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Discriminative Stimulus Properties of Mescaline: Mescaline or Metabolite?

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BROWNE, R. G. AND B. T. HO. *Discriminative stimulus properties of mescaline: mescaline or metabolite?* PHARMAC. BIOCHEM. BEHAV. 3(1) 109–114, 1975. – The purpose of this study was to investigate possible similarities in the interoceptive stimuli produced by mescaline and its metabolites. Rats were trained in a 2 lever operant chamber to discriminate between the drugged state (mescaline 25 mg/kg) and the nondrugged state (saline). Following acquisition of discriminative response control the rats were pretreated with either saline, aldehyde dehydrogenase inhibitors or amine oxidase inhibitors and tested stimulus generalization produced by i.p. injections of 3,4,5-trimethoxyphenylethanol (TMPE), 3,4,5-trimethoxyphenylacetaldehyde (TMPA), N-acetylmescaline, mescaline or saline. The results indicated that both aldehyde dehydrogenase and amine oxidase inhibitors enhanced the effects of mescaline, while TMPE, TMPA and N-acetylmescaline failed to exhibit generalization to the mescaline state, regardless of pretreatment. These findings do not indicate the role of a metabolite in the interoceptive cue produced by mescaline.

Drug discrimination Mescaline Mescaline metabolites Amine oxidase inhibitors
3,4,5-trimethoxyphenylethanol 3,4,5-trimethoxyphenylacetaldehyde N-acetylmescaline

THE IDEA that the behavioral effects of mescaline may be attributable to a metabolite was suggested in the 1950's when Harley-Mason *et al.* [14] observed that the peak behavioral effects do not coincide with the maximal concentration of mescaline in the brain. Since then several behavioral and biochemical attempts have been made to elucidate the possible role of metabolites in producing the psychotomimetic action of mescaline. For example, Smythies and Sykes [34] using the conditioned avoidance response observed that mescaline (25 mg/kg) initially depresses or inhibits the number of barrier crossings in the presence of an auditory conditioned stimulus but later induced a prolonged excitatory phase during which the reaction time is decreased. Smythies and Sykes interpreted this excitatory phase as resulting from a degradation product of mescaline.

The metabolism of biologically active amines, such as mescaline, has been extensively studied. While the majority of administered mescaline is excreted unchanged, apparently the major route of mescaline metabolism in man [6,7], cats [23], dogs [35] and rats [2] is via deamination to yield 3,4,5-trimethoxyphenylacetic acid. The metabolic intermediate in producing the acid from mescaline is the corresponding aldehyde (TMPA), which can also be reduced to 3,4,5-trimethoxyphenylethanol (TMPE). The alcohol has been detected in rat urine [12] and rat brain [16], but the aldehyde intermediate has not been isolated, presumably due to its great instability.

Further support for the involvement of metabolites in the behavioral effects of mescaline is the observation [11] that pretreatment with the aldehyde dehydrogenase inhibitor calcium carbimide enhances the behavioral disruptive effects of mescaline. Furthermore, these authors report [11] that, following the carbimide treatment, TMPE produces behaviorally disruptive effects similar to mescaline.

While there appears to be a difference in the brain and liver enzymes capable of deaminating mescaline [29], Ho *et al.* [16] have recently demonstrated that oxidative deamination may account for only a small percentage of brain metabolites following intravenously administered mescaline in the rat. It was further demonstrated that N-acetylation

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of mescaline is a major metabolic pathway [16]. Since N-acetylmescaline is reported to be inactive in man [7], N-acetylation has been considered an inactivation process.

The use of mescaline as a discriminative stimulus in the control of operant behavior by producing interoceptive cues has been demonstrated in several behavior paradigms [15, 26, 38]. The present study was undertaken to evaluate the possible similarity between the interoceptive stimuli produced by mescaline and its metabolites. It is hypothesized that if the mescaline cue is mediated by a metabolite, then such a metabolite should produce stimulus generalization to the mescaline state. Furthermore, if a metabolite is responsible for the stimulus properties of mescaline then it would be expected that blocking the metabolism of mescaline would reduce mescaline's discriminability.

METHOD

Animals

Twenty naive male Sprague-Dawley rats (225–250 g) obtained from Horton Labs (Oakland, Calif.) were used. Throughout the study the rats 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 the animals between 80 and 85% of their expected freefeeding weight based on the supplier's growth chart.

Behavioral Apparatus

Five 2 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 2 operant levers (Scientific Prototype, Model PCS-100) separated by 8 cm were mounted on the manipulandum approximately 3 cm above the grid floor of the operant chamber. A brass food tray 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 W 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.

Discrimination Training

The animals were trained to discriminate between internal states produced by i.p. injections of mescaline and saline by methods previously described [3,18]. Rats were shaped to respond on both operant levers such that only responses made greater than 15 sec apart were reinforced (DRL 15 sec schedule), and no lever preference was observed [3]. Daily 30 min sessions were run 5 days per week. Intraperitoneal injections of either 25 mg/kg of mescaline hydrochloride 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 reset the DRL interval timer.

Every fifth day animals were given an extinction test. During the 15 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 rats were given 20 days of actual training at which point they exhibited discrimination at better than 80% cue appropriate responses when tested with either mescaline or saline for at least two consecutive tests [3].

Generalization Testing

In order to test the degree of generalization to the mescaline state by metabolites of mescaline, animals were given series of 4 daily 30 min training sessions in the order SDDS where the training drug was mescaline (25 mg/kg), and tested during a 15 min extinction on a fifth day session. On these test days subjects were pretreated with saline, sodium diethyldithiocarbamate (DDC), disulfiram, calcium carbimide (Temposil), pargyline, semicarbazide or iproniazid as specified below. Fifteen min before the initiation of testing animals received an i.p. injection of either mescaline (10 or 25 mg/kg), TMPE (12.5 to 50 mg/kg), TMPA (25 mg/kg) or N-acetylmescaline (50 mg/kg). The order in which drugs were tested was randomized between animals and across weekly tests such that no rat received the same drug twice. Due to the lack of homogeneity of variance between treatment groups nonparametric statistics were chosen. Statistical analysis was performed using a two-tailed Mann-Whitney U [33].

Drugs and Administration

Dosages of all drugs are expressed as the salt except for TMPE, N-acetylmescaline and disulfiram. Mescaline purchased from Sigma Chemical Co. was administered as the hydrochloride salt in isotonic saline. TMPE, N-acetylmescaline and TMPA (as the bisulfite addition product from the Rosemund reduction of trimethoxyphenylacetyl chloride) were synethsized in our laboratories and were administered i.p. in saline. Sodium DDC (Sigma), pargyline hydrochloride (Abbott), iproniazid phosphate (Aldrich) and semicarbazide hydrochloride (Aldrich) were all administered i.p. in saline (1 ml/kg). In order to prevent calcium precipitation, immediately before use Temposil (Cyanamide of Canada) was mixed with 2 parts by weight of citric acid [9]; saline was added and the solution was sonified to facilitate rapid dissolution of Temposil. Disulfiram (Aldrich) was administered orally as a 10% suspension of TWEEN-80 and saline. The time interval between administration of the pretreatment compounds and the test drugs are given in Tables 1, 2 and 3.

RESULTS

Following 20 days of training rats are highly capable of discriminating the mescaline (25 mg/kg) from saline states (Table 1). In the absence of reinforcement feedback (extinction) the subjects make greater than 80 per cent of their responses on the lever previously paired with the appropriate state. When tested with mescaline at a dose lower than the training dose a reduction in discriminability occurs: when tested with 10 mg/kg of mescaline the rats

TABLE 1

POTENTIATION OF MESCALINE BY ALDEHYDE DEHYDROGENASE INHIBITORS

Pretreatment	Test Compound	% Mescaline Appropriate Responses*
None	Saline	19 ± 2.6 (20)
None	Mescaline (25 mg/kg)	86 ± 2.7 (20)
None	Mescaline (10 mg/kg)	56 ± 6.0 (20)
Disulfiram (25 mg/kg 24 hr)	Saline	20 ± 7.5 (4)
	Mescaline (10 mg/kg)	66 ± 13.0 (5)
Disulfiram (100 mg/kg 24 hr)	Saline	34 ± 15.0 (4)
	Mescaline (10 mg/kg)	80 ± 6.0 (5)†
Temposil (10 mg/kg 30 min)	Saline	30 ± 8.0 (5)
	Mescaline (10 mg/kg)	77 ± 3.0 (5) ‡

Test compounds were administered i.p. 15 min prior to the 15 min extinction test. Time intervals between pretreatment and administration of test compound are shown in the Pretreatment column.

*Each value represents the mean ± S.E.M. of the number of animals in parenthesis.

†Significantly different from mescaline (10 mg/kg), $p<0.025$ (Mann-Whitney U).

‡Significantly different from mescaline (10 mg/kg), $p<0.05$ (Mann-Whitney U).

make only 56 per cent of their total extinction responses on the lever previously paired with 25 mg/kg of mescaline (Table 1). The percent cue appropriate responses following mescaline at a dose of 10 mg/kg is significantly different from both training conditions ($p<0.005$, Mann-Whitney U).

As demonstrated in Table 1, pretreatment with either of the aldehyde dehydrogenase inhibitors disulfiram or Temposil potentiates the effects of 10 mg/kg of mescaline, resulting in a significant increase in the percentage of mescaline appropriate responding. This increase in mescaline-like responding was not due to disruptive effects of the pretreatment drug, since only nonsignificant changes in saline appropriate responses were exhibited by the subjects pretreated with disulfiram (100 mg/kg, or Temposil (10 mg/kg) prior to receiving saline (Table 1).

The above results indicated a possible involvement of an aldehyde metabolite in the discriminative stimulus properties of mescaline. Since the aldehyde metabolite of mescaline (TMPA) was initially elusive to synthesis, we examined the suggestion of Friedhoff and Goldstein [11] and treatment with the aldehyde dehydrogenase inhibitor Temposil before administering TMPE should increase the concentration of the aldehyde in vivo. As can be seen in Table 2, the effects of TMPE alone or in combination with an aldehyde dehydrogenase inhibitor failed to produce responding significantly different from saline. TMPA was eventually synthesized as the bisulfite addition product. However, as demonstrated in Table 2, TMPA in combination with Temposil did not generalize to the mescaline state.

Since N-acetylmescaline is a known metabolite of mescaline, and N-acetylation has been shown to preceed O-demethylation of mescaline [21], we examined the stimulus properties of this metabolite. As seen in Table 2, N-acetylmescaline at a dose of 50 mg/kg produced responses characteristic of saline.

Finally, in order to resolve the apparent discrepancy in the above results, we examined the effects of blocking mescaline metabolism at the deamination step with amine oxidase inhibitors. As can be seen in Table 3, amine oxidase inhibitors greatly potentiated the discriminability of a low dose of mescaline: the difference between mescaline appropriate responding following amine oxidase inhibitor pretreatment (70–90%) and mescaline alone (56%) is highly significant. Furthermore, these inhibitors did not significantly affect the discriminability of saline (Table 3).

DISCUSSION

The present study does not indicate a role for deaminated or N-acetyl metabolites in the production of internal discriminative stimuli by mescaline. The potentiation of mescaline appropriate responding by aldehyde dehydrogenase inhibitors (Table 1) suggested the involvement of the aldehyde or alcohol metabolite in the discriminative properties of mescaline. However, as seen in Table 2, there was no evidence for generalization to the mescaline state when the alcohol was administered at doses exceeding the training dose of mescaline (25 mg/kg). Furthermore, after receiving the alcohol or aldehyde metabolites with aldehyde dehydrogenase inhibitors, the rats only made responses characteristic of the saline state.

Friedhoff and Goldstein [11] reported that TMPE in combination with calcium carbimide (Temposil) produced what subjectively appeared to be "mescaline-like" effects in rabbits. However, while these authors reported potentiation of mescaline with Temposil in rats; no mention was given of effects produced by TMPE in rats, with or without Temposil pretreatment. Thus, failure of the present study to support Friedhoff and Goldstein's conclusion that TMPE or TMPA "formed from mescaline produce extremely potent biological effects at much lower doses than are required for

TABLE 2

LACK OF GENERALIZATION BY ALCOHOL, ALDEHYDE AND N-ACETYL METABOLITES OF MESCALINE

Pretreatment	Test Compound	% Mescaline Appropriate Responses*
None	TMPE (25 mg/kg)	11 ± 2.9 (10)
None	TMPE (50 mg/kg)	17 ± 5.9 (5)
Temposil (10 mg/kg 30 min)	Saline	30 ± 8.0 (5)
	TMPE (12.5 mg/kg)	30 ± 9.3 (5)
Temposil (25 mg/kg 30 min)	Saline	36 ± 10.0 (5)
	TMPE (25 mg/kg)	27 ± 6.6 (7)
DDC (300 mg/kg 24 hr)	Saline	8 ± 6.3 (5)
	TMPE (25 mg/kg)	12 ± 8.2 (5)
Temposil (10 mg/kg 30 min)	TMPA (25 mg/kg)	27 ± 9.0 (9)
None	N-Acetylmescaline (50 mg/kg)	30 ± 8.0 (5)

Test compounds administered i.p. 15 min before the initiation of a 15 min extinction test. Time interval between pretreatment and administration of test compound given in Pretreatment column.

*Values are the average of the number of animals in parenthesis ± S.E.M. and represents the percent of the total test responses made on the lever previously paired with mescaline during training.

TABLE 3

POTENTIATION OF MESCALINE BY AMINE OXIDASE INHIBITORS

Pretreatment	Test Compound	% Mescaline Appropriate Responses
Semicarbazide (25 mg/kg 15 min)	Saline	32 ± 9.1 (7)
	Mescaline (10 mg/kg)	85 ± 5.4 (7)*
Iproniazid (50 mg/kg 30 min)	Saline	34 ± 7.2 (7)
	Mescaline (10 mg/kg)	91 ± 3.2 (7)†
Pargyline (10 mg/kg 30 min)	Saline	15 ± 9.6 (7)
	Mescaline (10 mg/kg)	74 ± 6.4 (7)‡

Saline or mescaline was administered i.p. 15 min prior to the 15 min extinction test. Semicarbazide was administered 15 min and pargyline or iproniazid 30 min prior to mescaline or saline.

Each value the mean ± S.E.M. of the number of animals in parenthesis.

Discriminability of mescaline 10 mg/kg (56%) and saline (19%), Table 1.

*Significantly different from mescaline (10 mg/kg) $p<0.025$.

†Significantly different from mescaline (10 mg/kg) $p<0.05$.

‡Significantly different from mescaline (10 mg/kg) $p<0.005$.

mescaline itself" (p. 12 in [11]) may be due to species differences used in the two studies.

The apparent discrepancy in these results may be explained by the fact that disulfiram and Temposil in addition to the inhibition of aldehyde dehydrogenase have other pharmacological effects. For example, disulfiram is known to also inhibit dopamine-β-hydroxylase [13,22] as well as certain amine oxidase [1,19] by chelating the metal portion of these enzymes essential for activity. Hence, the facilitation of mescaline appropriate responding observed in the present study may be due to effects of these inhibitors on other neurochemical parameters, rather than accumulation of the aldehyde metabolite of mescaline.

The observation that amine oxidase inhibitors enhanced the effects of mescaline (Table 3) suggests that deaminated metabolites of mescaline are not involved in the discriminative cue produced by mescaline. It has been demonstrated that iproniazid and pargyline are capable of reducing deamination of mescaline by brain and liver both in vitro and in vivo [21, 29–30, 32]. However, the potentiating effects of these amine oxidase inhibitors does not appear to be the result of increased brain levels of mescaline. Shah and Himwich [32] observed that iproniazid and tranylcypromine decreased the levels of deaminated metabolites of mescaline, but had no effect on brain levels of mescaline. Furthermore, these authors, as well as others [21], have demonstrated that iproniazid pretreatment also increases the levels of N-acetylmescaline. As shown in Table 2, N-acetylmescaline at a dose of 50 mg/kg does not possess mescaline-like stimulus properties, negating the possibility that the potentiation was due to elevations of this metabolite.

An alternative explanation to account for the facilitating effects of pargyline and iproniazid on mescaline discriminability is that alterations in brain biogenic amines following these inhibitors may enhance the effects of mescaline. In support of this hypothesis is our results with semicarbazide. Semicarbazide appears to only inhibit mescaline oxidation in rabbit liver [8,17] and has no effect on deamination of mescaline in brain [29–30, 32]. Yet we observed a marked potentiation of mescaline following semicarbazide pretreatment. However, semicarbazide exerts pronounced effects on putative neurotransmitter systems [39]. Similarly, iproniazid [19,37] and pargyline [20, 24, 28] have an elevating influence on the levels of brain amines. This interpretation would be consistent with studies demonstrating that mescaline also produces effects on brain amines. For example, mescaline is known to increase brain levels of serotonin [10, 31, 36] and potentiate the effects of histamine by inhibiting histamine metabolism [5] – effects that would be expected following amine oxidase inhibition.

The idea that brain amines may be involved in mediating the discriminative stimulus properties of drugs has been suggested by several recent studies. For example, it has been demonstrated that depleting rat brain of norepinephrine, but not serotonin, abolishes the ability of rats to discriminate nicotine from saline [27]; while serotonin depletion blocks the discriminability of ethanol [25] and potentiates the stimulus properties of LSD [4]. Thus, enhanced discriminability of mescaline following either aldehyde dehydrogenase or amine oxidase inhibitor treatment observed in the present study may be attributable to effects of these drugs on brain biogenic amines, rather than actual effects on mescaline metabolism. We are currently investigating the results of systematic modification of brain biogenic amine systems on the discriminability of mescaline in an attempt to elucidate this possibility.

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