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A PHARMACOLOGIC COMPARISON OF 3,4-METHYLENEDIOXYAMPHETAMINE AND LSD IN THE CHRONIC SPINAL DOG *

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MDA (2.0 and 2.2 mg/kg) was compared to LSD (10 μg/kg) and d-amphetamine (3.2 mg/kg) in single dose, antagonism, cross tolerance and appetite suppression studies. In single doses MDA specifically resembled d-amphetamine by producing marked mydriasis, nictitating membrane retraction, stereotypy and darting eye movements and LSD by markedly facilitating the flexor reflex, producing continuous stepping, whining and eye tracking movements. LSD and MDA increased respiration, body temperature and the latency of the skin twitch reflex and produced behavioral arousal. Cyproheptadine antagonized the effects of LSD but was ineffective against MDA. Phenoxybenzamine antagonized the respiratory, pupillary and hyperthermic effects of MDA and the respiratory effect of LSD. Chlorpromazine antagonized many of the effects of LSD and MDA. Spinal dogs were made tolerant to the behavioral and physiologic effects of LSD. Cross tolerance developed to some but not all of the effects of MDA. In intact dogs MDA was 1/10 as potent as d-amphetamine in suppressing appetite. It is concluded that MDA has properties resembling both LSD and amphetamine.

3,4-Methylenedioxyamphetamine Tolerance Drug abuse LSD Anorexia Behavior Drug interactions

1. Introduction

3,4-Methylenedioxyamphetamine, commonly referred to as MDA or the Love Pill, has been abused presumably for its psychotomimetic effects. Early animal studies (Gunn et al., 1939) reported MDA to possess sympathomimetic actions and to be a more powerful central nervous system stimulant than amphetamine. Subsequent clinical evaluations have stated that MDA is approximately 3—4 times more potent than mescaline in producing what have been purported to be mescaline-like effects (Alles, 1959; Naranjo et al., 1967; Shulgin et al., 1969). The appearance of MDA as a drug of abuse has been primarily a result of its synthesis in clandestine laboratories and it has been sold as mescaline on the street. Generally, MDA is abused orally, although i.v. administration has been reported. Fatal and severe reactions to MDA have been reported by Richards and Borgstedt (1971) and Thiessen and Cook (1973). The present studies compare 3,4-methylenedioxyamphetamine with LSD in the chronic spinal dog, the LSD tolerant chronic spinal dog and the intact dog.

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2. Materials and methods

2.1. General procedure

The following studies were conducted in chronic spinal dogs and employed methods or modifications thereof which have been previously described (Martin and Eades, 1967; 1970; Martin et al., 1974; Vaupel et al., 1977). The dogs used in these studies were female, beagle-type dogs whose spinal cords had been transected at the T-10 or T-11 level. Throughout the course of these experiments, observations were made on the flexor reflex, the stepping reflex, respiration, pulse rate, pupillary diameter, skin twitch reflex latency, nictitating membrane width and body temperature. A programmed tetanic electrical stimulus was used to elicit the flexor reflex and both evoked and spontaneous spinal cord reflex activity were recorded on a kymograph. All flexor reflex measurements were expressed as a percentage of the mean of the responses elicited during the control period. Salivation, rhinorrhea and lacrimation were scored as absent, slight, moderate or perfuse as defined by Martin et al. (1974) and were respectively assigned the values of 0, 1, 2 and 3 for statistical purposes. Similarly the general activity classes were scaled and defined as follows: unresponsive (0) — not responding to external stimuli; sleeping (1) — resting quiescently with eyes closed, either continuously or more often intermittently; quiet (2) — free from excessive movements, peaceful with occasional exploratory head movements; restless (3) — frequent head movements, occasional twisting of body or tugging at leg restraints; struggling (4) — efforts to escape, sometimes violently, characterized by nearly continuous tugging at the foot restraints, body twisting and head movements. Vocalizations, stereotypic head movements and eye movements as described by Vaupel et al. (1977) were treated as nonparametric data.

2.2. Interaction studies

The pharmacologic interactions of three antagonists, cyproheptadine, phenoxybenzamine, and chlorpromazine, with LSD and MDA were investigated. The antagonists were chosen for the following reasons. Cyproheptadine is a selective antagonist of LSD, tryptamine and LSD-like psychotogens (Martin and Eades, 1970; Vaupel and Martin, 1976) and phenoxybenzamine has been shown to be primarily an α-adrenergic blocking drug in the chronic spinal dog (Martin and Eades, 1967; 1970). Chlorpromazine possesses mixed antagonist properties as it antagonizes both α-adrenergic and amphetamine-type actions as well as antagonizes the effects of LSD-like hallucinogens (Martin and Eades, 1968; 1970). There were 8 treatment conditions (see below) administered to 6 dogs as part of 2 successive Latin square designs used to compare the interactions of MDA and MMDA (3-methoxy-4,5-methylenedioxyamphetamine) (Nozaki et al., in preparation) with LSD. A saline—saline treatment was obtained at the end of the above series of experiments. Each dog was tested at 7 day intervals. After completing all the experiments we found that our method of heating phenoxybenzamine to dissolve it in saline produced a partial decomposition. The phenoxybenzamine experiments with LSD and MDA were repeated using phenoxybenzamine dissolved in acidified saline. 4 of the original 6 dogs were used again and 2 new dogs were added. The experimental protocol was as follows: control measurements were obtained for a 30 min period after which either cyproheptadine (0.2 mg/kg), phenoxybenzamine (1.0 mg/kg), chlorpromazine (5.0 mg/kg) or saline was injected over 20 min (30th to 50th min) at a rate of 0.5 ml/min. Half an hour later, either LSD (10 μg/kg) or MDA (2.2. mg/kg) was infused over 40 min (80th to 120th min) at a rate of 0.5 ml/min using a peristaltic pump. Observations were continued for 1 h following the second infusion. The drugs were administered intravenously through an indwelling cannula inserted into the foreleg.

2.3. Tolerance and cross tolerance studies

Control responses to LSD (10 μg/kg), MDA (2.0 mg/kg), d-amphetamine (3.2 mg/kg), 2,5-

dimethoxyamphetamine (2.4 mg/kg), β-phenethylamine (9.2 mg/kg) and saline were obtained at weekly intervals in 6 dogs using a Latin square design. The 2,5-dimethoxyamphetamine, phenethylamine and amphetamine data have been presented elsewhere (Vaupel et al., 1976; 1977). Control observations were obtained over 30 min following which MDA, LSD or saline was infused over 40 min at a rate of 0.5 ml/min. Post-infusion observations were made for 30 min. At the conclusion of these experiments, silastic catheters were implanted in the jugular veins of the dogs and they were made tolerant to LSD, 30 μg/kg/day, using a programmed infusion sequence (Vaupel et al., 1977). The 6 drug treatments were again administered to the LSD tolerant dogs. During the time when the dogs were tolerant to LSD, they were tested every 4th day. Following the completion of these studies, the daily LSD infusion schedule was stopped. 6 weeks later, post-LSD tolerance responses to LSD and saline were obtained (Vaupel et al., 1977).

2.4. Studies on appetite suppression

The effects of MDA (0.275, 0.413, 0.550, 0.620, 0.93, 1.10, 1.395 and 2.093 mg/kg), d-amphetamine (0.03125, 0.0625, 0.125, 0.25 and 0.50 mg/kg), LSD (1.25, 2.5, 5, 10 and 20 μg/kg) and saline on food intake were tested in female beagle-type dogs housed in individual cages and having free access to water. Food was withheld for 23 h and then the dogs were given access to 500 g of dry dog chow between 09.30 and 10.30 h and the amount of food consumed was measured. Drugs were dissolved in saline and were administered by s.c. injection 1 h before feeding time once a week. Mean control levels of food intake for each dog were calculated using the values obtained from the 5 days preceding and following the day of drug administration. Drug effects on food intake were expressed as a percentage of the control level.

2.5. Statistics

Areas under the time action curves, stepping reflex onset latencies and temperature differences were calculated as previously described (Vaupel et al., 1977). Statistical comparisons were made using independent or paired *t*-tests. Latin square analyses were used to study time-related changes in the cross tolerance studies and the appetite suppression data were analyzed using a bioassay for cross-over data. Behavioral data were evaluated using χ^2 and analysis of variance techniques.

2.6. Drugs

The drugs used were LSD tartrate, d,l-3,4-methylenedioxyamphetamine HCl (Dr. R. Willette and Dr. M. Joffe, National Institute on Drug Abuse, and Dr. A.T. Shulgin), phenoxybenzamine HCl (Dr. H.J. Anlage, Smith, Kline and French Laboratories), cyproheptadine HCl (Dr. C.A. Stone, Merck, Sharp and Dohme), chlorpromazine HCl (Smith, Kline and French) and d-amphetamine sulfate (Mr. C.D. Bloomer, Smith, Kline and French Laboratories). Cyproheptadine was dissolved in warm saline and phenoxybenzamine in acidified saline, pH 1.9. The remaining drugs were readily soluble in saline. All drugs were prepared immediately prior to their administration and were infused at room temperature.

3. Results

3.1. Agonist effects

Some of the actions of LSD and MDA in the interaction studies are summarized in fig. 1 and table 1. LSD (10 μg/kg) and MDA (2.2 mg/kg) facilitated the flexor reflex and elicited the stepping reflex, increased respiration, dilated pupils, prolonged the skin twitch latency and elevated body temperature. LSD caused a significant tachycardia, whereas MDA produced a nonsignificant slowing. Although the LSD hyperthermia was not

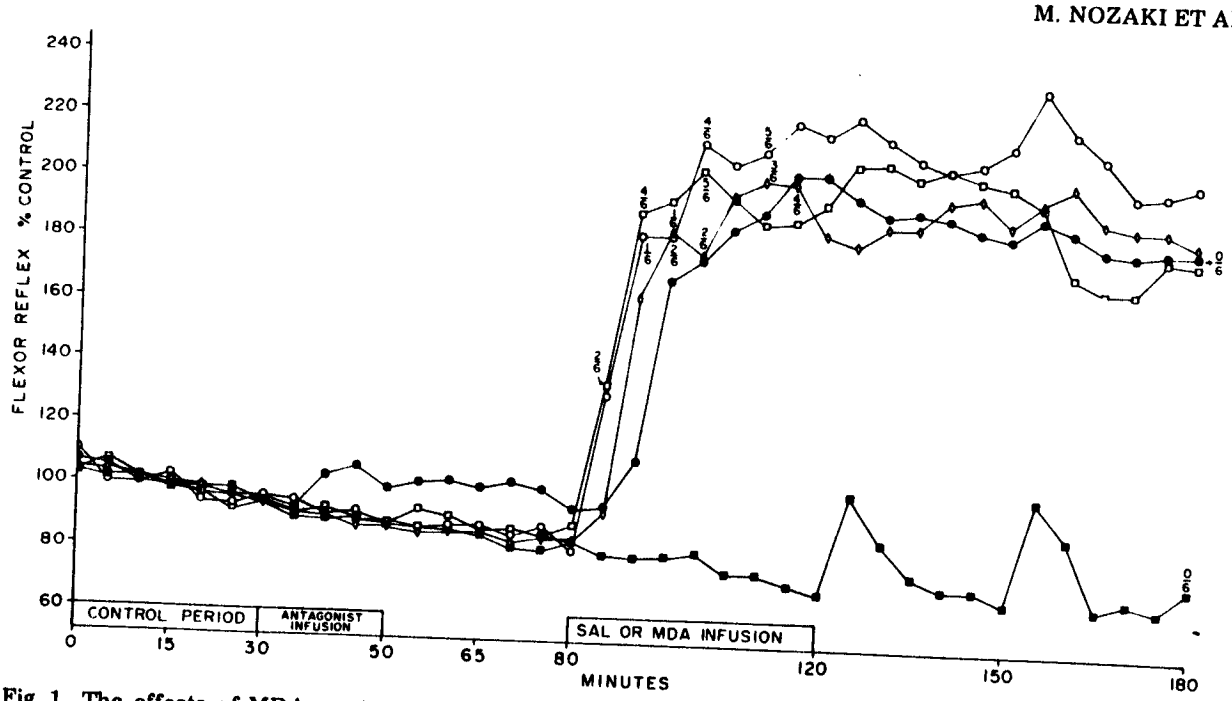

Fig. 1. The effects of MDA on the flexor and stepping reflexes and modification of these actions by phenoxybenzamine, cyproheptadine and chlorpromazine in the chronic spinal dog. The proportion of the dogs which developed the stepping reflex at a particular time is shown by the fraction for each treatment condition. ○——○, Saline — MDA (2.2 mg/kg); □——□, phenoxybenzamine (1.0 mg/kg) — MDA (2.2 mg/kg); ◇——◇, cyproheptadine (0.2 mg/kg) — MDA (2.2 mg/kg); ●——●, chlorpromazine (5.0 mg/kg) — MDA (2.2 mg/kg); ■——■, saline — saline.

statistically significant in this study, pooling these data with those from the cross tolerance study demonstrated that the small 0.1°C increase in temperature produced by LSD was significant for 12 dogs. Additionally the pooled comparisons showed that MDA (2.2 and 2.0 mg/kg) produced quantitatively greater effects than LSD on the stepping reflex, pupils, the skin twitch, the nictitating membrane and body temperature.

3.2. *Antagonist effects*

Cyproheptadine, phenoxybenzamine and chlorpromazine all significantly constricted pupils. Tachycardia developed upon the administration of cyproheptadine and phenoxybenzamine and both phenoxybenzamine and chlorpromazine relaxed the nictitating membrane. The latency of the skin twitch reflex was markedly lengthened by chlorpromazine which confounded the measurement of the analgesic properties of LSD and MDA.

3.3. *Interactions*

As shown in table 1, cyproheptadine (0.2 mg/kg) effectively antagonized the effects of LSD on spinal cord reflexes, respiration, pulse, pupil size and the skin twitch reflex. Following cyproheptadine pretreatment LSD produced an apparent relaxation of the nictitating membrane when compared to pretreatment with saline although neither drug by itself affected the nictitating membrane. Phenoxybenzamine was effective only in reducing the increase in respiration produced by LSD (table 1), whereas chlorpromazine significantly reduced all of LSD's effects except mydriasis (table 1). Phenoxybenza-

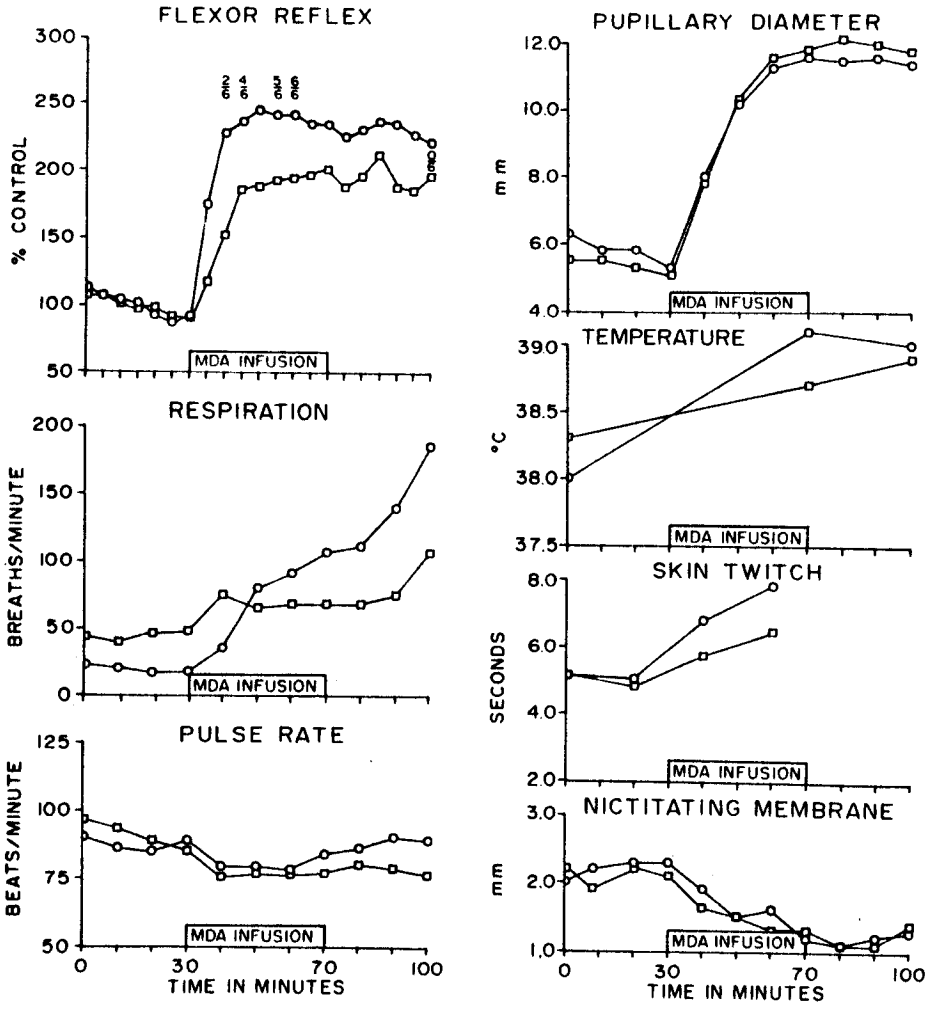

Fig. 2. Demonstration of cross tolerance to 3,4-methylenedioxyamphetamine (MDA 2.0 mg/kg) in LSD tolerant dogs receiving 30 μg/kg/day of LSD. In the flexor reflex panel, the development of the stepping reflex and the proportion of dogs exhibiting the stepping reflex at a particular time are indicated by the fraction. ○———○, Pre-tolerance control (n = 6); □———□, LSD tolerance (n = 6).

mine potentiated the facilitatory effect of LSD on the flexor reflex.

Chlorpromazine was the most effective antagonist of MDA studied as it successfully reduced all of the significant actions of MDA except for the retraction of the nictitating membrane (table 1). On the other hand, cyproheptadine failed to significantly antagonize any action of MDA (table 1). Phenoxybenzamine occupied an intermediate position as it was able to significantly reduce the increases in respiration, pupillary diameter and temperature produced by MDA (table 1).

3.4. LSD tolerance and MDA cross tolerance studies

The effects of LSD and MDA in the non-tolerant and LSD tolerant spinal dog are summarized in table 2, and fig. 2 illustrates

TABLE 1

Summary of the interaction studies. The values in each column are the mean area, except for the stepping reflex and temperature, ± S.E.M. and are based on an n of 6. All comparisons are based on paired *t*-tests and one-tail *p* values except for comparisons of PBZ—LSD to SAL—LSD and PBZ—MDA to SAL—MDA which were made using group *t*-tests. The superscript cc indicates the appropriate saline control to evaluate the effects of LSD (SAL—LSD) and MDA (SAL—MDA) and the levels of significance are indicated by the superscript located to the upper left above the mean for each set of values. The superscript c indicates the control treatment against which the effects

Drug 1	Drug 2	Flexor reflex (% · min)	Stepping reflex (min to onset)	Respiration (breaths/ min · min)	Pulse (beats/ min · min)
SAL	SAL^{cc}	−316 ± 92	No stepping	−1300 ± 1986	−218 ± 167
SAL	LSD^{c}	$^{0.01}$2817 ± 388	$^{0.05}$70 ± 12	$^{0.05}$7051 ± 2035	$^{0.05}$350 ± 112
CYP	LSD	616 ± 285 $^{0.01}$	No stepping	2281 ± 971 $^{0.05}$	−275 ± 214 $^{0.05}$
PBZ	LSD	4010 ± 522 $^{0.05}$	58 ± 19	968 ± 394 $^{0.01}$	277 ± 580
CPZ	LSD	89 ± 220 $^{0.01}$	No stepping	−1058 ± 981 $^{0.01}$	8 ± 100 $^{0.01}$
SAL	MDA^{c}	$^{0.01}$3355 ± 823	$^{0.01}$33 ± 14	$^{0.05}$6407 ± 1709	−255 ± 176
CYP	MDA	2241 ± 522	50 ± 16	5688 ± 2241	−555 ± 224
PBZ	MDA	2830 ± 486	25 ± 15	1197 ± 347 $^{0.01}$	3 ± 137
CPZ	MDA	1478 ± 351 $^{0.05}$	No stepping	5 ± 283 $^{0.01}$	312 ± 330
SAL—LSD^{c}	vs. SAL—MDA^{c}	NS	NS	NS	NS

the effects of MDA. In the nontolerant dog the physiologic actions of LSD and MDA were the same as those in the interaction study except for effects of LSD on the skin twitch and temperature. The lack of effect of LSD on the skin twitch is not in agreement with results obtained in the interaction study and in subsequent experiments using 15 μg/kg of LSD. Taken together, the consensus of data suggests that LSD prolongs skin twitch latency. LSD also produced a small but significant increase in body temperature. Dogs were quiet during the preinfusion periods and when they have received saline (Vaupel et al. 1977). The major behavioral changes produced by LSD (10 μg/kg) in the nontolerant dog were behavioral arousal, restlessness, whining and tracking. Dogs receiving LSD chronically exhibited a high degree of direct tolerance to 10 μg/kg of LSD for all the significant physiologic measures and behavioral effects except temperature (table 2). During the infusion of LSD the LSD tolerant dogs remained either quiet or asleep. In the nontolerant dog, MDA (2.0 mg/kg) produced extreme restlessness, whining, head tossing, head rocking, darting eye movements, tracking and panting. Also there were increases in rhinorrhea from slight to profuse and in salivation from slight to moderate. When MDA was administered to LSD tolerant dogs facilitation of the flexor reflex was significantly reduced although the degree of cross tolerance was noticeably less than tolerance to LSD (fig. 2 and Vaupel et al., 1977). Like LSD, MDA did not evoke the stepping reflex in LSD tolerant dogs. The LSD tolerant dogs were also cross tolerant to the ability of MDA to produce hyperthermia and increase the skin twitch latency. There was no cross toler-

of the antagonists were evaluated with the level of significance shown by the superscript to the upper right above the S.E.M. The absence of the stepping reflex is shown. The effects of LSD and MDA are compared in the bottom line showing only the level of significances or lack of it (NS). The abbreviations used are: SAL = saline, LSD = lyserigc acid diethylamide, MDA = 3,4-methylenedioxyamphetamine, CYP = cyproheptadine, PBZ = phenoxybenzamine and CPZ = chlorpromazine.

Pupillary diameter (mm · min)	Skin twitch reflex (sec · min)	Nicitating membrane (mm · min)	Temperature (°C change)
−11.8 ± 4.0	−3.28 ± 14.39	3.5 ± 1.2	−0.2 ± 0.1
$^{0.01}$18.5 ± 9.9	$^{0.05}$42.35 ± 12.70	−6.6 ± 5.0	0.1 ± 0.2
−3.6 ± 6.4 $^{0.05}$	−4.33 ± 8.60 $^{0.05}$	7.9 ± 2.1 $^{0.01}$	0.4 ± 0.2
17.7 ± 2.4	47.63 ± 17.66 $^{0.01}$	16.5 ± 7.0	−0.2 ± 0.1
2.2 ± 3.4	11.24 ± 10.18 $^{0.01}$	11.3 ± 8.3	−0.6 ± 0.2
$^{0.01}$177.2 ± 24.0	$^{0.01}$101.42 ± 27.72	$^{0.01}$−16.8 ± 4.1	$^{0.01}$1.0 ± 0.3
199.6 ± 10.8	76.14 ± 15.38	−22.4 ± 6.0	0.6 ± 0.2
82.6 ± 10.2 $^{0.01}$	62.96 ± 25.06	−50.7 ± 18.0	0.4 ± 0.1 $^{0.05}$
49.2 ± 6.6 $^{0.01}$	−2.25 ± 31.39 $^{0.05}$	−19.0 ± 3.2	−0.9 ± 0.2 $^{0.01}$
0.01	0.05	NS	0.05

ance to the actions of MDA on pulse rate, pupillary diameter, the nictitating membrane, salivation and rhinorrhea. The onset of the restlessness and struggling was delayed and the peak behavioral effect of MDA was less than in the nontolerant state, resulting in the development of partial tolerance to MDA (table 2). Dogs continued to whine, exhibit tracking, stereotypy and panting. No behavioral changes have been seen in saline control experiments (Vaupel et al., 1977).

3.5. Appetite suppression

Using a 12 point bioassay, d-amphetamine and MDA were shown to suppress food intake in a dose related manner (fig. 3). The criteria for a valid bioassay were fulfilled and MDA was shown to be 10 times less potent than d-amphetamine as an appetite suppressant in the dog. Saline did not exert any significant effect in food intake. The two lowest doses of LSD increased food consumption while larger doses had no significant effect.

4. Discussion

A comprehensive series of data has been obtained in the dog from single dose, interaction, tolerance and appetite suppression studies permitting the assessment of LSD and amphetamine-like properties of MDA. Previously we reported on the actions of d-amphetamine (3.2 mg/kg) which, in the chronic spinal dog, differentiate it from LSD (Vaupel et al., 1976). Amphetamine-like effects produced by MDA included marked mydriasis, retraction of the nictitating membrane, stereotypic head movements, darting eye movements and appetite suppression. MDA resem-

TABLE 2

Tolerance and cross tolerance results. Responses to SAL (saline), LSD (lysergic acid diethylamide) and MDA (3,4-methylenedioxyamphetamine) during the 2 treatment conditions are shown as the mean area, except for the stepping reflex and temperature, ± S.E.M. Comparisons were made using one-tail paired *t*-tests. In the nontolerant dog control responses to LSD and MDA were compared to saline and the level of statistical significance is shown by the superscript located above the mean. Direct tolerance to LSD and cross tolerance to MDA and saline were assessed by comparing responses obtained in the LSD tolerant dog to the appropriate nontolerant control. Superscripts indicating levels of significance for these comparisons are located above the S.E.M.

	Saline		LSD 10 μg/kg		MDA 2.0 mg/kg	
	Non-tolerant dog	LSD tolerant dog	Non-tolerant dog	LSD tolerant dog	Non-tolerant dog	LSD tolerant dog
Flexor reflex (% · min)	−276 ± 144	−356 ± 153	$^{0.05}$2591 ± 960	−44 ± 131$^{0.05}$	$^{0.05}$1808 ± 532	951 ± 414$^{0.01}$
Stepping reflex (min to onset)	No stepping	No stepping	$^{0.01}$32 ± 3	No stepping$^{0.01}$	$^{0.01}$18 ± 3	No stepping$^{0.01}$
Respiration (breaths/ min · min)	8 ± 132	−14 ± 109	$^{0.05}$3122 ± 1165	598 ± 127$^{0.05}$	$^{0.05}$5301 ± 2201	1593 ± 677
Pulse (beats/ min · min)	2 ± 63	108 ± 101	$^{0.05}$392 ± 117	−122 ± 73$^{0.05}$	−302 ± 189	−357 ± 247
Pupilary diameter (mm · min)	−11.6 ± 6.0	−3.4 ± 5.3	$^{0.01}$21.8 ± 5.2	3.5 ± 3.7$^{0.05}$	$^{0.01}$168.9 ± 18.9	178.2 ± 21.2
Nicitating membrane (mm · mm)	1.2 ± 4.7	8.9 ± 4.3	6.5 ± 2.1	3.6 ± 5.0	$^{0.05}$−24.8 ± 7.1	−21.3 ± 6.6
Temperature (°C change)	−0.2 ± 0.0	0.2 ± 0.4	$^{0.05}$0.1 ± 0.1	0.2 ± 0.3	$^{0.01}$1.0 ± 0.1	0.3 ± 0.3$^{0.05}$
Skin twtch (sec · min)	1.8 ± 6.7	−13.6 ± 15.0	−1.7 ± 24.5	−13.1 ± 19.6	$^{0.01}$62.4 ± 16.3	30.6 ± 18.6$^{0.01}$
n	6	6	6	6	6	6

bled LSD by markedly facilitating the flexor reflex, eliciting the stepping reflex, producing whining and causing tracking movements with the eyes.

The interaction studies again confirmed that cyproheptadine is a more selective antagonist of LSD than phenoxybenzamine (Martin and Eades, 1970; Vaupel et al., 1977). The potentiation of the LSD effect on the flexor reflex by phenoxybenzamine has been observed in previous studies (Vaupel et al., 1977). Cyproheptadine failed to significantly antagonize any of the effects of MDA although there were trends for reductions in its action on the flexor and stepping reflexes, the skin twitch and body temperature. Phenoxybenzamine which antagonizes the flexor reflex and pupillary effects of the α-agonist methoxamine and d-amphetamine in the spinal dog (Martin and Eades, 1968) significantly reduced the respiratory, mydriatic and hyperthermic effects of MDA, indicating the involvement of noradrenergic mechanisms. Chlorpromazine was the most effective antagonist of those tested against MDA but it similarly reduced many of the effects of LSD.

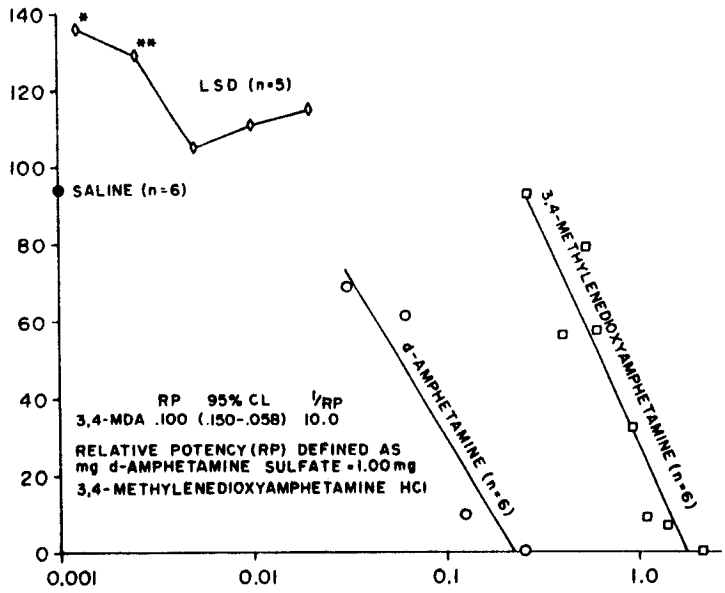

Fig. 3. Appetite supression studies demonstrating the anorexigenic effect of 3,4-methylenedioxyamphetamine. The relative potency was calculated using a 12 point bioassay. Effects of each dose of LSD were compared to saline using paired *t*-tests for 5 dogs. * $p < 0.05$; ** $p < 0.01$. Ordinate: % of control food intake; abscissa: dose (mg/kg).

The effects of 2.2 mg/kg of MDA and 10 μg/kg of LSD which were determined to be equivalent in dose ranging studies can be compared in fig. 1 and table 1. MDA had a somewhat more rapid onset of action in facilitating the flexor reflex and evoking the stepping reflex and so the effectiveness of this dose of MDA may have been somewhat larger than the equivalent dose of LSD. For this reason a smaller dose of MDA (2.0 mg/kg) was employed in the tolerance-cross tolerance study. As can be seen in table 2, LSD produced a greater degree of facilitation, whereas the onset of stepping was shorter for MDA. These doses are thus more equipotent.

A high degree of tolerance developed to the physiological and behavioral effects of LSD, however, LSD tolerant dogs are not cross tolerant to amphetamine (Vaupel et al., 1976). The LSD tolerant dogs were cross tolerant to the effects of MDA on spinal cord reflexes, the skin twitch and temperature. No cross tolerance to the pupillary or nictitating membrane effects was seen and only partial cross tolerance to the behavioral effects of MDA developed.

Thus there are several lines of evidence that indicate that MDA has both LSD-like and amphetamine-like actions: (1) effects in the non-tolerant chronic spinal dog had features of both prototypic drugs, (2) cyproheptadine was more effective against LSD than MDA, whereas phenoxybenzamine was more effective against MDA and (3) the LSD tolerant dog was cross tolerant to some of the actions of MDA.

Other investigators have identified both LSD or mescaline-like activity in MDA. Mescaline and MDA produced similar EEG changes in the cat (Fairchild et al., 1967) and on the conditioned avoidance response in the rat (Davis et al., 1976). More recently Griffiths et al. (1976) found that MDA, like amphetamine, will maintain self-infusion performance in the baboon as well as suppress appetite. Paton (1975) also demonstrated that

MDA released and inhibited the uptake of norepinephrine in noradrenergic neurons. It, therefore, appears that the mode of action of MDA is not simple since LSD may act on tryptaminergic or serotonergic receptors and amphetamine may act directly or indirectly on noradrenergic, dopaminergic and possibly other receptors.

None of the clinical studies evaluating the subjective effects of MDA has employed objective standardized measures with appropriate controls. In fact direct comparisons between LSD and amphetamine have not been made using validated instruments for measuring subjective effects. Nevertheless, the euphoria reported by subjects receiving low doses of LSD is similar to the subjective effects produced by amphetamine (Isbell et al., 1956; Rosenberg et al., 1963; Haertzen, 1966; Martin et al., 1971; Martin and Sloan, in press). The clinical data available for MDA suggest that it produces feelings in the direction of euphoria (Alles, 1959; Naranjo et al., 1967; Richards, 1972). Reports of MDA-induced hallucinations are inconsistent and are relatively few in number (Alles, 1959; Richards and Borgstedt, 1971; Richards, 1972). An evaluation of anecdotal reports of the subjective effects produced by MDA is consistent with our findings that MDA is amphetamine-like and that it also may produce LSD-like perceptual changes.

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