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A PHARMACOLOGICAL COMPARISON OF 3-METHOXY-4,5-METHYLENEDIOXYAMPHETAMINE AND LSD IN THE DOG

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Summary

3-Methoxy-4,5-methylenedioxyamphetamine (MMDA), which has been reported to have hallucinogenic actions in man, was compared to LSD in single dose, antagonist interaction, cross-tolerance and appetite suppression studies in the dog. In single doses, MMDA partially resembled LSD: both facilitated the flexor reflex and produced tachypnea, hyperthermia, and analgesia; however, MMDA had greater activity than LSD in producing mydriasis. Only LSD consistently elicited the stepping reflex and produced tachycardia. In both the interaction studies and cross-tolerance studies in LSD-tolerant dogs the effects of MMDA were generally not like those of LSD, except for its spinal cord facilitatory effect. Cyproheptadine antagonized most of the effects of LSD but only the facilitatory effect of MMDA on the flexor reflex. On the other hand, phenoxybenzamine antagonized the mydriasis, analgesia, and hyperthermia caused by MMDA but not LSD. Cross-tolerance to MMDA developed only to its effects on the flexor and skin twitch reflexes. In intact dogs, the anorexigenic potency of MMDA was 16 times less than that of *d*-amphetamine. It is concluded that MMDA has primarily amphetamine-like activity with some LSD-like actions.

Introduction

3-Methoxy-4,5-methylenedioxyamphetamine (MMDA) has been reported to have psychotomimetic activity in man with the intoxication syndrome being qualitatively similar to that of mescaline [1 - 3]. In the present study, pharmacologic, physiologic, and behavioral effects of MMDA were compared with those of LSD in the nontolerant and LSD-tolerant chronic spinal dog. Because of the structural similarities between MMDA and amphetamine, their anorexic effects were also compared in the intact dog.

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Materials and methods

The following studies were conducted in chronic spinal or intact female beagle-type dogs using methods and modifications which have been described previously [4 - 6]. Observations were made on the flexor reflex, stepping reflex, respiration, pulse rate, pupillary diameter, skin twitch reflex latency, nictitating membrane width, and body temperature during the experiments.

In the interaction studies, eight treatment conditions (Figs. 1 and 2) were administered to 10 chronic spinal dogs using a crossover design. The saline–saline treatment was obtained at the end of the above series of experiments. The dogs were tested at intervals of 1 week or longer. Cyproheptadine, a selective antagonist of LSD and tryptamine [7], phenoxybenzamine, an α-adrenergic blocking agent, and chlorpromazine, which has tryptaminergic, α-adrenergic and dopaminergic blocking properties [7, 8], were used. Doses of LSD and MMDA were selected on the basis of producing equieffective facilitative effects on the flexor reflex. Doses of phenoxybenzamine, cyproheptadine, and chlorpromazine, which antagonized facilitation of the flexor reflex caused by methoxamine, LSD, and LSD and amphetamine respectively [5, 6], were used. The drugs and dosages employed were: LSD tartrate, 0.010 mg/kg; *dl*-3-methoxy-4,5-methylenedioxyamphetamine HCl, 5.0 mg/kg (Drs. R. Willette and M. Joffe, National Institute on Drug Abuse, and Dr. A. T. Shulgin); cyproheptadine HCl, 0.2 mg/kg (Dr. C. A. Stone, Merck, Sharp

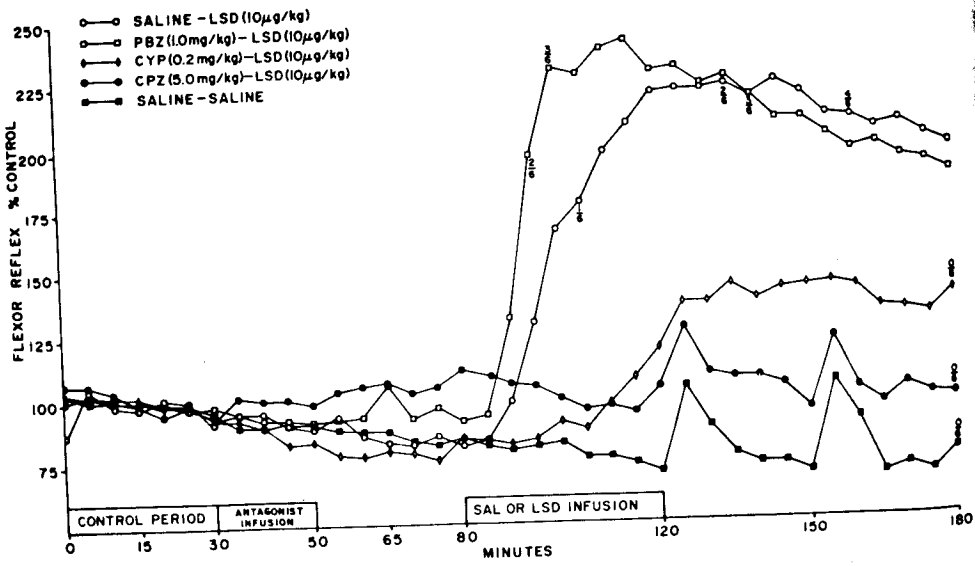

Fig. 1. The effects of lysergic acid diethylamide (LSD) on the flexor and stepping reflexes and modification of these actions by phenoxybenzamine (PBZ), cyproheptadine (CYP), and chlorpromazine (CPZ) in the chronic spinal dog. The proportion of the dogs (n = 6) which developed the stepping reflex at a particular time is shown by the fractions for each treatment condition.

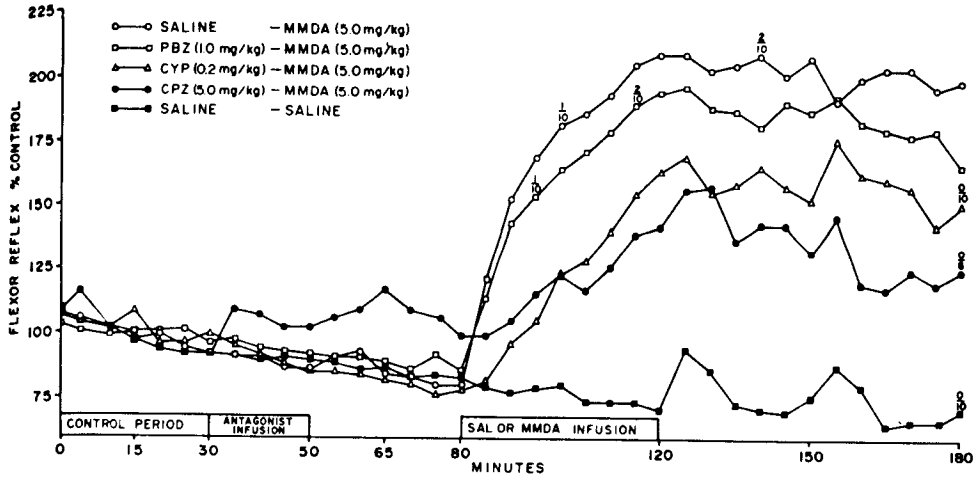

Fig. 2. The effects of 3-methoxy-4,5-methylenedioxyamphetamine (MMDA) on the flexor and stepping reflexes and modification of these actions by phenoxybenzamine (PBZ), cyproheptadine (CYP), and chlorpromazine (CPZ) in the chronic spinal dog. The proportion of the dogs (n = 10) which developed the stepping reflex at a particular time is shown by the fractions for each treatment condition.

and Dohme); phenoxybenzamine HCl, 1.0 mg/kg (Dr. H. J. Anlage, Smith, Kline and French Laboratories); and chlorpromazine HCl, 5.0 mg/kg. Doses were expressed as salts.

In the single dose and interaction studies, control measurements were obtained for a 30 min period after which either the antagonist or saline was injected over 20 min at a rate of 0.5 ml/min. Half an hour later, either LSD, MMDA, or saline was infused over 40 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.

In the cross-tolerance studies, control responses to LSD, MMDA, and saline were obtained at weekly intervals in 6 chronic spinal dogs having chronically implanted jugular vein catheters using a crossover design. MMDA (5.0 mg/kg), LSD (0.015 mg/kg), or saline was infused over 40 min at a rate of 0.5 ml/min following a 30 min control period. Observations were continued for 30 min after the infusion. The dogs were then made tolerant to 30 μg/kg of LSD per day [6]. During the time the dogs were tolerant to LSD, they were tested every 4th day with either LSD, MMDA, or saline.

In the appetite suppression studies, the effects of MMDA (0.5, 1.0, 2.0 mg/kg), *d*-amphetamine (0.03 - 0.50 mg/kg), and LSD (1.25 - 20 μg/kg) on food intake during a 1 h period were compared in 6 or 12 female beagle-type intact dogs housed in individual cages; the dogs were deprived of food for 23 h but had free access to water. Daily food intake was measured for 1 h (between 09:30 and 10:30) each morning. Drugs were dissolved in saline and were administered subcutaneously 1 h before feeding every 6th day. Mean control levels of food intake for each dog were calculated using the values

obtained for 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. These data were analyzed as previously described [6] by comparing areas of the time action curves during agonist infusion periods from the 80th-120th min in the single dose and interaction studies and the 30th-70th min in the cross-tolerance study. Stepping reflex onset latencies from the beginning of the agonist infusion and temperature differences between the start of an experiment and the end of the agonist infusion were also analyzed. Either independent or paired *t*-tests were used to make statistical comparisons for the interaction and cross-tolerance studies. Appetite suppression data were analyzed using a bioassay [9].

Results

Single dose studies

As can be seen in Figs. 1 and 2 and Table 1, both LSD (10 μg/kg) and MMDA (5.0 mg/kg) facilitated the flexor reflex, increased respiratory rate, dilated pupils and prolonged the skin twitch latency indicating an analgesic effect. LSD produced stepping in 4 of 6 dogs and MMDA in 2 of 10. Fragmentary stepping was seen in the other dogs. LSD produced a tachycardia, whereas MMDA had no effect on the heart rate. The temperature increase produced by LSD was not statistically significant, while MMDA caused statistically significant hyperthermia and retracted the nictitating membrane. In many respects the behavioral effects of LSD and MMDA were similar, both producing arousal, restlessness, whining, and tracking or staring. Dogs receiving LSD did not exhibit the barking and howling observed in some dogs following MMDA.

Interaction studies

As shown in Figs. 1 and 2 and Table 1, cyproheptadine antagonized the effects of LSD on the flexor reflex, stepping reflex, respiration, pulse rate, pupillary diameter, and skin twitch latency, and yet it only significantly antagonized the effects of MMDA on the flexor reflex and stepping reflex in the two dogs exhibiting them. Phenoxybenzamine reduced the increase in respiration produced by both LSD and MMDA and also antagonized the effects of MMDA on pupillary diameter, skin twitch latency, and body temperature (Table 1). On the other hand, phenoxybenzamine potentiated the facilitation of the flexor reflex produced by LSD (Table 1). Chlorpromazine antagonized almost all of the effects of LSD and MMDA (Table 1).

LSD tolerance and MMDA cross-tolerance studies

Pre-tolerant responses to LSD and MMDA differed from the single dose study in that LSD-induced hyperthermia was significant, and MMDA did not affect the nictitating membrane (Figs. 3 and 4). Dogs receiving LSD chronically exhibited a high degree of direct tolerance to 15 μg/kg of LSD for all

TABLE 1

Summary of single dose and interaction studies

Drug 1	Drug 2	Flexor reflex (% min)	Stepping reflex (min to onset)	Respiration (breaths/ min min)	Pulse (beats/ min min)	Pupillary diameter (mm min)	Skin twitch reflex (s min)	Nictitating membrane (mm min)	Temperature (°C change)	n
SAL	SAL[cc]	−316 ± 92	No stepping	−1300 ± 1986	−218 ± 167	−11.8 ± 4.0	−3.28 ± 14.39	3.5 ± 1.2	−0.2 ± 0.1	6
SAL	LSD[c]	2817[.01] ± 388	70[.05] ± 12	7051[.05] ± 2035	350[.05] ± 112	18.5[.01] ± 9.9	42.35[.05] ± 12.70	−6.6 ± 5.0	0.1 ± 0.2	6
CYP	LSD	616 ± 285[.01]	No stepping[.05]	2281 ± 971[.05]	−275 ± 214[.05]	−3.6 ± 6.4[.06]	−4.33 ± 8.60[.05]	7.9 ± 2.1[.05]	0.4 ± 0.2	6
PBZ	LSD	4010 ± 522[.05]	58 ± 19	968 ± 394[.01]	277 ± 580	17.7 ± 2.4	47.63 ± 17.66	−16.5 ± 7.0	−0.2 ± 0.1	6
CPZ	LSD	89 ± 220[.01]	No stepping[.05]	−1058 ± 981[.01]	8 ± 100[.01]	2.2 ± 3.4	−11.24 ± 10.18[.01]	11.3 ± 8.3	−0.6 ± 0.2	6
SAL	MMDA[c]	3483[.01] ± 688	88 ± 9	5846[.01] ± 1949	80 ± 138	92.2[.01] ± 9.7	83.39[.01] ± 11.70	−14.1[.01] ± 3.9	0.1[.05] ± 0.1	10
CYP	MMDA	1457 ± 315[.05]	No stepping	3032 ± 1849	−130 ± 121	103.4 ± 5.4	70.24 ± 12.19	−13.6 ± 3.2	0.1 ± 0.1	10
PBZ	MMDA	2712 ± 467	85 ± 10	32 ± 185[.01]	3 ± 202	51.0 ± 5.9[.01]	42.34 ± 9.66[.01]	−19.1 ± 14.2	−0.2 ± 0.1[.01]	10
CPZ	MMDA	693 ± 162[.01]	No stepping	1413 ± 1802[.01]	610 ± 223[.05]	28.3 ± 4.7[.01]	−49.92 ± 15.09[.01]	14.2 ± 6.7[.01]	−1.1 ± 0.2[.01]	6
SAL	LSD	NS	NS	NS	NS	0.01	0.005	NS	NS	
SAL	MMDA									

The values in each column are the mean area, except for the stepping reflex and temperature, standard error and numbers of animals. The comparisons are based on paired t-tests except for the comparisons of PBZ–LSD to SAL–LSD and PBZ–MMDA to SAL–MMDA which employed group t-tests. The superscript cc indicates the appropriate saline control for evaluating the effects of LSD (SAL–LSD) and MMDA (SAL–MMDA) and the levels of significance are indicated by the superscript located to the right of the mean for each set of values. The superscript c indicates the control treatment against which the effects of the antagonists were evaluated with the level of significance shown by the superscript to the right of the standard error. The absence of stepping reflex is shown. The effects of LSD and MMDA are compared in the bottom line showing only the levels of significance or lack of it (NS). The abbreviations used are: SAL = saline, LSD = lysergic acid diethylamide, MMDA = 3-methoxy-4,5-methylenedioxyamphetamine, CYP = cyproheptadine, PBZ = phenoxybenzamine, and CPZ = chlorpromazine.

TABLE 2

Tolerance and cross-tolerance results

	Saline		LSD 15 μg/kg		MMDA 5.0 mg/kg	
	Nontolerant dog	LSD-tolerant dog	Nontolerant dog	LSD-tolerant dog	Nontolerant dog	LSD-tolerant dog
Flexor reflex (% min)	−68 ± 111	−194 ± 103	902$^{.01}$ ± 201	−259 ± 188$^{.01}$	1354$^{.01}$ ± 283	546 ± 149$^{.01}$
Stepping reflex (min to onset)	No stepping	No stepping	33 ± 8	No stepping	59 ± 9	67 ± 3
Respiration (breaths/ min min)	13 ± 52	−27 ± 94	1894$^{.05}$ ± 823	−47 ± 120$^{.05}$	2607$^{.05}$ ± 1171	2856 ± 1194
Pulse (beats/min min)	−148 ± 185	−58 ± 87	278$^{.05}$ ± 56	−203 ± 86$^{.01}$	76 ± 80	13 ± 72
Pupillary diameter (mm min)	−1.1 ± 3.2	−3.1 ± 6.4	27.0$^{.05}$ ± 15.2	−3.8 ± 2.7$^{.05}$	97.0$^{.01}$ ± 14.0	84.7 ± 6.7
Nictitating membrane (mm min)	0.8 ± 4.7	−2.8 ± 2.0	4.7 ± 3.0	−3.8 ± 1.9	−0.5 ± 3.4	−5.9 ± 2.7
Temperature (°C change)	0.0 ± 0.1	0.1 ± 0.1	0.6$^{.01}$ ± 0.1	−0.1 ± 0.1$^{.01}$	0.4$^{.05}$ ± 0.1	0.2 ± 0.1
Skin twitch (s min)	−1.1 ± 6.7	0.0 ± 7.0	54.3$^{.05}$ ± 19.5	18.0 ± 5.0	43.3$^{.01}$ ± 13.2	16.5 ± 6.7$^{.05}$
n	6	6	6	6	6	6

Responses to SAL (saline), LSD (lysergic acid diethylamide) and MMDA (3-methoxy-4,5-methylenedioxyamphetamine) during the two treatment conditions are shown as the mean area, except for the stepping reflex and temperature, standard error and numbers of animals. Comparisons were made using one-tail paired *t*-tests. In the nontolerant dog, control responses to LSD and MMDA were compared with those to saline and the level of statistical significance is shown by the superscript located to the right of the mean. Direct tolerance to LSD and cross-tolerance to MMDA and saline were assessed by comparing responses obtained in the LSD-tolerant dog. Superscripts indicating levels of significance for these comparisons are located to the right of the standard error.

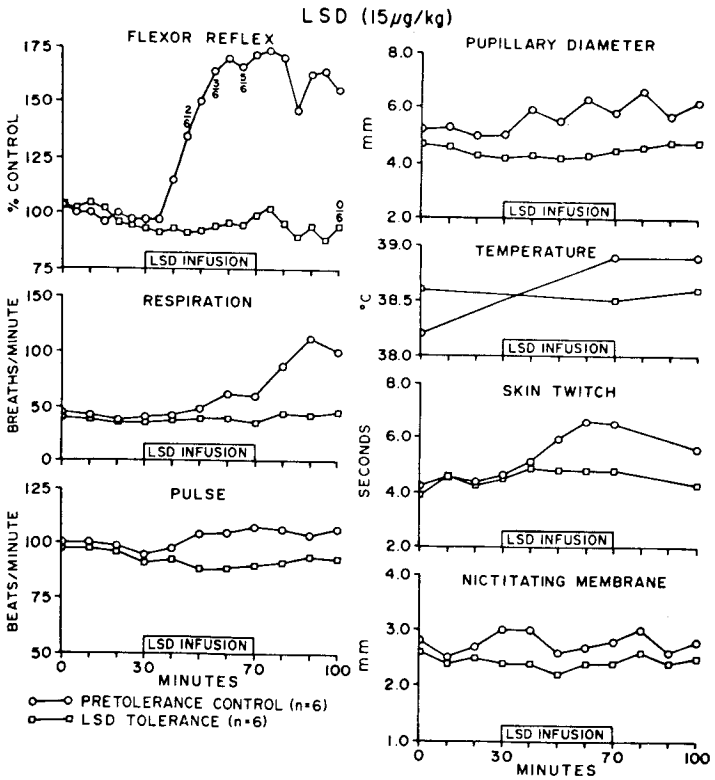

Fig. 3. Demonstration of direct tolerance to LSD. The LSD-tolerance studies were conducted in dogs receiving 30 μg/kg per day of LSD. The proportion of the dogs which developed the stepping reflex at a particular time is shown by the fractions for each treatment condition.

the significant physiologic (Fig. 3 and Table 2) and behavioral ($P < 0.01$, Fig. 5) measures except the skin twitch. LSD-tolerant dogs were cross-tolerant only to the facilitation of the flexor reflex and prolongation of the skin twitch latency produced by MMDA (Fig. 4 and Table 2). In addition, there was no cross-tolerance to the behavioral effects of MMDA in dogs tolerant to LSD ($P < 0.1$, Fig. 5). As can be seen in Fig. 5 and Table 2, saline did not produce any physiologic or behavioral changes in the pre-tolerant or LSD-tolerant dog.

Appetite suppression

Using a 6-point bioassay, *d*-amphetamine and MMDA were shown to suppress food intake in a dose-related manner (Fig. 6). The criteria for a valid bioassay were fulfilled, and MMDA was shown to be 16.1 times less potent than *d*-amphetamine as an appetite suppressant in the dog. At low doses, LSD enhanced food intake but had no effect on the appetite in dose levels of 5.0-20 μg/kg.

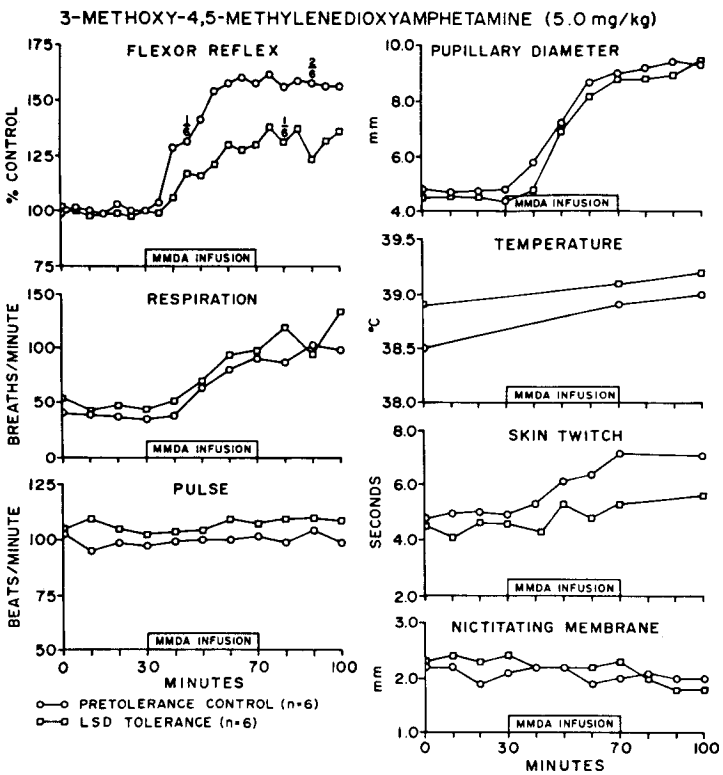

Fig. 4. Demonstration of cross-tolerance to 3-methoxy-4,5-methylenedioxyamphetamine (MMDA) in LSD-tolerant dogs receiving 30 μg/kg per day of LSD. The proportion of the dogs which developed the stepping reflex at a particular time is shown by the fractions for each treatment condition.

Discussion

MMDA produced some pharmacologic effects similar to both LSD and amphetamine. It resembled LSD in that its marked facilitatory effect on the flexor reflex was antagonized by cyproheptadine but not phenoxybenzamine, it produced tracking and staring, and cross-tolerance developed to its effects on the flexor and skin twitch reflexes. MMDA resembled amphetamine in that it produced a marked degree of mydriasis, usually failed to elicit stepping, and suppressed appetite, and phenoxybenzamine but not cyproheptadine antagonized its effects on pupils, the skin twitch reflex, and body temperature [10]. No cross-tolerance was seen to its effects on pupils, respiration, temperature, or behavior. To allow a comparison of the relative contribution of the LSD and amphetamine-like properties of MMDA, a ratio of the ED_{50} for appetite suppression to the equieffective dose with respect to LSD necessary for facilitation of the flexor reflex was calculated for LSD, MMDA, and amphetamine. The ratios were 7.0 for LSD, 0.2 for MMDA, and 0.002 for amphetamine, indicating the intermediary status of MMDA.

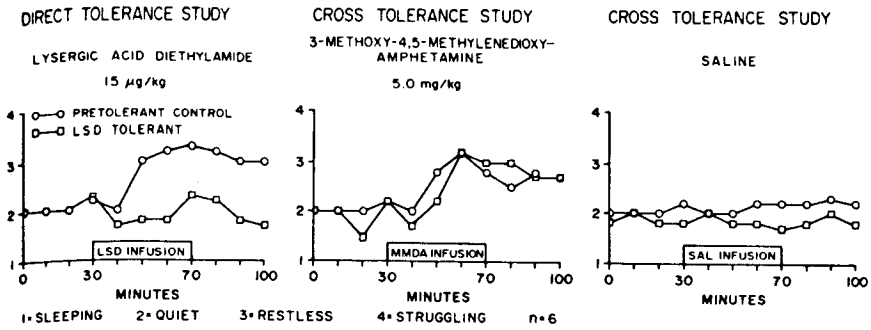

Fig. 5. Behavioral changes produced by LSD and MMDA in the pre-tolerant and LSD-tolerant dog.

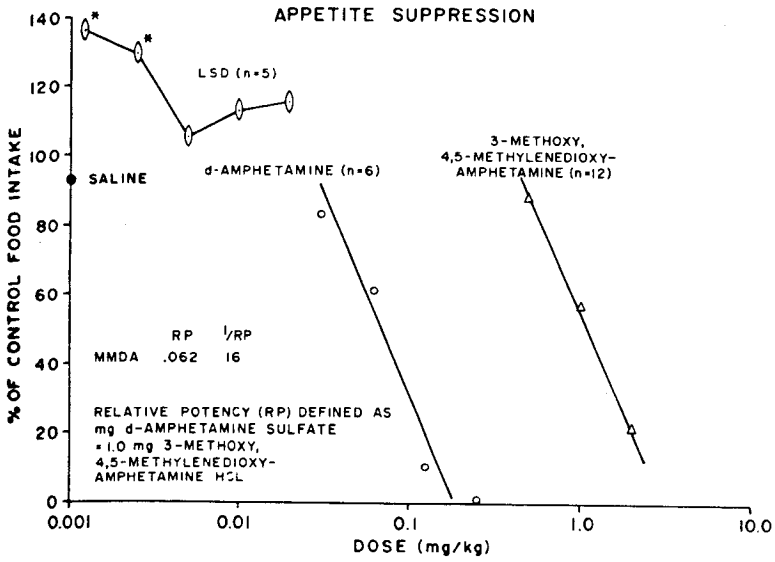

Fig. 6. Appetite suppression studies demonstrating the anorexigenic effect of LSD, amphetamine and 3-methoxy-4,5-methylenedioxyamphetamine in the intact dog.

The facts that neither phenoxybenzamine nor cyproheptadine completely antagonized the spinal cord reflex effects of MMDA, nor its effect on the nictitating membrane, and that there was no cross-tolerance to its apparent LSD-like behavioral effects in the LSD-tolerant dog suggest that MMDA may have yet other types of action. Possibly some of the pharmacological effects of MMDA may involve dopaminergic systems since chlorpromazine antagonized the majority of its effects; however, other mechanisms, possibly phenethylaminergic [11], may also be involved. Thus, we feel that these data probably suggest that MMDA has a more complicated mode of action than does either LSD or amphetamine.

There is a large body of evidence indicating that the anorexic effects of amphetamine are mediated by catecholaminergic mechanisms [12 - 19].

Since MMDA contains the amphetamine nucleus within its structure and because its log dose–response curve parallels that of amphetamine in the appetite suppression studies, a similar mechanism of action may be tentatively presumed.

The effects of LSD on appetite in the dog appear to be more complex [20]. In the present study, food intake was increased by small doses (1.25 - 2.5 μg/kg) of LSD, whereas doses up to 20 μg/kg had no effect. Subsequent unpublished studies have shown that large doses (160 μg/kg) do suppress appetite and the LSD regression line was not parallel to that of amphetamine. Since serotonin antagonists fail to antagonize the psychotomimetic action of LSD [21] and cyproheptadine, a specific tryptamine blocker, antagonizes the facilitatory effects on the flexor reflex caused by LSD or tryptamine but not by 5-hydroxytryptophan in both chronic spinal dogs [7] and rats [22], it has been suggested that LSD acts as a tryptaminergic agonist [7, 23] and that this mode of action is responsible for its hallucinogenic effects. It has also been postulated that LSD stimulates serotonin (5-HT) receptors [24 - 26] and that LSD and 5-HT have similar central nervous system actions [25, 27].

Possibly the appetite suppressant effects of LSD involve a serotonergic or tryptaminergic mechanism. In support of a serotonergic mechanism are the following: the intraventricular administration of *p*-chlorophenylalanine decreases forebrain 5-HT levels and causes hyperphagia and obesity [28]. Additionally, fenfluramine, which increases serotonin activity, is an anorexic substance and its effect is antagonized by the serotonin blocker methergoline, though not by methysergide [18]. However, a tryptaminergic anorexic mechanism cannot be rejected since cyproheptadine inhibits the anorexic effect of fenfluramine in rats.

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