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Role of Serotonin in the Discriminative Stimulus Properties of Mescaline

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BROWNE, R. G. AND B. T. HO. *Role of serotonin in the discriminative stimulus properties of mescaline.* PHARMAC. BIOCHEM. BEHAV. 3(3) 429–435, 1975. – Rats were trained to discriminate intraperitoneally administered mescaline from saline in a two-lever operant chamber for food reinforcement. Reward was contingent upon responses made greater than 15 sec apart (DRL-15) on the appropriate lever paired with either drug or saline administration. Following the establishment of discriminative response control by mescaline, the animals were tested for stimulus generalization produced by mescaline after: (a) blockade of peripheral and central serotonin (5-HT) receptors with cinanserin, methysergide, or cyproheptadine; (b) blockade of peripheral 5-HT receptors with xylamidine tosylate; and (c) depletion of brain 5-HT with the tryptophan hydroxylase inhibitor p-chlorophenylalanine (PCPA). The results show that all three central 5-HT antagonists greatly reduced the discriminability of mescaline while the peripheral antagonist, xylamidine tosylate, was without effect. Furthermore, these agents at the doses employed did not affect the discriminability of saline. Depletion of 5-HT with PCPA potentiated the effects of a sub-threshold dose of mescaline and slightly reduced the discriminability of saline. The results indicate that mescaline produces its discriminative stimulus properties by directly stimulating central serotonergic receptors.

Drug discrimination Mescaline Serotonin Cinanserin Methysergide Cyproheptadine PCPA

STIMULI which are present when a response is reinforced tend to increase the probability that the response will again be emitted. Similarly, in a discrimination task, animals can learn to perform one response in the presence of one stimulus and a different response in the presence of a second stimulus. It is now well established that a large number of drugs are capable of acting as discriminative stimuli [27]. Presumably discriminations based on differential drug states are mediated by the interoceptive cues induced by such drugs [26]. Recently the use of drug discrimination paradigms has created a new approach to the neurochemical elucidation of the mechanism by which drugs act on the brain. For example, Schechter and Rosecrans have demonstrated [31] that in rats trained to discriminate nicotine from saline, depletion of brain catecholamines, but not serotonin (5-HT) reduced the discriminability of nicotine, implying that the cueing properties of nicotine are catecholaminergically mediated. Similarly, Huang and Ho [22] demonstrated that blockade of central dopaminergic receptors with pimozide completely antagonized the discriminative stimulus properties of amphetamine.

Since the early demonstration by Gaddum [16] that d-lysergic acid diethylamide (LSD) in very low concentrations antagonized certain actions of 5-HT, many attempts to implicate serotonin in the mechanism of action of psychotomimetic drugs have been reported [1–4, 8, 13, 14, 19, 23, 38]. While increasing evidence suggests that these drugs directly stimulate 5-HT receptors both peripherally and centrally [1, 2, 8, 13, 14, 19], there is as yet very little behavioral data to support this contention. Indeed, the only consistent finding is that depletion of brain 5-HT potentiates the behavioral effects of LSD [3, 6, 40]. Attempts to examine the influence of serotonergic receptor blockers on the behaviorally disrupting effects of psychotomimetic agents has produced conflicting data showing either potentiation [40], antagonism [11,42], or no effect [21].

The use of mescaline as a discriminative stimulus in the control of operant behavior by producing interoceptive cues has been well demonstrated in several behavioral paradigms [5, 20, 30, 43]. The present study was undertaken to evaluate the role of serotonin in the discriminative stimulus properties of mescaline. It was hypothesized that

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if the cue produced by mescaline is related to 5-HT antagonism, then the centrally acting serotonin antagonists should generalize to the stimulus properties of mescaline. Alternatively, if mescaline produces its cueing effect by direct 5-HT receptor stimulation, then these same 5-HT antagonists should reduce the discriminability of mescaline. Furthermore, we anticipated that depletion of brain serotonin with the tryptophan hydroxylase inhibitor PCPA (parachlorophenylalanine) should potentiate the discriminability of mescaline, as has been reported for LSD [6].

METHOD

Animals

Naive male Sprague-Dawley rats (225–250 g) obtained from Horton Labs (Oakland, California) 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 weekends in quantities adjusted to maintain the rats 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 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

Pretraining. On the first day of pretraining the rats were placed in the operant chambers for 30 min with noncontingent 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 DRF schedule the animal must allow a specified amount of time to elapse between one reinforcement and the availability of the next reinforcement. Premature responses reset the interval timer; while after the specified interval has elapsed the first response will result in reinforcement. Responses on the lever designated incorrect also reset the interval timer to prevent chaining of responses between the two levers. Two days on one lever under DRL-5 sec were followed by two days of training on the other lever under DRL-5. Subsequently two days on each lever on a DRL-10 followed by two days on each lever on DRL-15 were given. DRL-15 sec (unlimited hold) served as the schedule of reinforcement throughout the remainder of the experiment.

Training and extinction testing. Twenty-five rats were run in 5 daily sessions per week. Intraperitoneal injections of either 15 mg/kg of mescaline (as the hydrochloride salt) in isotonic saline or saline were given 15 min before the 30 min sessions. Injection volumes were 1 ml/kg. The sequence of 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 sessions following saline injections only responses made on the left lever were rewarded. Responses on the inappropriate lever re-set the DRL interval timer.

On the first day, and every fourth session thereafter, no responses during the first 5 min of the 30 min session were reinforced (extinction). 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 semirandom 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 animal received five extinction tests following mescaline and five following saline.

Generalization Testing

Time-course and dose-response. In order to test the degree of generalization to the mescaline state at various doses of mescaline or at various times after injection, the rats were given series of four daily training sessions in the order SDDS and tested during a 10 min extinction on a fifth session. No training occurred after these testing sessions nor for the following two days. For time-course determinations on these test days, the animals were injected i.p. with mescaline 15 mg/kg and allowed to remain in their home cages for 15 to 360 min before the initiation of the 10 min extinction test. For dose-response determination the rats were injected with mescaline (5.0 to 25.0 mg/kg) 15 min before the test. The order in which doses and times after injection of mescaline were tested was randomized between subjects and across weekly tests such that no rat ever experienced the same time-course or dose more than once.

Serotonin antagonists. The rats were run in the SDDS sequence of four daily sessions and one 10 min extinction test session per week. On these test days the animals were pretreated with cinanserin, methysergide, cyproheptadine or xylamidine tosylate as specified below. Fifteen min before the initiation of testing, the animals received an i.p. injection of either mescaline (15 mg/kg) or saline. The order in which pretreatment drugs were tested was randomized between animals and across weekly tests such that the rat never received the same pretreatment drug twice.

Serotonin depletion. The rats were not run for two weeks to allow any residual effects of the above experiment to dissipate. To insure maintenance of the discrimination, the animals were then given four days of training in the order SDDS and one extinction test with one half the rats tested with saline and one half with mescaline. The animals were then injected i.p. with the methyl ester of PCPA (100 mg/kg) for three days. Forty-eight hr after the last injection of PCPA the rats were tested with either saline or mescaline (7.5 mg/kg) as described above.

TABLE 1

EFFECTS OF ANTISEROTONERGIC AGENTS ON MESCALINE DISCRIMINATION

Pretreatment	N	Test Compound	% Mescaline Appropriate Responses*	Average Total Responses
None	15	Mescaline (15 mg/kg)	84.5 ± 3.6	43.0 ± 4.2
None	15	Mescaline (7.5 mg/kg)	55.6 ± 8.1	48.7 ± 2.4
None	10	Saline	17.2 ± 4.2	46.5 ± 3.1
Cinanserin	10	Saline	22.6 ± 3.0	38.6 ± 3.8
(15 mg/kg, 30 min)	10	Mescaline (15 mg/kg)	29.0 ± 5.9†	39.6 ± 5.8
Methysergide	10	Saline	31.0 ± 7.8	48.6 ± 5.2
(5 mg/kg, 30 min)	10	Mescaline (15 mg/kg)	49.3 ± 7.1†	43.0 ± 2.8
Cyproheptadine	10	Saline	27.0 ± 7.9	41.2 ± 5.7
(5 mg/kg, 30 min)	10	Mescaline (15 mg/kg)	38.6 ± 9.1†	33.5 ± 3.4
Xylamidine Tosylate	10	Saline	26.7 ± 6.0	47.4 ± 3.7
(1 mg/kg, 90 min)	10	Mescaline (15 mg/kg)	81.7 ± 3.6	41.4 ± 5.9
PCPA Methylester	10	Saline	38.7 ± 3.4§	29.0 ± 3.7§
(100 mg/kg for three days, tested 48 hr after last injection)	10	Mescaline (7.5 mg/kg)	83.9 ± 5.5[a]	28.2 ± 2.9[a]

*Each value represents the mean ± S.E.M. of the number of animals (N) indicated. Values are the percentage of the total responses made during a 10 min extinction test on the lever previously paired with mescaline. Test compounds were administered i.p. 15 min prior to the 10 min extinction test. Time between administration of pretreatment and test compounds is given in the pretreatment column.

†$p<0.002$ different from mescaline, 15 mg/kg (2-tail Mann-Whitney U)

‡$p<0.025$ different from mescaline, 7.5 mg/kg (2-tail Mann-Whitney U)

§$p<0.02$ different from saline (2-tail Mann-Whitney U)

[a]$p<0.002$ different from mescaline, 7.5 mg/kg (2-tail Mann-Whitney U)

Drugs

Dosages of all drugs are expressed as the salts. Mescaline purchased from Sigma Chemical Co. was administered as the hydrochloride salt in isotonic saline. Cinanserin [2'-(3,3-dimethylaminopropyl)thiocinnamanilide] was purchased from Nutritional Biochemicals and administered in saline. Methysergide (Sansert, Sandoz Pharmaceuticals, N.J.) was administered as the maleate in saline. Cyproheptadine hydrochloride (Merck, Sharp and Dohme Research Laboratories, N.J.) was dissolved in 15% aqueous propylene glycol. Xylamidine tosylate (The Wellcome Research Laboratories, England) was dissolved in saline. PCPA as the methyl ester (Regis Chemical Co.) was also dissolved in saline. All injection volumes were 1 ml/kg. Time intervals between administering the pretreatment compounds and the test drugs are given in Table 1.

Pentobarbital Discrimination

In order to evaluate the specificity of the above pharmacological manipulations, a group of ten naive rats were trained to discriminate saline from 10 mg/kg of pentobarbital sodium (American Pharmaceutical Co.) as described above. Following acquisition of the discrimination these rats were tested for the effects of the serotonin antagonists and PCPA on the discriminability of pentobarbital.

Statistical Analysis

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 [35].

RESULTS

Acquisition of Discriminative Response Control

As shown in Fig. 1 mescaline at a dose of 15 mg/kg can serve as a strong discriminative stimulus. After about twenty days of training the rats stabilize at a criterion of greater than 80% cue appropriate responses when tested with either mescaline or saline. It is important to note that on the first day of training the rats do not exhibit a preference for either lever. Indeed, as indicated in Fig. 1, the rats made essentially half of their test responses on each lever during their first exposure to the drug state.

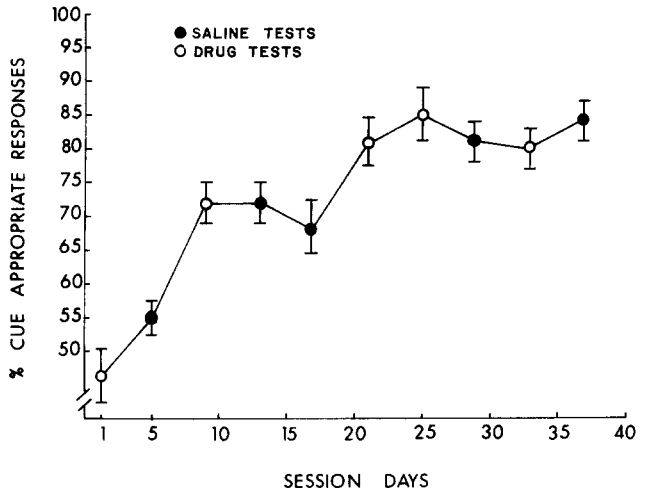

FIG. 1. Acquisition of discrimination between 15 mg/kg of mescaline and saline administered 15 min. before the session. Ordinate: percentage of total extinction responses made during the first 5 min of the session on the mescaline-correct or saline-correct lever. Abcissa: session days on which tests were administered. Each point is the mean ± S.E.M. of 25 rats.

Dose-response and Time Course

Figure 2 depicts the generalization gradient produced by various doses of mescaline. A marked decrement in discrimination accuracy occurs when the animals were tested with doses of mescaline below the 15 mg/kg training dose. The results shown in Fig. 2 indicates that the cue produced by mescaline is a continuum rather than an all-or-none phenomenon. That doses of mescaline higher than the 15 mg/kg training dose do not greatly increase mescaline appropriate responding is indicative of a ceiling effect. Doses of mescaline higher than 25 mg/kg were not tested since response rate decrements began to occur with doses of mescaline higher than 25 mg/kg.

Figure 3 represents the generalization gradient exhibited by the rats at increasing times after injection. The peak in mescaline (15 mg/kg) appropriate responding was observed at 30 min. after injection, but was not significantly different from the 15 min. delay used during acquisition. At 90 min. post-injection the subjects' mescaline appropriate responses were significantly lower than those observed after only 15 min. and by 360 min. the rats exhibited responding characteristic of saline.

Serotonin Antagonists

Table 1 lists the effects of serotonin receptor blockers on the discriminability of mescaline and saline. In addition the average total responses made on both levers during the 10 min extinction tests are included for the different treatments. As can be seen in the response column of Table 1, the total number of responses exhibited by the rats under mescaline is not significantly different from the number of responses following saline administration. Furthermore, the doses of the serotonin antagonists used had no influence on the overall number of responses. However, it is clear from Table 1 that pretreatment with the central 5-HT antagonists cinanserin, methysergide, and cyproheptadine greatly

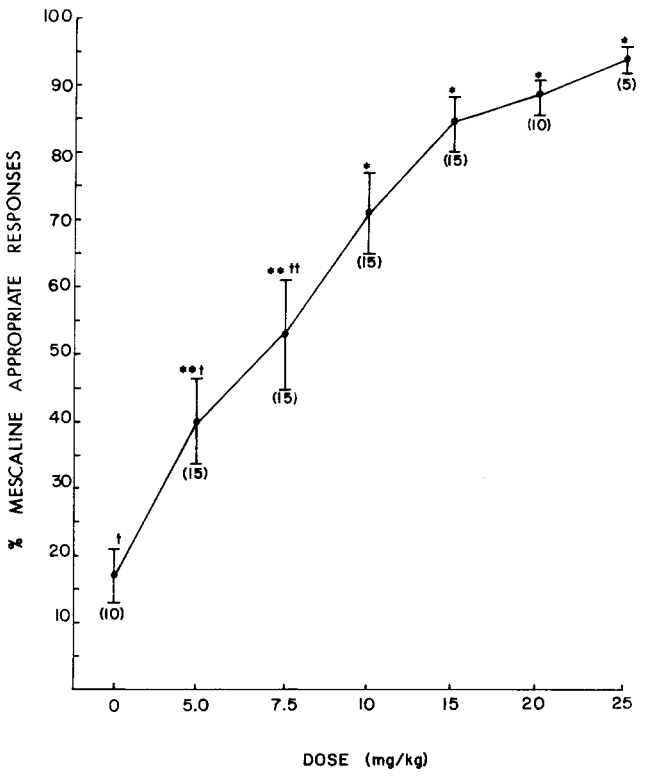

FIG. 2. Dose-response generalization gradient exhibited by rats trained to discriminate 15 mg/kg of mescaline from saline. One 10 min test per week was interposed among four training sessions per week subsequent to acquisition. All doses of mescaline were administered 15 min before the test. Values are the mean ± S.E.M. of the number of animals in parenthesis and represents the percentage of total test responses made on the lever previously paired with mescaline 15 mg/kg. *$p<0.002$ different from saline, **$p<0.02$ different from saline, †$p<0.002$ different from mescaline 15 mg/kg, ††$p<0.02$ different from mescaline 15 mg/kg.

reduce the discriminability of mescaline, as reflected by an increased number test responses on the lever previously paired with saline (i.e. less than 50% mescaline appropriate responses). Indeed, following pretreatment with cinanserin the effects of mescaline were altered to a point not significantly different from that of saline. It is of importance to note that while the 5-HT antagonists tended to slightly reduce the discriminability of saline (e.g. from 17% to 31% for methysergide), such a disruption in saline discrimination did not attain significance. As seen in Table 1, the peripheral 5-HT antagonist, xylamidine tosylate, failed to affect the stimulus properties of mescaline.

Serotonin Depletion

The results presented in Table 1 indicate that depletion of brain 5-HT with PCPA significantly potentiates the effects of mescaline. At the sub-threshold dose of 7.5 mg/kg of mescaline the rats exhibit about 55% mescaline appropriate responses. Following PCPA pretreatment the discriminability of this does of mescaline is increased to more than 80% mescaline-like responses. However, there was a significant reduction in the discriminability of saline

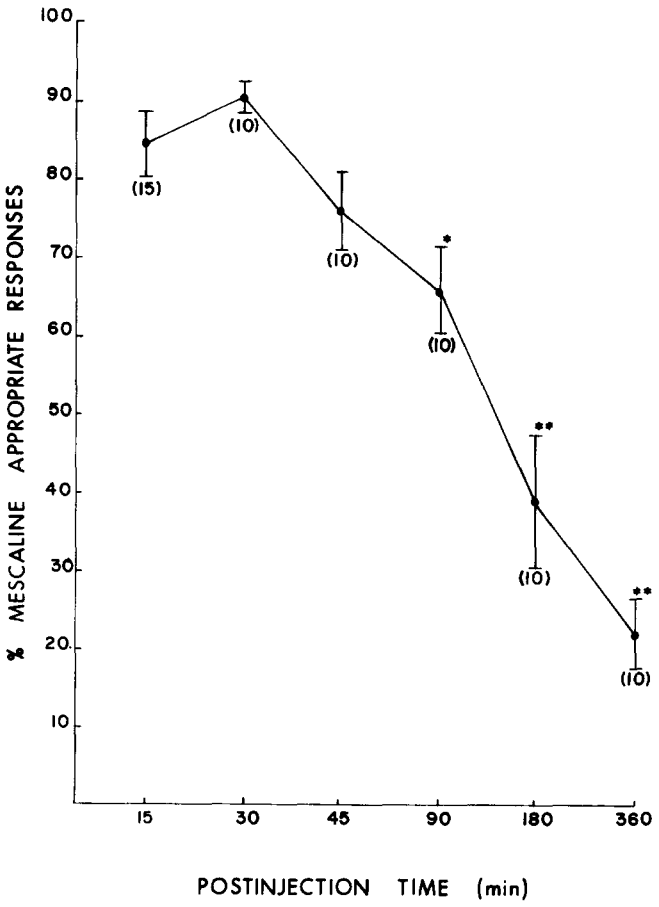

FIG. 3. Time-course generalization in rats trained to discriminate 15 mg/kg of mescaline from saline administered 15 min before the sessions. Values are the mean ± S.E.M. of the number of animals in parenthesis. Ordinate: percent of total responses during a 10 min test on the lever previously paired 15 min after mescaline (15 mg/kg) administration. Abcissa: time after the injection of 15 mg/kg of mescaline when test was initiated. *$p<0.02$ different from mescaline 15 min after injection, **$p<0.002$ different from mescaline 15 min after injection.

produced by PCPA pretreatment (Table 1). Furthermore, the PCPA affected a large diminution in the number of responses following both saline and mescaline administration (Table 1).

Pentobarbital Discrimination.

Table 2 shows the effects of the 5-HT antagonists and PCPA on rats trained to discriminate 10 mg/kg of pentobarbital from saline. Clearly cinanserin failed to affect the discriminability of either saline or pentobarbital in these animals. Similarly, methysergide, cyproheptadine and xylamidine tosylate had no noticeable effect on the ability of rats to discriminate pentobarbital. PCPA consistently reduced the discriminability of saline in these pentobarbital trained rats, but because of the small number of subjects this effect just failed to reach statistical significance. More importantly however, PCPA pretreatment had no observable effect on low dose pentobarbital discrimination (Table 2).

DISCUSSION

The results of the present study strongly suggest that the discriminative stimulus properties of mescaline are mediated by central 5-HT receptor stimulation. This conclusion is supported by our findings (Table 1) that three structurally different CNS serotonin receptor blockers [15, 17, 28, 37, 42] all disrupted the cueing effects of mescaline. While these antiserotonergic agents do have other pharmacological properties [17, 37, 41], their overriding similarity is their acceptance as serotonin receptor blockers. Furthermore, our results are consistent with biochemical evidence [2] as well as experiments on umbilical vasculature [14] which indicate a direct receptor stimulation by mescaline.

That the peripheral 5-HT antagonist xylamidine tosylate failed to disrupt the cueing effect of mescaline suggests that the discriminative properties of mescaline are CNS mediated, consistent with our previous findings [5]. Winter [42] has shown that xylamidine tosylate at the dose used in the present study, could not antagonize the rate disrupting effects on operant behavior of a known hallucinogen, N,N-diethyltryptamine; but that xylamidine tosylate could antagonize a systemically administered dose of 5-HT which produced a comparable pause in responding. While the dose of xylamidine used in the present study is sufficient to antagonize the peripheral effects of 5-HT [10], it is possible that systemic effects attributable to mescaline might not be blocked by this dose. Further studies are in progress to examine this possibility.

The conclusion that mescaline produces its cueing effect by direct 5-HT receptor stimulation is supported by our results with PCPA (Table 1). That a potentiation rather than an antagonism of mescaline's effects occurred following depletion of brain serotinin is suggestive of a direct rather than indirect action of mescaline on 5-HT receptors. However, since it is well established that PCPA does not completely eliminate 5-HT stores, there exists the possibility that mescaline may be acting indirectly by releasing 5-HT. Indeed, using the push-pull cannula to preload radioactive serotonin, Tilson and Sparber [38] have demonstrated that mescaline apparently releases and/or blocks the reuptake of 5-HT, while LSD inhibited the release of radioactive 5-HT. Certainly further studies involving reductions of brain 5-HT stores will be necessary in order to differentiate a direct from an indirect action of mescaline on 5-HT receptors.

It is of interest to note that Cameron and Appel [6] have demonstrated a potentiating effect of PCPA on LSD discriminability. The question remains as to why PCPA treatments would result in accentuating the effects of mescaline or LSD. Since it has been shown [33,34] that drugs often influence the brain levels or metabolism of mescaline, we examined the effects of PCPA on the uptake and metabolism of mescaline (unpublished). We found that PCPA did not significantly alter either the uptake or metabolism of ^{14}C-mescaline, negating the obvious possibility that potentiation was due to altered brain levels of mescaline.

That the various pharmacological manipulations used in the present study are specific for mescaline discriminability is evidenced by the results presented in Table 2. Indeed, with the exception of PCPA, these agents were without significant effect on pentobarbital discrimination, suggesting specificity for the effects of these agents on the cueing properties of mescaline. The disruptive effects of PCPA on

TABLE 2

EFFECTS OF ANTISEROTONERGIC AGENTS ON PENTOBARBITAL DISCRIMINATION

Pretreatment	N	Test Compound	% Pentobarbital Appropriate Responses*
None	10	Pentobarbital (10 mg/kg)	89.5 ± 2.6
None	10	Pentobarbital (5 mg/kg)	51.5 ± 3.0
None	10	Saline	16.9 ± 3.6
Cinanserin (15 mg/kg, 30 min)	5	Saline	24.2 ± 8.0
	5	Pentobarbital (10 mg/kg)	85.0 ± 4.5
Methysergide (5 mg/kg, 30 min)	5	Pentobarbital (10 mg/kg)	84.2 ± 7.7
Cyproheptadine (5 mg/kg, 30 min)	5	Pentobarbital (10 mg/kg)	87.4 ± 5.5
Xylamidine Tosylate (1 mg/kg, 90 min)	5	Pentobarbital (10 mg/kg)	90.6 ± 3.5
PCPA Methylester (100 mg/kg for three days, tested 48 hr after last injection)	5	Saline	33.0 ± 7.9
	5	Pentobarbital (5 mg/kg)	58.6 ± 3.2

*Each value is the mean ± S.E.M. of the number of animals (N) indicated. Values are the percentage of the total responses made during a 10 min extinction test on the lever previously paired with pentobarbital (10 mg/kg).

saline discrimination may be in part due to a toxic manifestation of the drug, since not only was the number of responses significantly reduced by this pretreatment, but also the discriminability of saline in both mescaline and pentobarbital trained rats was altered. However, it is important that PCPA had no potentiating effects on low dose pentobarbital discrimination, again suggesting some degree of specificity.

While this manuscript was in preparation, Hirschhorn and Rosecrans [21] reported that neither methysergide nor cyproheptadine were capable of producing significant alterations in the discriminative stimulus properties of LSD. Since these authors have previously shown that mescaline and LSD produce similar cues [20,30], the present results appear to be in contradiction with their findings [21]. Although their study employed a different hallucinogen (LSD), a slightly different schedule of reinforcement, and slightly different doses of cyproheptadine and methysergide, a resolution of this discrepancy between their data and our own will require further study. Perhaps, as suggested by Haigler and Aghajanian [19], mescaline and LSD have different effects on serotonin neurons and such a proposed difference, while not reflected by the discriminative stimuli produced by these two hallucinogens, is demonstrated by the ability of the serotonin antagonists to block the cue produced by mescaline, but not LSD.

Recently, Winter [43] has demonstrated that an isomer of mescaline, 2,3,4-trimethoxyphenylethylamine, has stimulus properties similar to mescaline (3,4,5-trimethoxyphenylethylamine) but is reportedly non-hallucinogenic. In preliminary findings we also observed a generalization to the mescaline cue by 15 mg/kg of the 2,3,4 isomer and this generalization could be blocked by cinanserin. Thus, the question remains as to the exact nature of the stimuli to which rats attend when given different drugs that exhibit stimulus generalization. Quite possibly interactions between several neurochemical systems are involved in producing these stimuli and, for mescaline at least, it appears that serotonin is of major importance. The present study does not rule out the possibility that other neurotransmitters may contribute to the stimulus properties of mescaline. Indeed, there is a large body of data [7, 9, 18, 24, 25, 29, 32, 34, 36, 39,40] demonstrating effects of mescaline on other neurochemical systems. However, we could not observe any suggestive effects on mescaline discrimination following pretreatment with atropine, phentolamine, propranolol, amphetamine, strychnine, pimozide, or picrotoxin. The consistent effects of serotonin antagonists observed in the present study is therefore indicative that the cue produced by mescaline is a concomitant of CNS serotonergic receptor stimulation.

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NOTE ADDED IN PROOF

Recently J. C. Winter (*Archs int. Pharmacodyn, in press*) has been able to replicate the antagonism of mescaline discrimination with cinanserin.

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