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Induction of Phencyclidine-Like Behavior in Rats by Dextrorphan But Not Dextromethorphan

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SZÉKELY, J. I., L. G. SHARPE AND J. H. JAFFE. *Induction of phencyclidine-like behavior in rats by dextrorphan but not dextromethorphan*. PHARMACOL BIOCHEM BEHAV **40**(2) 381–386, 1991.—The behavioral effects of dextromethorphan (DM), dextrorphan (DO) and phencyclidine (PCP) were compared in rats. DO (15–120 mg/kg) was similar to PCP (1.25–20 mg/kg) in inducing dose-dependent locomotor hyperactivity, stereotypy and ataxia. DM (15–120 mg/kg) induced moderate hyperactivity only at the higher doses about 45 min after treatment. DM and DO modified the locomotor facilitation induced by 10 mg/kg PCP in opposite directions. Pretreatment with DO facilitated, whereas DM dose-dependently inhibited PCP-elicited hyperactivity. Although the metabolism of DM in rats is unknown, the recently reported abuse of DM in humans may occur by its conversion to DO in the organism, i.e., to a metabolite which produces PCP-like effects.

Dextromethorphan Dextrorphan Drug abuse Phencyclidine Locomotor activity Stereotypy

SPORADIC abuse of dextromethorphan (DM) has been reported over the past 20 years (27), recently mostly among adolescents (Keenan, G. R., personal communication). The pharmacological basis for this abuse has never been convincingly explained. DM is the dextrorotary morphinan analog of codeine with antitussive but no other opiate effects (13). It does not induce analgesia in animals (2) and it does not substitute for morphine in opiate addicts (11). Being a (+)-isomer, DM is not expected to bind to opiate receptors. Earlier studies emphasized primarily the dysphoric and psychotomimetic effects when high doses of DM were administered (14,21). Nevertheless, several reports indicate that an overdose of DM in humans might induce euphoria and eventually slight psychic dependence (27).

In humans and dogs DM is rapidly converted to dextrorphan (DO) by demethylation (1,26), which is also an antitussive (2). Therefore, DO is believed to be an active metabolite of DM (1,27). Indeed, DM and DO share several other pharmacological properties as well; 1) both attenuate the neurotoxic effect of glutamate (3,7); 2) they inhibit the NMDA-induced convulsions in vitro (32) and in vivo (5,20); 3) both bind to the phencyclidine (PCP)-receptors (23, 29, 31); and 4) both displace certain ligands of the putative sigma receptors (12, 16, 19). However, in a few studies, DM and DO showed different effects. DM binds to specific binding sites in the brain where DO is a very weak ligand for these receptors (4). In drug discrimination assays in monkeys both compounds generalize to PCP (10), but in rats only DO substitutes for PCP (9). DM generalizes to DO in pigeons trained to discriminate the latter from saline (8).

It is well established that in appropriate doses, PCP induces locomotor hyperactivity and stereotypy in rats (18, 22, 30). However, DM and DO have not been examined in this aspect yet. To clarify whether DM or DO exert PCP-like actions in vivo, we compared the PCP-induced changes in spontaneous activity with those elicited by DM and DO (Experiment 1). Thereafter, we compared the eventual modulation by DM and DO of PCP-induced behavioral effects (Experiment 2).

METHOD

Subjects

Male rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing 350–400 g at the beginning of the experiments were used. The animals were housed four per cage on 12-h light/dark schedule (lights on at 6 a.m.) in a temperature-controlled (23 ± 1°C) colony room. Purina rat chow and water were continuously available in the home cages. Sixteen animals were used in Experiment 1 and another group of 20 in Experiment 2.

Apparatus

Four activity chambers (Omnitech Electronics, Columbus, OH) were used to record the locomotor activity and to observe the animals' behavior. The activity chambers (42 × 42 × 25 cm) with clear plastic sides and plastic floors were located in a separate dimly lit observation room. White noise was used to mask any extraneous noise. The temperature was kept constant (as in the colony room). The locomotor activity (number of interruptions of the infrared lightbeams) was recorded automatically every 15 min.

Design and Procedure

Testing took place once a week always between 4 p.m. and 8 p.m. On each experimental day the animals were allowed to

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acclimate to the testing room for 30 min before drug treatment. In each session the rats received a pretreatment (SC) and 15 min later a treatment (IP) injection. Immediately thereafter they were placed singly into the activity chambers and continuously observed for 1 h. In addition to automatic measurement of the total locomotor activity, the stereotyped behavior was quantitated by checking the presence or absence of 8 behavioral signs characteristic of PCP-induced excitation of the serotonergic system. These behaviors were forepaw treading, head weaving, hindleg abduction, back-pedalling, tremor, circling, gagging and Straub-tail (18). Thus, for each 15-min period the maximum score was 8. Ataxia was also observed and rated in intensity from 0 to 5 using a rating scale developed specifically for characterizing the PCP-induced behavior (30). Scores of 1 and 2 = slight and moderate ataxia, respectively; score 3 = partial loss of righting reflex, with stomach touching the floor; scores 4 and 5 = lying on their belly and or side, respectively and only pawing the air. To minimize variability the observations were made by the same experimenter (J.I.S.) on every observation day. For statistical analysis the ataxia and stereotypy scores recorded during the four subsequent 15-min periods were added. Thus the maximum scores for stereotypy and ataxia were 32 and 20, respectively.

Since 3 drugs were examined at 4–5 dose levels by themselves or in combination (see below) there were 13 different drug conditions in Experiment 1 and 8 drug combinations in Experiment 2. To conduct these experiments using each rat only once would have required hundreds of animals. Therefore, the experiment was designed so that each rat was tested once a week until it had experienced each of the doses of each drug. This design reduced the error arising from interindividual variability. Every third or fourth week each rat was tested after receiving vehicle only. Thus the control condition was regularly repeated. To acclimate the animals to the procedure both Experiment 1 and 2 were begun by sessions in which the rats only received vehicles 15 and 0 min prior to placement in the activity cages. (The data collected in these sessions were not processed.)

Experiment 1. A counter-balanced block-design was used. The doses of DM and DO were 15, 30, 60 and 120 mg/kg and those of PCP were 1.25, 2.5, 5, 10 and 20 mg/kg. Half of the animals received PCP first then DM and DO, the others were treated with the same substances in opposite order. In one subgroup, the doses were increased in a stepwise manner, in the other one the same doses were given in decreasing order. DM and DO were administered 15 min prior to the measurement, whereas PCP was injected just before putting the animals into the activity boxes. In view of the subsequent drug combination experiments (Experiment 2) the vehicle was given at the time of the other injection. Every third or fourth session served as control in which only the two vehicle injections were administered.

Experiment 2. In this series of experiments the modulation of PCP-induced effects by DM and DO was examined in a separate group of rats. As in Experiment 1 each animal received successively all the 8 possible drug combinations having one session every week. Since in the first Experiment 10 mg/kg PCP elicited the highest degree of locomotor activation, this dose was combined with 15, 30, 60 and 120 mg/kg of DM and DO, respectively. Drug treatments were counterbalanced in this series as above. In the interposed control sessions (held every third or fourth week as in Experiment 1) animals received vehicle + PCP (10 mg/kg) treatment, so in Experiment 2 control values indicate the effect of PCP by itself.

Drugs

Dextromethorphan·HBr (DM) and dextrorphan tartrate (DO) (Hoffmann-La Roche Inc., Nutley, NJ) were dissolved in distilled water and injected SC. Because of poor water solubility, these were dissolved in 15 mg/ml and injected in volumes ranging between 1 to 8 ml/kg b.wt. At the highest dose (120 mg/kg) the solution was injected into two different sites. In control sessions corresponding volume of distilled water was injected. Phencyclidine·HCl (NIDA) was dissolved in saline and injected IP in a constant volume of 1.0 ml/kg.

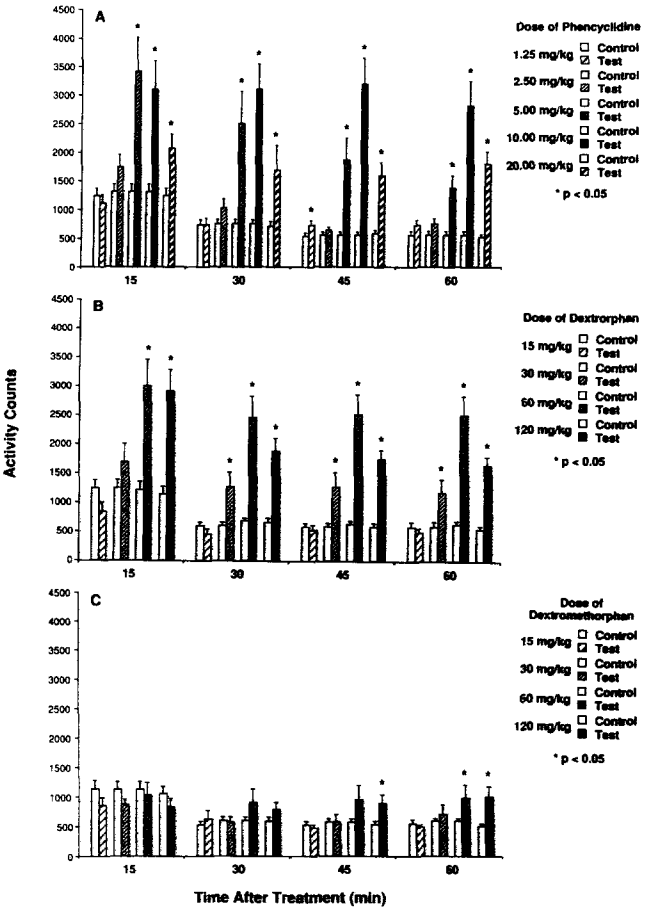

FIG. 1. Effect of phencyclidine (A), dextrorphan (B) and dextromethorphan (DM) (C) on the spontaneous locomotor activity. Activity counts in the four successive 15-min observation periods. The same animals (n = 16) were successively examined with various doses of the three drugs. DM and DO were injected 15 min prior to, whereas PCP immediately before measurement. In the intervening control sessions only vehicle injections were given at the appropriate times. *$p<0.05$: upon comparing treatment and control sessions by planned comparisons where MANOVA showed significant overall effect.

Data Analysis

Data were subjected to two- and three-way analysis of variance for repeated measures (MANOVA) (within-subject design) whereupon treatment, dose, and in the case of locomotor activity, the time (elapsed since treatment) were the main effects. MANOVA was followed by planned comparisons which used the F statistics to compare pairs of means to estimate the duration of drug effects or range of effective doses if MANOVA revealed any time × treatment or dose × treatment interaction. For computations, the software CSS™ (Complete Statistical Sys-

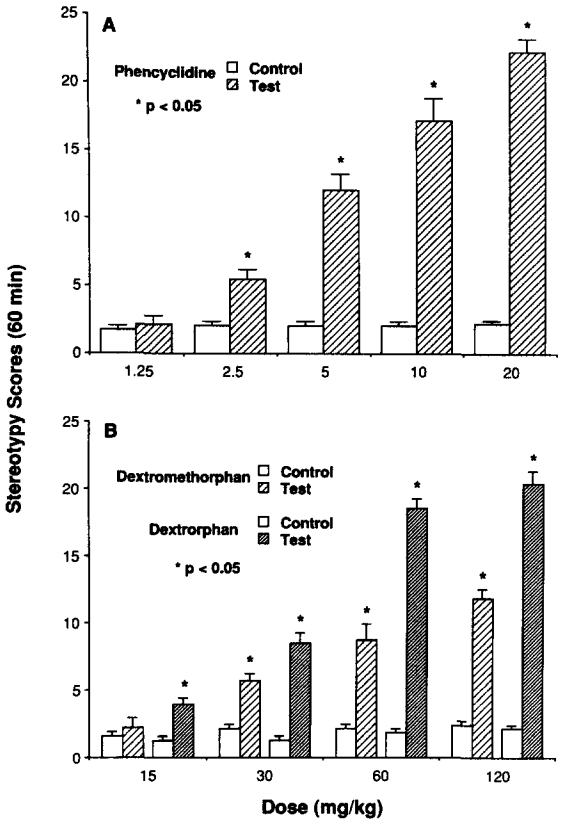

Fig. 2. Stereotypy induced by phencyclidine (A), dextrorphan and dextromethorphan (B). Total of stereotypy scores recorded in the four successive 15-min observation periods. See Fig. 1 for further details.

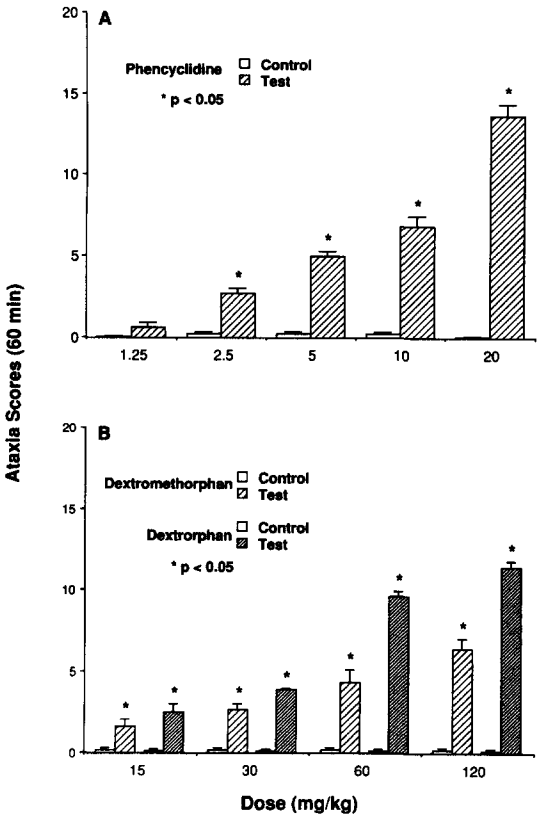

FIG. 3. Ataxia induced by phencyclidine (A), dextrorphan and dextromethorphan (B). Total of ataxia scores recorded in the four successive 15-min observation periods. See Fig. 1 for further details.

tem, StatSoft Inc., Tulsa, OK) was used. During the planned comparisons the average of the preceding and subsequent control sessions (vehicle followed by vehicle in Experiment 1 and vehicle followed by PCP in Experiment 2) were compared with those obtained upon drug sessions (DM, DO or PCP alone in Experiment 1 and DO or DM followed by PCP in Experiment 2). To examine the dose-effect curves for parallelism the parallel-line bioassay was used (6).

RESULTS

Experiment 1

Figure 1A shows that PCP induced a very strong, dose-dependent locomotor facilitation; the overall treatment, $F(1,15) = 68.76$, time, $F(3,45) = 41.87$, and dose, $F(4,60) = 8.85$, effects were significant ($p<0.001$). The dose × treatment interaction also was significant, $F(4,60) = 8.73$, $p<0.001$. Comparing the drug effects with saline by paired comparisons, the effect of PCP was statistically significant at the three higher dose levels and its most effective dose was 10 mg/kg. The locomotor activity produced by PCP was typically characterized by ambulation combined with circling, backpedalling, head weaving and other stereotypic signs listed in the Method section. With higher doses the animals' movements became more and more uncoordinated making them unable to circle, back-pedal, etc., or even to make any gross body movements.

The action of DO (Fig. 1B) was qualitatively very similar to that of PCP with significant overall treatment, $F(1,15) = 43.63$, $p<0.001$, dose, $F(3,45) = 13.31$, $p<0.001$, and time, $F(3,45) = 68.81$, $p<0.001$, effects. Examining the doses separately, 30, 60 and 120 mg/kg of DO induced statistically significant hyperactivity ($p<0.05$). Furthermore, as seen with PCP, the highest dose did not result in the most intense locomotor activation, i.e., the dose-effect curves of both PCP and DO were slightly curvilinear.

However, in the case of DM (Fig. 1C), only the overall time effect, $F(3,45) = 34.18$, $p<0.001$, time × treatment, $F(3,45) = 11.65$, $p<0.001$, and time × dose interactions, $F(9,135) = 2.51$, $p<0.01$, were significant. [The overall dose-effect showed borderline significance; $F(3,45) = 2.25$, $0.05<p<0.10$.). The higher doses of DM (60, 120 mg/kg) caused a moderate facilitation of locomotion but only in the third and fourth 15-min periods of observation, i.e., 45–75 min after pretreatment.

Comparing the drug effects to each other, there was hardly any difference between the overall effects of PCP and DO, $F(1,15) = 4.45$, $p = 0.0498$. However, the overall effect of DM significantly differed from those of PCP, $F(1,15) = 54.33$, $p<0.001$, and DO, $F(1,15) = 79.28$, $p<0.001$. In addition, the maximums of the activity counts seen after by PCP and DO were similar (2500–4000, i.e., about 3–4-fold elevation), whereas DM only caused a moderate increase (Fig. 1). For parallel-line bioassay (6) the activity counts were collapsed over time and the highest doses of PCP and DO were omitted to analyze only the linear portion of the dose-effect curves. The dose-response curves of DO and PCP were parallel with a potency ratio (PCP vs. DO)

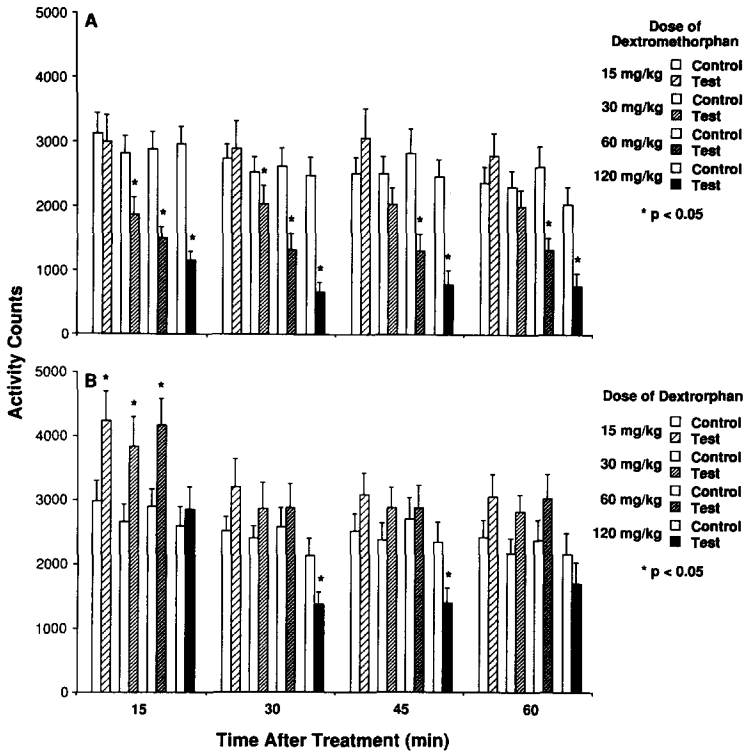

FIG. 4. Effect of dextromethorphan (DM) (A) and dextrorphan (DO) (B) on phencyclidine (PCP)-induced locomotor hyperactivity. Activity counts in the four successive 15-min observation periods. The SC injection of DM or DO was followed in 15 min by 10 mg/kg PCP IP immediately before measurements. The same animals (n = 20) were pretreated successively with the various doses of DM and DO. In the intervening control sessions only 10 mg/kg PCP was given 15 min after a vehicle injection.

of 11.26 (95% confidence interval: 6.04–22.60). Thus the potency of PCP in elicitation of locomotor hyperactivity is about an order of magnitude higher than that of DO. In contrast, dose-response curve for DM was not parallel with those of either PCP or DO.

PCP, DM and DO also induced dose-dependent stereotypy (Fig. 2A and B). $F(1,15) = 105.25$, $p<0.001$; $F(1,15) = 526.86$, $p<0.001$ and $F(1,15) = 204.88$, $p<0.001$ in regard of the overall treatment effects of DM, DO, and PCP, respectively. The corresponding dose effects are $F(3,45) = 35.60$, $p<0.001$ for DM; $F(3,45) = 129.80$, $p<0.001$ for DO and $F(4,60) = 59.70$, $p<0.001$ for PCP. At the highest dose the efficacy of DO was similar to that of PCP. However, DO proved to be more effective than DM in inducing stereotypy, $F(1,15) = 89.75$, $p<0.001$. According to paired comparisons the difference is significant at doses above 15 mg/kg ($p<0.05$). According to parallel-line bioassay the potency ratio (PCP vs. DO) was 7.46 (95% confidence interval: 6.36–8.74). As in the case with locomotor hyperactivity, there was a significant ($p<0.05$) deviation from parallelism when comparing DM with the other substances in the induction of stereotypy. (In addition as in the case of locomotion the DM-induced stereotypy appeared only toward the end of the observation period.)

Furthermore, PCP induced dose-dependent ataxia (Fig. 3A) with significant overall treatment, $F(1,15) = 821.81$, $p<0.001$, and dose effects, $F(4,60) = 79.38$, $p<0.001$. DM and DO also induced dose-dependent ataxia (Fig. 3B). The overall treatment effects were significant for DM, $F(1,15) = 51.14$, $p<0.001$, and DO, $F(1,15) = 883.55$, $p<0.001$, as well. The corresponding dose effects were, $F(3,45) = 48.78$, $p<0.001$ for DM and $F(3,45) = 148.15$, $p<0.001$ for DO. The ataxia was pretty strong at the highest levels of PCP (20 mg/kg) and DO (120 mg/kg). Namely scores 4 and 5 (i.e., total scores above 10) mean that the rats were unable to make coordinated whole-body movements (30). However, the ataxia induced by DM was considerably weaker than that elicited by DO, $F(1,15) = 35.43$, $p<0.001$. According to paired comparisons the difference is significant at doses above 15 mg/kg. According to parallel-line bioassay (6) the dose-response curves of DO and PCP were parallel and the potency ratio (PCP vs. DO) was 6.65 (95% confidence interval: 5.79–7.62). In this respect too, the dose-response curve of DM was significantly ($p<0.05$) different from those of PCP and DO.

Thus PCP and DO showed very similar pharmacological profiles of activity as opposed to DM. Only the former induced drastic (3–4-fold) increase in locomotor activity and the slope of the dose-response curve of DM was statistically different from those of DO and PCP according to all the three measures. To further examine this issue in the subsequent series of experiments (Experiment 2) the interaction of DM and DO with the PCP-induced changes was examined.

Experiment 2

In this series of experiments the animals were treated with 10 mg/kg PCP in the control sessions. As shown in Fig. 4A DM dose-dependently inhibited the PCP-induced hyperactivity. Ac-

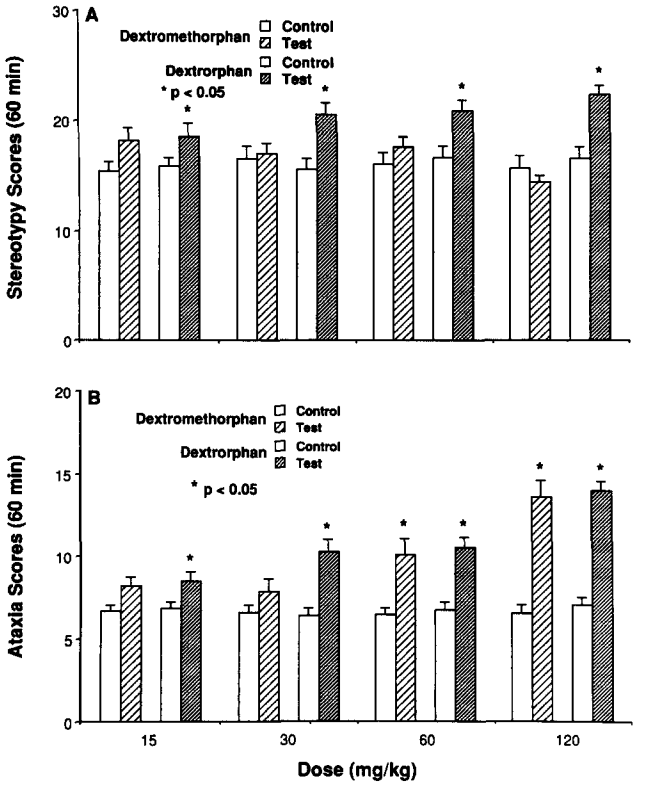

FIG. 5. Effect of dextromethorphan and dextrorphan on phencyclidine-induced stereotypy (A) and ataxia (B). Total of scores recorded in the four successive 15-min observation periods. See Fig. 4 for further details.

cording to MANOVA the overall treatment, $F(1,19)=16.12$, $p<0.01$, dose, $F(3,57)=8.46$, $p<0.001$, and time, $F(3,57)=3.94$, $p<0.05$, effects all were significant. DO, on the other hand, did not induce dose-dependent inhibition (Fig. 4B). Contrarily, in the first 15 min statistically significant facilitation was seen with all but the highest dose of DO. Although the highest dose of DO (120 mg/kg) inhibited the PCP-elicited hyperactivity, this was obviously due to motor incapacitation. In the case of DO the overall dose, $F(3,57)=8.29$, $p<0.001$, and time, $F(3,57)=27.05$, $p<0.001$, effects, in addition the dose × treatment, $F(3,57)=2.83$, $p<0.05$, and time × treatment, $F(3,57)=10.03$, $p<0.001$, interactions were significant.

With respect to PCP-induced stereotypy the two drugs again produced different effects. DM did not modify the PCP-induced stereotypy, whereas DO significantly enhanced this behavior (Fig. 5A). However, its effect was not dose-dependent. According to MANOVA the overall effect of DO was significant, $F(1,19)=37.09$, $p<0.001$, but neither the overall dose-effect nor the dose-treatment interaction was significant.

In contrast to these differences, the effects of DM and DO on PCP-induced ataxia were similar; both induced dose-dependent enhancement of ataxia (Fig. 5B). The overall treatment effects of both DM, $F(1,19)=50.42$, $p<0.001$, and DO, $F(1,19)=73.70$, $p<0.001$, were significant and there was no statistically significant difference between their overall effects. Furthermore, their overall dose-effect, $F(3,57)=15.91$, $p<0.001$, and the dose-treatment interaction, $F(3,57)=15.04$, $p<0.001$, also were significant, i.e., the aggravation by antitussives of PCP-elicited ataxia was dose dependent.

DISCUSSION

As seen in Experiment 1, DO, the main metabolite of DM in humans and dogs (1,26), induced strong locomotor facilitation, stereotypy and ataxia similarly to PCP. The dose-response curves of PCP- and DO-induced locomotor facilitation were slightly curvilinear, whereas the intensity of stereotypy and ataxia increased linearly with dose. The apparent curvilinear character of locomotor facilitation was due in all probability to the motor incapacitation seen at the highest dose-levels of PCP and DO. In contrast, DM induced relatively weak facilitation of locomotion only 45–75 min after its SC injection. The slope of its dose-response curve deviated significantly from that of DO and PCP. The long latency of this facilitating effect may be due to accumulation of its metabolite DO. The metabolism of DM is relatively rapid in humans (1, 21, 26) and dogs (1) but no data are available on the metabolism of DM in rats, but in general drugs are metabolized in rodents more rapidly than in humans.

In Experiment 2, 15–30–60 mg/kg DO enhanced all three PCP- induced behaviors, although 120 mg/kg inhibited the PCP-induced locomotor facilitation probably due to gross motor incapacitation caused by ataxia. The apparent inhibitory influence of ataxia on locomotor activity seems to occur with stereotypy as well. For example, the ataxia that occurred after combining PCP with DM or DO may have interfered with the locomotor components of stereotypy as back-pedalling and circling. Therefore, ataxia-induced suppression of some components of stereotypy could have prevented the additive effects of the PCP-DO combination on stereotypy not speaking about the "ceiling effect" (Fig. 5A).

On the other hand, DM dose-dependently inhibited the PCP-induced hyperactivity. It is unlikely that DM's antagonism of the locomotor effect of PCP is due to the ataxia and stereotypy induced by DM. Namely, DO facilitated the PCP-elicited hyperactivity (Fig. 4B) at doses which caused significantly stronger ataxia than DM (Fig. 3B).

Collectively both experiments indicate the same conclusions: DM and DO have different psychopharmacological profiles and only DO has true PCP-like properties. These conclusions agree with others in that DM binds to sites which do not bind DO (4). That is why activation of the high-affinity DM sites (4) may antagonize some of the behavioral effects of PCP-like drugs. The controversy concerning the PCP-like stimulus properties of DM and DO (8–10) can be explained by supposing that, depending on the time of testing, species examined, dose and route of administration, DM might or might not be metabolized to DO at the moment of testing.

DM in high doses, has been reported to be either dysphoric (14,21) or sufficiently euphoric to be abused (27). On the other hand, it is well known that there are great genetically determined interindividual differences in the metabolism of DM in humans (15, 17, 25, 28). It has been proposed (24) that the sporadic abuse of DM is due to its conversion to DO, which has PCP-like pharmacological character. The present experimental data lend support for this hypothesis (24). Individual metabolic capacity might be one of the factors determining the vulnerability of the subjects to abuse of DM. The differences in individual metabolic capacity to convert DM to DO might also explain the variability in the subjective responses to DM. Nevertheless, these data only provide indirect evidence since the metabolism of DM in rats has not been examined yet. On the other hand, the DM-induced dysphoria remains a puzzling issue. For exam-

ple, there is no evidence to indicate that activation of the σ-receptors induces psychotomimetic effects [see (24)]. A recent review indicates that they are caused by the κ-agonist properties of purported σ-receptor ligands (24). We think that the present experimental data might help to explain the contradictions in the related clinical findings.

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