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Phencyclidine-Like Behavioral Effects of 2-Methyl-3,3-diphenyl-3-propanolamine (2-MDP)

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TANG, A. H., A. A. CANGELOSI, R. A. CODE AND S. R. FRANKLIN. *Phencyclidine-like behavioral effects of 2-methyl-3,3-diphenyl-3-propanolamine (2-MDP).* PHARMACOL BIOCHEM BEHAV 20(2) 209–213, 1984.—2-Methyl-3,3-diphenyl-3-propanolamine (2-MDP) produced effects in animals similar to those produced by the dissociative anesthetics such as phencyclidine (PCP). Specifically, it shared the discriminative stimulus properties of PCP in rats trained to discriminate PCP (1 mg/kg) from saline; at higher doses, it disrupted brightness discrimination and stimulated locomotor activities in rats trained to avoid shocks in an automated Y-maze; and it produced surgical anesthesia when injected IV to rhesus monkeys. These pharmacological activities were observed only with the levo-isomer of 2-MDP. The dextro-isomer was either inactive or produced opposite effects, depending on the tests. Among several related diphenylpropylamines, 2-MDP represents the optimal structure for potency of PCP-like effects since changes in the amino, 2-methyl and 3-hydroxy groups reduced the potencies of the PCP-like discriminative properties.

Phencyclidine Behavioral effects Rhesus monkeys Discriminative stimulus Brightness discrimination Dissociative anesthetics

THE dissociative anesthetics, represented by phencyclidine (PCP), have a well-defined spectrum of pharmacological activities in the central nervous system [4,7]. In rats and mice, a moderate dose of PCP produced locomotor stimulation, ataxia and stereotypic behaviors [16]. Higher doses produced severe tremors and a cataleptic state [5]. In other species (e.g., subhuman primates) PCP produced a unique cataleptic anesthesia with profound analgesia [6] which is the basis of its veterinary use. In addition to PCP and ketamine, which are chemically related, two dioxolan derivatives, dexoxadrol and etoxadrol, have been clinically evaluated as dissociative anesthetics and analgesics [11, 20, 21]. However, each of these drugs was found to produce significant psychological and behavioral side effects which limited their usefulness in humans.

Reports of acute psychosis-like conditions produced by high doses of PCP have led some investigators to compare it to the psychotomimetic opiates. Zukin and Zukin [23] found that N-allylnormetazocine (SKF-10047) displaced (^{3}H)-PCP from specific binding sites in rat brain membrane preparations. Using drug discrimination procedures in rats, Teal and Holtzman [18] showed that rats trained to discriminate cyclazocine from saline generalized completely to PCP and ketamine. Subsequent studies with *in vitro* receptor binding [8,22] and drug discrimination [2,3] further demonstrated stereospecificities in the PCP-like properties. Based on the above test methodologies, members of three chemical classes have been shown to have PCP-like effects: arylcyclohexylamines (e.g., PCP), dioxolans (dexoxadrol and etoxadrol) and benzomorphans (cyclazocine and SKF-10047).

A series of diphenylpropanolamines were synthesized by Moffet *et al.* [12] for CNS activities. Although these compounds are structurally related to some anticholinergics and histamine (H_1) antagonists, it was shown that the introduction of a methyl group in the 2-position (e.g., 2-MDP) greatly reduced the anticholinergic effects while retaining anticonvulsant and other CNS activities [10]. Neuropharmacological studies of 2-MDP in animals have suggested some similarities to PCP (unpublished observations) which prompted us to further compare this compound to PCP in more specific behavioral tests. We chose the PCP discrimination procedure which has been shown to be specific for this class of drugs at moderate doses [14]. At a higher dose, PCP and other dissociative anesthetics disrupted simultaneous brightness discrimination in rats trained to avoid shocks in an automated Y-maze [17]. This procedure was used to demonstrate the behavioral disruptive and locomotor stimulant effects in rats. In addition, the two optical isomers of 2-MDP were evaluated as injectable anesthetics in rhesus monkeys.

METHOD

Discriminative Stimulus Properties of PCP

Fifteen male Sprague-Dawley rats were trained to discriminate the effects of PCP (1 mg/kg,SC) from saline injections in a two-lever, food-reinforcement procedure. Four BRS/LVE rat operant chambers were employed with two levers placed on either side of a food dispenser. Rats were trained daily on an FR-10 schedule of lever depression for food reinforcement (45 mg Noyes pellets). Treatments alter-

nated between PCP and saline on a semi-random basis and occurred 30 min prior to session start. Half the group was reinforced for depressing the right-hand lever on PCP pretreatment days, and half the left-hand lever. On saline days the depression of the opposite lever was reinforced. On either day, responding on the incorrect lever had no programmed consequences. The lever assignment remained consistent for each rat throughout training and tesing.

Studies of stimulus generalization began after each rat performed such that the correct lever was the first to receive 10 responses in each of five consecutive PCP and saline training sessions. Stimulus generalization test sessions were separated by at least one PCP and one saline training session. Additional training sessions were carried out for individual rats so that test sessions were always preceded immediately by at least one saline and PCP session with correct discriminations.

Test drugs were injected SC 30 min prior to testing and responses on either lever were reinforced (FR-10). The percentage of selection of the "PCP lever" over the entire test session was used to evaluate the degree of stimulus generalization. Drug effects on response rates were also computed using the combined responses on both levers over the entire session. Each training or testing session was terminated when 75 reinforcements were produced, or after the elapse of 30 minutes, whichever occurred first.

Brightness Discrimination in a Shock Avoidance Task

The shock avoidance procedure in an automated Y-maze was originally described by Barrett *et al.* [1]. A detailed description of the procedure used in this laboratory has been reported [17]. The apparatus was a symmetrical Y-shaped box having a dimension for each arm of 21×12×12 cm connected by a triangular area of 12 cm on each side. A shock generator delivered scrambled DC current through steel bars of the chamber floor. Three jewel lights behind the transparent walls at the end of each arm could be selectively illuminated as the discriminated stimuli. Each arm was equipped with a photocell detector midway from the end to register movements of the rat. Four such Y-mazes were housed in individual sound-attenuated enclosures with a house light and masking noise. Each experimental session consisted of 25 discrete trials, separated by inter-trial-intervals (ITI's) of 40 sec. The sessions were signalled by the illumination of the overhead houselight. During ITI's, none of the lights at the end of the arms were illuminated and movements of the rat from one arm to another had no consequence. A trial began with the illumination of two of the three arms, including the arm currently occupied by the rat. The distribution of left or right arm illuminations, with respect to the occupied arm, was randomly selected. Movement of the rat into the unlighted arm immediately extinguished all arm illuminations and started the next ITI. Movements into a lighted arm had no programmed consequence. Entries into either a lighted (incorrect) or darkened (correct) arm during the first five seconds of a trial were recorded as *avoidance attempts*. In the absence of a correct entry (into the dark arm) within the first 5 seconds of a trial, shock (0.5 mA) was delivered through the grid floor and remained on until a correct entry into the dark arm was made, which immediately terminated the trial. Entry into a lighted arm during shock also had no programmed consequence. Entries into either a lighted or darkened arm during shock were recorded as *escape attempts*. Shock was automatically terminated when no correct entry was made in 10 sec (15 sec after the beginning of a trial).

Performance of the avoidance-escape task in the Y-maze was expressed by the following values: (a) % avoidance attempts (% of trials in the session where there was at least one arm-entry into either the lighted or darkened arm during the first 5 seconds of a trial before the onset of shock), (b) % correct discrimination (% of trials in the sessions where the initial arm-entry, either from avoidance or escape attempts, was a choice of the dark arm); subsequent movements in a trial were not used to evaluate discrimination, and (c) number of non-contingent arm-entries during ITI's.

A group of more than 60 male rats of the Fischer 344 strain were trained in the Y-maze to reach a criterion of 85% correct in brightness discrimination. They were then given one testing and one re-training session per week with at least 2 days between sessions. In test sessions, rats were assigned randomly to treatment groups of 7 or 8 rats each, with one group receiving saline. All drugs were administered SC 30 minutes prior to the sessions. For statistical evaluations, each drug-treatment group was compared to the parallel saline group, using a two-tailed Dunnett's *t*-test for multiple comparisons.

Anesthesia in Rhesus Monkeys

Six adult rhesus monkeys *(Macaca Mulatta)* of either sex were used. Half of the monkeys had a previous history of behavioral and drug studies, but were drug-free for more than 3 months at the time of this study. Drug solution was injected into the small saphenous vein. Gross behaviors and degree of anesthesia were evaluated by two experimenters, one of which has extensive experience using phencyclidine for routine handling of subhuman primates in the colony. Observations were made first with the animals restrained in chairs and then after they were returned to the home cage.

Drugs

Stereoisomers of 2-methyl-3,3-diphenyl-3-propanolamine (2-MDP) and related analogs in Table 1 were synthesized by Dr. R. B. Moffett of The Upjohn Company, Kalamazoo, MI. All the compounds were hydrochloride salts. Dexoxadrol HCl, levoxadrol HCl and etoxadrol HCl were also synthesized in the laboratories of The Upjohn Company. (±)N-allylnormetazocine HCl was kindly supplied by Dr. R. Willette of the National Institute on Drug Abuse. (±)Cyclazocine was supplied by Sterling-Winthrop Research Institute. Phencyclidine HCl (Sernylan, Bio-Ceutic Lab), ketamine HCl (Ketalar, Parke-Davis Lab) and trihexyphenidyl HCl (Artane, Lederle Lab) were obtained from commercial sources. All durgs were dissolved in 0.9% saline for SC injection with the exception of (±)cyclazocine which was dissolved in distilled water with a small amount of citric acid. Levoxadrol was suspended in 0.25% methylcellulose and injected IP. All doses were expressed as the salts.

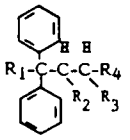
RESULTS

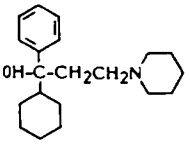
PCP-Like Discriminative Stimulus Properties

Figure 1 shows that (-)2-MDP and dexoxadrol produced dose-related increases in the percentage of PCP-appropriate lever-choice in stimulus generalization tests. Both compounds produced complete substitution (100%) at the highest dose. The (+) isomer of 2-MDP and levoxadrol were much

TABLE 1

3,3DIPHENYLPROPYLAMINES STUDIED FOR PCP-LIKE DISCRIMINATIVE STIMULUS PROPERTIES IN RATS



Compound[1]	R_1	R_2	CR^3R^4
2-MDP	OH	CH_3	$CHNH_2$
I	OH	CH_3	$CHN(CH_3)_2$
II	OH	CH_3	CH-N
III	H	CH_3	CH-N
IV	OH	H	CCH_3-N
V	OH	H	CH-N
Trihexyphenidyl			

[1]Moffett *et al. J Med Chem* **14**: 1088, 1971.

less effective in producing PCP-like discriminative effects, even at doses which reduced the response rate to a very low level. For the compounds in Fig. 1, all the animals completed the sessions, except after 10 mg/kg of (+)2-MDP with which two of the six rats emitted no response at all.

Other compounds which also produced high percentages of PCP-appropriate lever choice include etoxadrol, (±)N-allylnormetazocine (SKF-10047) and ketamine (Table 2). Replacement of the primary amino group by pyrrolidine (Compound II) in 2-MDP retained most of the PCP-like discriminative effects. Further change of the hydroxy group to hydrogen or change from 2-methyl to hydrogen greatly reduced the activities (Compounds III, IV and V). Substitution of the primary amine in 2-MDP by dimethylamino group (I) also greatly reduced the PCP-like properties. The structurally related anticholinergic drug, trihexyphenidyl, was included for comparison and exhibited no substitution. Cyclazocine produced only a partial generalization to the PCP discriminative stimulus at doses which greatly reduced the response rate. However, a combination of 3 mg/kg of naloxone and 1 mg/kg of (±)cyclazocine produced greater than 80% PCP-appropriate lever choice with no reduction in response rate (data not shown).

Simultaneous Brightness Discrimination in a Shock-Avoidance Task

In this test procedure, in which rats were trained to enter a dark arm in the symmetrical Y-maze in order to avoid or escape foot shock, a relatively high dose of PCP (3 mg/kg) reduced the percentage of correct choices while also increasing the number of movements between trials (Table 3). A

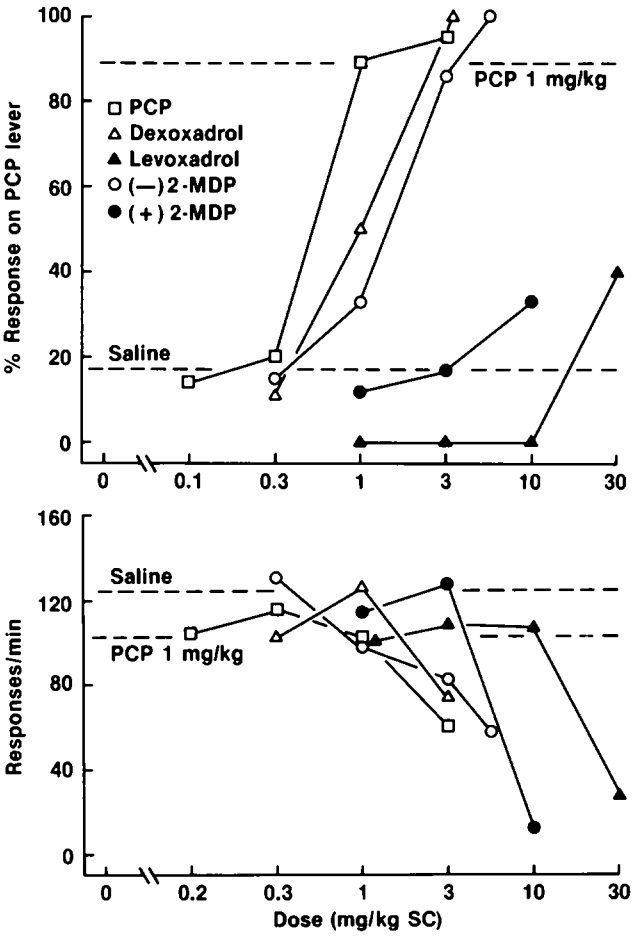


FIG. 1. Stimulus generalization for the discriminative effects in rats trained to discriminate 1 mg/kg of PCP from saline injections. Each data point represents the average from 6–8 rats. The upper panel shows the percentage of lever choice in test sessions. The lower panel shows response rates from either lever over the test sessions.

similar effect was produced by (-)2-MDP at 30 mg/kg. In contrast, the (+) isomer of 2-MDP had an opposite effect in that avoidance attempts were reduced significantly along with reduced ITI movements. Simultaneous brightness discrimination was unchanged. Combinations of 10 or 30 mg/kg of (+)2-MDP and PCP (3 mg/kg) or (−)2-MDP (30 mg/kg) failed to restore the disruption of brightness discrimination, although the stimulation of ITI movements was reduced (data not shown).

Anesthesia in Rhesus Monkeys

(−)2-MDP was injected IV to four monkeys. In the first two monkeys, the drug was injected in incremental doses while restrained in a chair. After a 1 mg/kg dose, there was calmness, ptosis, salivation and reduced spontaneous movements. Additional doses up to a total of 5 mg/kg produced a cataleptic state with weak responses to manipulation. Most of the overt effects disappeared six hours after the injections.

To the other two monkeys, (−)2-MDP was injected IV at 10 mg/kg within 30 seconds. There was an immediate loss of consciousness, with no response to strong pressure or pin

TABLE 2

STIMULUS GENERALIZATION FOR THE DISCRIMINATIVE STIMULUS EFFECTS OF PCP IN RATS

Compounds	Dose Range Tested (mg/kg)	Maximum Generalization: Dose (mg/kg)	% PCP Lever Choice*	Response Rate (min −1)‡	% Rats Selecting PCP Lever/ No. Rats Tested†
Etoxadrol HCl	0.3 - 3.0	1	100.0	96.6	7/7
(±) N-allylnor-metazocine	1.0 -10.0	10	98.5	22.2	6/6
Ketamine HCl	1.0 -10.0	10	90.1	45.7	8/9
Compound II	3.0 -30.0	30	78.8	56.3	5/6
(±) 2-MDP	1.0 -30.0				
Compound V	3.0 -30.0	10	50.8	74.5	3/6
(±) Cyclazocine	0.03- 0.3	0.3	35.8	38.7	2/6
Compound I	3.0 -30.0	30	34.2	78.7	1/6
Trihexyphenidyl HCl	0.3 - 3.0	3	32.8	35.5	2/6
Compound IV	10.0 -30.0	30	29.2	68.5	1/6
Compound III	10.0 -30.0	30	16.7	83.7	1/6

*Group average at the optimal dose for maximum generalization.

†Individual rats emitting greater than 80% of the responses over the session on the PCP lever are represented as positive responders.

‡Response rate at saline sessions = 109.7 ± 7.5/minute.

TABLE 3

EFFECTS OF PCP AND 2-MDP ON THE PERFORMANCE ON SHOCK AVOIDANCE BY RATS IN THE AUTOMATED Y-MAZE

Treatment	Dose mg/kg SC	N	% Avoidance Attempts	% Correct Discrimination	Inter-trial Movements
Saline	—	8	73 ± 6	89 ± 3	62 ± 12
PCP	1	8	77 ± 5	91 ± 2	62 ± 7
PCP	3	8	90 ± 5*	68 ± 4†	270 ± 66†
Saline	—	8	95 ± 1	95 ± 2	85 ± 14
(−)2-MDP	10	7	100	87 ± 6	89 ± 19
(−)2-MDP	30	8	76 ± 10	59 ± 3†	174 ± 25†
Saline	—	8	96 ± 1	97 ± 1	66 ± 12
(+)2-MDP	10	7	98 ± 1	96 ± 2	64 ± 1
(+)2-MDP	30	8	55 ± 12†	95 ± 3	28 ± 6*

†$p<0.01$; *$p<0.05$ Compared to the parallel saline-treated group.

prick to the skin. Skeletal muscle tone was maintained or even strengthened, giving the cataleptic characteristics similar to anesthesia with phencyclidine. The fourth monkey had an infectious abscess at the temple area measuring one square inch. An incision was made to remove the infected material with irrigation and closure of the incision with sutures. The entire procedure lasted 20 minutes and was carried out under 10 mg/kg injection of (−)2-MDP as the sole anesthetic agent with complete satisfaction.

The (+) isomer of 2-MDP was injected IV also to four monkeys, two of which received (−)2-MDP previously. The first two monkeys were given (+)2-MDP at 10 mg/kg within 30 seconds. There were no observable behavioral effects other than salivation and tremors. To the other two monkeys (+)2-MDP at 15 mg/kg was injected. One monkey developed a clonic convulsive seizure about 1 minute after the injection and lasted 15 minutes. Thereafter the animal was grossly ataxic for several hours. The second monkey receiving 15 mg/kg of (+)2-MDP exhibited only profuse salivation and severe body tremors. The overt behavioral effects at these doses suggested no anesthetic or analgesic potential for (+)2-MDP.

DISCUSSION

This investigation demonstrated that 2-methyl-3,3-diphenyl-3-propanolamine (2-MDP) has PCP-like properties. In the rat, it shared the discriminative stimulus effects of

PCP at lower doses, and at higher doses disrupted brightness discrimination and increased locomotor activities. In the monkey, 2-MDP produced effective anesthesia after IV injection. The above activities resided entirely in the levo-isomer of 2-MDP, and several structural analogs had lesser PCP-like activities.

The drug discrimination procedure provided one of the most specific tests for the behavioral effects of PCP [3, 9, 13, 14]. The results in general agree very well with studies of (^{3}H) PCP binding in rat brain preparations [8,22], including similar stereospecificities. It is interesting to note that, in contrast to the dioxadrol stereoisomers, PCP-like effects were found predominantly in the levo-isomer of 2-MDP. On the other hand, no marked pharmacological difference was found between the stereoisomers of ketamine [19]. (+)N-allylnormetazocine was only slightly more potent than its (−) isomer for PCP-like discriminative effects, but (−) cyclazocine was about 10 times more potent than (+) cyclazocine in rats trained to discriminate PCP from saline [15]. Not surprisingly there is no consistency between optical rotation and the PCP-like discriminative effects. The absolute configuration of each compound must be known before structures and biological activity can be correlated with these compounds. The demonstration that modifications of several functional groups in 2-MDP reduced the PCP-like properties nevertheless sheds some light on the structural activity relationship.

The dissociative anesthetics as well as cyclazocine and N-allylnormetazocine disrupted a simultaneous brightness discrimination in rats when given at high doses which also increased locomotor activities [17]. These properties could be related to the psychic disturbances produced by high doses of these compounds in man. As in the PCP-discrimination paradigm, only the (−) isomer of 2-MDP exhibited the motor stimulation and disruption of brightness discrimination, while the (+) isomer appeared to have an opposite effect in reducing avoidance responses. This isomer was found neither to antagonize the behavioral disruptive effects of (−)2-MDP nor to produce dissociative anesthesia in the monkeys.

In conclusion, (−)2-MDP has characteristics of a dissociative anesthestic like PCP in monkeys. Behavioral studies in rats suggest that if used as an anesthetic in man it would probably produce a similar set of psychotomimetic side-effects. The relatively restricted structural features conferring PCP-like discriminative properties may add to the understanding of the site or receptors activated by this class of drugs.

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