Furthermore if the *Ss* were allowed to remain in their home cages for 30 min following the intraventricular injection of 50 μg of mescaline before the initiation of testing, there was no change in response rate or percent mescaline-like responses (unpublished observation).

However, at a larger intraventricular dose of 75 μg of mescaline (Fig. 5A) there appears a significant generalization to the cue produced by i.p. administration of 25 mg/kg of mescaline. Due to the disruption of

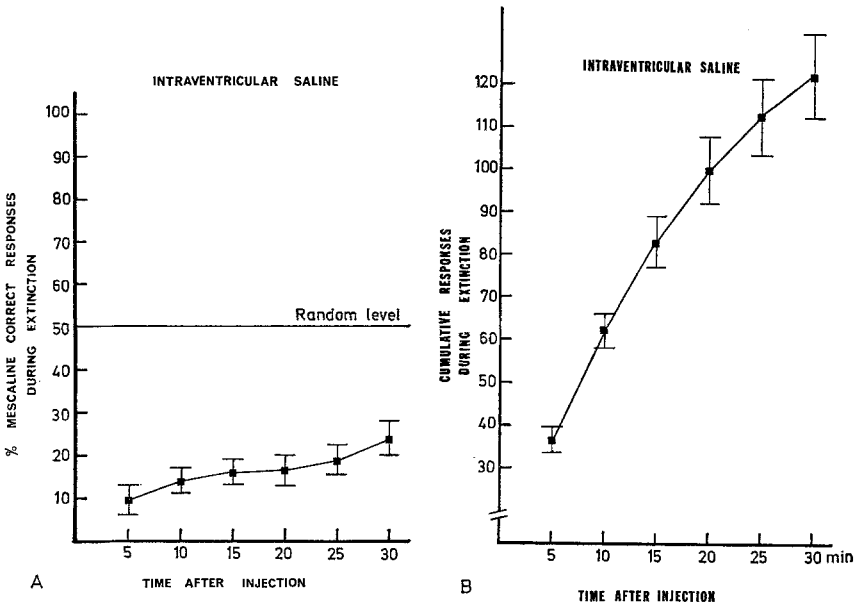


Fig. 3 A. Generalization gradient produced by intraventricularly administered saline in *Ss* trained to discriminate systemically administered mescaline from saline. Each point is the mean ± S.E.M. of 14 animals and represents the percent of total cumulative responses over a 30-min extinction made on the lever previously paired with i.p. mescaline (mescaline correct)

Fig. 3 B. Total cumulative responses made on both levers as a function of time after an intraventricular injection of isotonic saline. Each point is the mean ± S.E.M. of 14 animals

response rate at this dose, *Ss* were left in their home cages 30 or 60 min after the intraventricular injection. As can be seen in Fig. 5 B, this allows response rate to make a slight recovery without affecting the discriminability of the drug. Intraventricular doses higher than 75 μg resulted in response rates too low to be considered a reliable indication of the observed further increase in generalization.

*Intraventricular N-Methylated Mescaline Analogs.* Fig. 6 B indicates that intraventricular injection of NMM produces a dose-related reduction in response rate. However, the magnitude of this effect was not as great as that observed following mescaline. The generalization gradient produced by intraventricular NMM does not appear to be well defined. Indeed, an intraventricular injection of 50 μg of NMM demonstrated a weak generalization at about 65%, while doses either higher or lower than 50 μg generated random and saline responses respectively (Fig. 6 A).

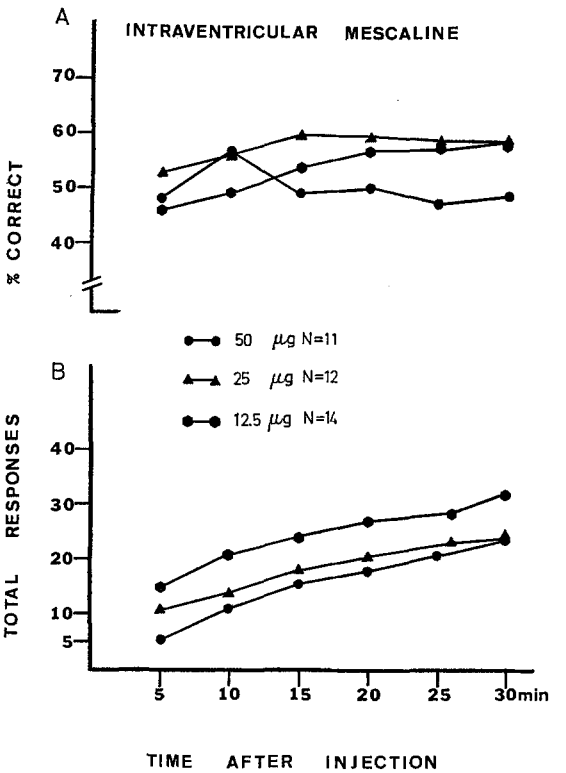


Fig. 4A. Percent of total cumulative responses made on the mescaline lever during a 30-min extinction test immediately following various doses of intraventricularly administered mescaline

Fig. 4B. Total cumulative responses made on both levers during extinction following intraventricular mescaline

Intraventricular DMM (Fig. 7A) tends to exhibit a dose-dependent generalization to the mescaline state which apparently dissipated with time. That is, within the first 5 min following the injection of 200 or 300 μg of DMM *Ss* made greater than 70% mescaline appropriate responses. By the end of the 30-min test *Ss* were making more saline appropriate responses. Since these figures represent cumulative responses, the change-over from responding on predominantly one lever to responding on the other lever is a requisite to make such a substantial change in the cumulative profile.

There was very little effect on response rate produced by intraventricular DMM. As seen in Fig. 7B response rate following 50 μg of DMM appears essentially the same as the response rate after saline (Fig. 3B). A

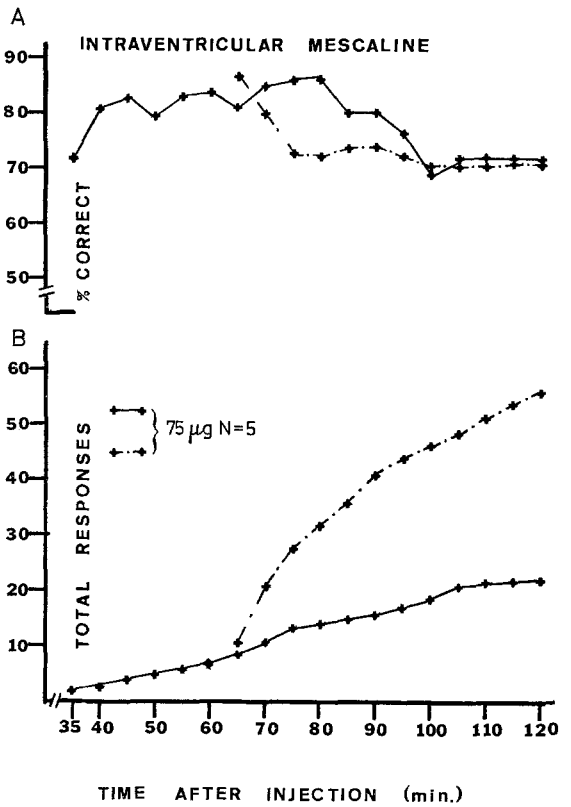


Fig. 5 A. Percent mescaline appropriate responses during extinction following 75 μg of mescaline. The test was initiated 30 min (solid line) or 60 min (broken line) after the intraventricular injection

Fig. 5 B. Total cumulative responses during extinction 30 or 60 min after a 75-μg intraventricular injection of mescaline

dose of 100 μg of DMM demonstrated some rate reducing effects on responding (Fig. 7 B). However, doses of DMM higher than 100 μg did not further increase the magnitude of this disruption.

The results of a typical extinction test following an i.p. dose of 25 mg/kg of mescaline are included in Fig. 8 to demonstrate that response rate is not a factor in the production of the interoceptive mescaline cue. As can be seen in Fig. 8 A, i.p. administered mescaline produces a high level of accuracy (greater than 80% correct) that does not dissipate with time. The response rate during this i.p. mescaline test (Fig. 8 B) is not significantly different from the response rate produced by saline (Fig. 3 B).

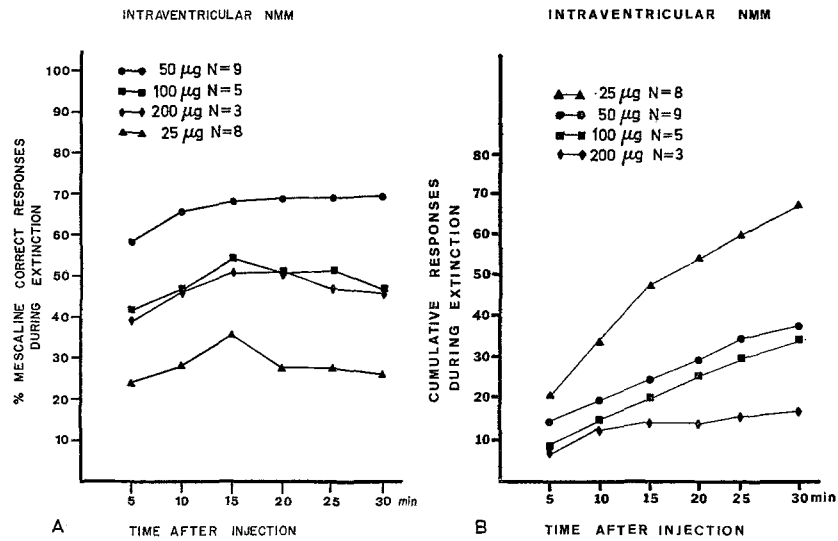


Fig. 6 A. Generalization gradient produced by intraventricular injections of various doses of N-methylmescaline (NMM). The extinction tests were initiated immediately following the injections

Fig. 6 B. Effect of intraventricular NMM on response rate. Values are the cumulative responses made on both levers

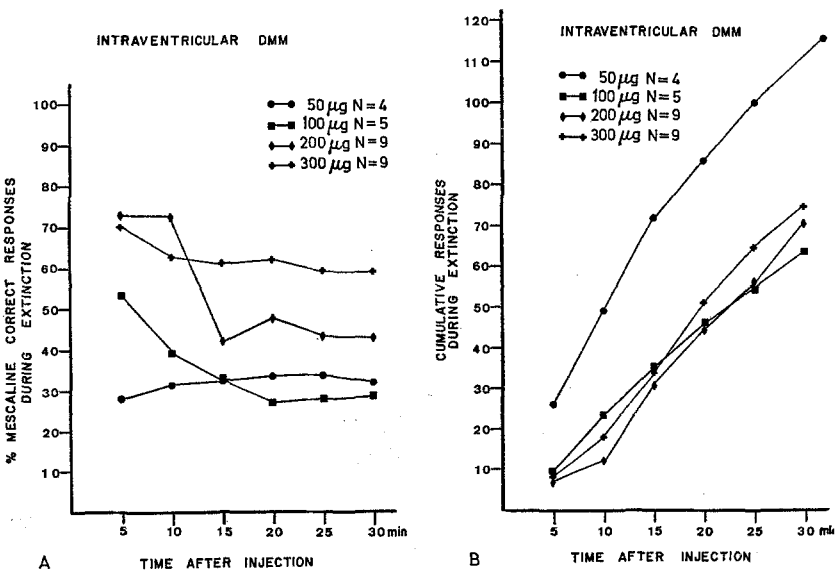


Fig. 7 A. Generalization following various doses of intraventricularly administered N,N-dimethylmescaline (DMM). Extinction tests were initiated immediately following the injection

Fig. 7 B. Cumulative responses made on both levers during a 30-min extinction test following intraventricular administration of DMM (50—300 μg)

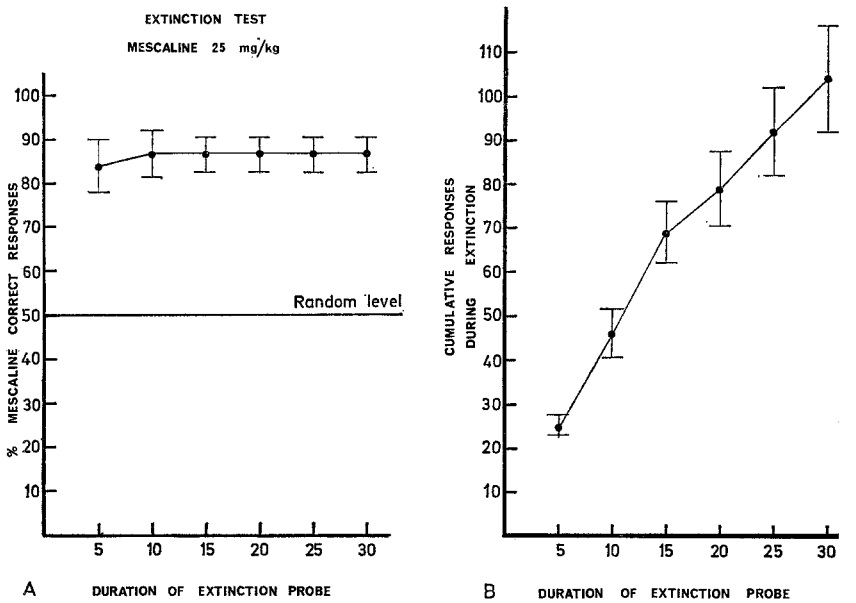


Fig. 8 A and B. Effects of systemically administered mescaline (25 mg/kg) on response accuracy (A) and response rate (B). Extinction test was initiated 15 min after the i.p. injection. Each point is the average ± S.E.M. of 12 *Ss*. Subjects consistently throughout the 30-min test made better than 80% of their responses on the lever previously paired with mescaline during training (A). Systematically administered mescaline does not produce reductions in response rate (B)

## Discussion

The present study is consistent with the findings of Hirschhorn and Winter (1971) in demonstrating the ability of mescaline to produce strong discriminative stimuli. However, these authors, using a lower training dose of mescaline (10 mg/kg) could only demonstrate a 70% discrimination after fifteen training sessions. Hence, it is not unexpected that the dose of mescaline used in the present study (25 mg/kg) produced a more rapid, stronger discrimination (Fig. 1), consistent with dose-related acquisition rates (Overton, 1966, 1969).

The results of generalization produced by i.p. administered DMM (Fig. 2) suggest that this compound and mescaline have similar stimulus properties. However, since the dose of DMM needed to produce a dose-related generalization to the mescaline state was twice that of mescaline, N-methylation does not appear to be a metabolic process involved in producing the stimulus properties of mescaline. Indeed, if DMM were more potent than mescaline or an "active metabolite" of mescaline, lower doses of DMM would have produced a generalization, as is the case with LSD (Hirschhorn and Winter, 1971), where μg quantities of

LSD generalize to the cue produced by mg doses of mescaline. In addition, this lower potency cannot be explained in terms of differences in blood brain barrier permeability, since increasing alkylation of mescaline would increase permeability, as inferred by an increased chloroform-water partition coefficient (Bradley, R. J. Personal communication). Furthermore, Vogel *et al.* (1973) observed that, following i.p. administration of either bisnormacromerine (3,4-dimethoxyphenylethanolamine) or macromerine (N,N-dimethyl-3,4-dimethoxyphenylethanolamine) to rats four to ten times more dimethylated compound reached the brain. These same authors reported that the level of the monomethylated derivative (normacromerine) was not less than bisnormacromerine. If the same is true in the mescaline series, the absence of generalization produced by i.p. NMM (Fig. 2) cannot be explained in terms of a permeability barrier.

The generalization produced by intraventricularly injected mescaline is indicative of a CNS locus in the cueing effect of mescaline. While doses of mescaline up to 50 μg are incapable of producing a high level of generalization, this may be due to insufficient amounts of mescaline reaching distal sites following intraventricular administration. Hence, as the dose of mescaline is increased to 75 or 100 μg, more drug would then reach distal loci producing the observed generalization.

The observation that DMM is capable of producing generalization following systemic but not intraventricular administration poses a difficulty in interpretation. While variables such as differences in diffusion, absorption or metabolism of the drug cannot be ruled out, it seems unlikely that these factors alone would account for an all-or-none phenomenon. An alternate interpretation of these results is that the *Ss* attend to peripheral stimuli produced by mescaline, and when tested centrally mescaline but not DMM might somehow mimic these stimuli. This interpretation seems unlikely since it has been shown that drugs which are devoid of central effects do not produce stimulus generalization (Morrison and Stephenson, 1969; Schechter and Rosecrans, 1972b). Furthermore, Richards *et al.* (1973) has recently demonstrated that rats trained to discriminate amphetamine from saline exhibit stimulus generalization when amphetamine is administered intraventricularly, while the para-hydroxy metabolite of amphetamine failed to generalize regardless of the route of administration.

The observed differences in stimulus generalization produced by systemic and intraventricular administration of DMM may be due to what Overton refers to as "transfer test overinclusiveness" (Overton, 1973). Thus, at certain doses, drugs from entirely different pharmacological classifications will occasionally generalize to each other. For this reason Winter has recently questioned the validity of generalization gradients in drug discriminations. When rats were trained to discrimi-

nate mescaline from saline and later tested with 2,4,5-trimethoxyphenylethylamine (a non-hallucinogenic analog of mescaline), the *Ss* made responses typical of mescaline (Winter, 1973). Perhaps in Winter's study, as in the present one, generalization produced by systemic administration of mescaline analogs is such an example of transfer test overinclusiveness. Therefore, it would be of interest to test the 2,4,5-trimethoxylated analog for generalization following direct central administration.

In one sense the observations of Smythies and Sykes (1966) that increasing N-methylation of mescaline reduces the inhibitory effects of mescaline in certain behavioral paradisms is substantiated in the present study where mescaline produces a large decrement in response rate, NMM a moderate decrease and DMM only a slight reduction in response rate following intraventricular injections. However, it is important to differentiate between response rate and response accuracy. That the dose-dependent diminution of response rate following intraventricular mescaline is not a requisite for the *Ss* to make mescaline appropriate responses is seen in Fig. 8A and 8B. When administered systemically, mescaline produces its interoceptive cue (Fig. 8A) without a concomitant reduction of response rate (Fig. 8B). Indeed, the rate of responding following i.p. mescaline is not significantly different from saline administration.

The present study cannot rule out the possibility that an "active metabolite" may play a role in mediating the interoceptive stimuli produced by mescaline. Thus, large intraventricular doses of mescaline would be necessary in order to accumulate sufficient amounts of such a metabolite to yield a "mescaline cue". The elucidation of this possibility awaits further studies utilizing intraventricular administration of other mescaline metabolites.

This study was a part of a thesis submitted by the first author to the University of Texas Graduate School of Biomedical Sciences in partial fulfillment for the degree Master of Science.

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