

ORIGINAL INVESTIGATION

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Evaluation of the reinforcing properties and phencyclidine-like discriminative stimulus effects of dextromethorphan and dextrorphan in rats and rhesus monkeys

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Abstract *Rationale:* Dextromethorphan (DXM) and its metabolite, dextrorphan (DXO) have neuroprotective and anticonvulsant properties through their activity as *N*-methyl-D-aspartate (NMDA) receptor channel blockers. Based on this receptor activity, coupled with reports of DXM abuse, both were evaluated for abuse potential and phencyclidine (PCP)-like behavioral effects in two animal models. *Objectives and methods:* The discriminative stimulus properties of DXO and DXM were tested in rats (3–56 mg/kg DXM, i.p. and 2.2–40.9 mg/kg DXO, i.p.) and rhesus monkeys (0.3–10 mg/kg DXM, i.m. and 0.25–8.0 mg/kg DXO, i.m.) trained to discriminate PCP from saline using a standard two-lever drug-discrimination paradigm under a fixed-ratio (FR) schedule of food reinforcement. In a second set of experiments, i.v. self-administration of DXO (10–100 µg/kg/infusion) and DXM (10–1000 µg/kg/infusion) were tested under a FR schedule of reinforcement in monkeys trained to lever press for infusions of PCP during daily 1-h sessions. *Results:* In rats, both DXM and DXO produced a dose-dependent substitution for PCP. When tested in monkeys, DXM yielded partial (1 monkey) and full (2 monkeys) substitution for PCP, while DXO substituted fully for PCP in all four subjects tested. In the self-administration study, in five of the six subjects, at least one dose of DXM served as a positive reinforcer, maintaining infusion rates above those for saline. For DXO, at least one dose maintained infusion numbers well above mean saline infusion numbers in all subjects. *Conclusions:* Taken together, these data show that DXM has some PCP-like

effects in rats and monkeys, but that they are more reliably produced by its metabolite, DXO. Thus, high doses of DXM may have some PCP-like abuse potential in humans but this potential may be associated with, or enhanced by, metabolism of DXM to DXO.

Key words Dextromethorphan · Dextrorphan · Phencyclidine · Self-administration · Drug discrimination · Monkey · Rat

Introduction

Dextromethorphan (3-methoxy-17-methylmorphinan; DXM), a common over-the-counter (OTC) cough suppressant, is a dextrorotary morphinan, which does not bind to opioid receptors but, instead, binds with high affinity ($k_i=12\text{--}57\text{ nM}$) to a site associated with sigma-site ligands and with low affinity ($k_i=0.51\text{--}2.5\text{ }\mu\text{M}$) to the phencyclidine (PCP) channel-site of the *N*-methyl-D-aspartate (NMDA) receptor (Murray and Leid 1984; Coughenour et al. 1988; Klein and Musacchio 1989). DXM's primary metabolite, dextrorphan (3-hydroxy-17-methylmorphinan; DXO) (Ramachander et al. 1977), binds with low affinity to the DXM high-affinity site ($k_i=310\text{ nM}$) and with high affinity to the PCP-site ($k_i=23\text{--}170\text{ nM}$) (Coughenour et al. 1988; Franklin and Murray 1992). Studies *in vitro* have demonstrated that DXM and DXO block NMDA-induced Ca^{2+} currents (Netzer et al. 1993), have neuroprotective properties (Goldberg et al. 1987) and block epileptiform activity (Aram et al. 1989). Results of *in vivo* studies are also consistent with both compounds acting as NMDA antagonists. For example, DXM and DXO have been shown to attenuate seizure activity and provide neuroprotection secondary to ischemic insult (Chapman and Meldrum 1989; Steinberg et al. 1993). More recent studies have investigated these compounds, especially DXM, for antinociceptive activity (France et al. 1989; Mao et al. 1993) and their ability to modulate tolerance and dependence to opioids (Elliott et al. 1994).

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Because of their numerous potential beneficial therapeutic effects, various NMDA receptor antagonists have been investigated for clinical use. Difficulty arises in obtaining medications with an acceptable therapeutic index of desirable effects relative to motor impairment and PCP-like behavioral effects (Willetts et al. 1990; Balster and Willetts 1996). DXM has been in use as a nonprescription antitussive for over 30 years and has demonstrated a high margin of safety. At normal antitussive doses (15–30 mg every 6–8 h), DXM appears to have minimal side effects, including no PCP-like psychological and behavioral effects (Bem and Peck 1992). Based on this, DXM is being investigated in clinical trials for treating pain and various acute and chronic neurodegenerative conditions (Walker and Hunt 1989; Schmitt et al. 1994; Ikjaer et al. 1997). DXM's relatively good clinical profile is purportedly due to several characteristics of its interaction with the NMDA channel site, which are different from those seen with high-affinity channel blockers, such as PCP and dizocilpine (Leander et al. 1988; Rogawski 1992). However, while normal antitussive doses of DXM produce minimal central nervous system (CNS) effects, at higher doses it can produce PCP-like effects such as ataxia, dizziness, euphoria, and tactile and visual hallucinations (Isbell and Fraser 1953). In addition, there have been occasional reports of abuse and dependence (Fleming 1986; Walker and Yatham 1993; Wolfe and Caravati 1995). Original abuse-potential studies of DXM focused on possible morphine-like abuse liability and concluded the abuse potential to be low (Isbell and Fraser 1953). In light of DXM's activity as a NMDA antagonist, coupled with increased investigation of its use for a variety of neurological disorders and clinical reports of abuse, it is useful to reexamine the behavioral pharmacological profile of DXM. Therefore, DXM was evaluated for PCP-like behavioral effects and reinforcing effects in two animal models. DXO was also tested to evaluate whether metabolism might play a part in DXM's behavioral effects.

In the first set of studies, rats and rhesus monkeys trained to discriminate PCP from no drug administration were tested with DXO and DXM. Drug discrimination studies in animals are considered to be predictive of subjective effects in humans and, therefore, useful in abuse-potential assessment (Holtzman 1990; Balster 1991b). This procedure has been used to compare the behavioral effects of site-selective NMDA antagonists, and results have shown that the discriminative stimulus effects of antagonists active at different sites on the NMDA receptor complex are not identical (Balster and Willetts 1996). Typically, channel-blocking NMDA antagonists, such as PCP, ketamine and dizocilpine, substitute fully for each other regardless of the training drug (Balster 1991a). Previous testing with DXO has shown it to substitute fully for PCP and dizocilpine in rats and monkeys with a potency correlated with its PCP-site binding affinity (Holtzman 1980, 1982; France et al. 1991). Results with testing of DXM have been less consistent. When DXM is compared with PCP-site NMDA antagonists, the level

of substitution is dependent on the specific testing procedure, species tested, route of administration and the training drug (Holtzman 1980, 1982, 1994; Herling et al. 1981; France et al. 1991).

Additional information about DXM's abuse potential and behavioral effects was obtained from an i.v. self-administration study in rhesus monkeys. The results of these studies in monkeys have demonstrated a good correlation between drugs self-administered by monkeys and those abused by humans (Johanson and Balster 1978; Balster 1991b). This model has been useful in the study of the abuse potential of PCP and other PCP-like NMDA antagonists, such as dexoxadrol and ketamine, which have reinforcing effects (Brady et al. 1982b; Slifer and Balster 1983; Beardsley et al. 1990). Previous studies have shown that DXO has reinforcing properties (Young and Woods 1981); however, DXM has not been evaluated in a similar paradigm. With the current knowledge that DXO and DXM function as NMDA antagonists, both compounds were tested in monkeys trained to self-administer PCP.

Materials and methods

Virginia Commonwealth University is accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and all experimental protocols were approved by the Virginia Commonwealth University Institutional Animal Care and Use Committee. Laboratory practices and animal care were consistent with current National Institutes of Health (NIH) guidelines.

Drug discrimination in rats

Six adult male albino rats (COBS CD, Charles River, Wilmington, Del.) were trained to discriminate injections of 1.25 mg/kg PCP from saline, as previously described (Willetts and Balster 1988a). They were individually housed with free access to water under a 12-h light/12-h dark cycle. Food (Harlan Teklad Rodent Diet, Williamston, Ill.) access was restricted in order to increase lever-pressing for food.

The subjects were trained daily (Monday–Friday) during 30-min sessions in standard two-lever operant conditioning chambers (Coulbourn Instruments, Lehigh Valley, Pa.). Completion of a fixed ratio (FR) 32 on the correct lever resulted in delivery of a 45-mg food pellet (P.J. Noyes Company, Inc., Lancaster, N.H.). PCP and saline were given i.p. under a double alternation schedule, 15 min prior to session start. During sessions, a white stimulus light located centrally above both levers was illuminated. Incorrect responding reset the FR for correct-lever responding. Test sessions were conducted on Tuesday and Friday if the subjects met the following criteria on the four preceding training sessions (two PCP and two saline): (1) first FR completed on the correct lever, and (2) greater than 85% correct-lever responding over the entire session. During test sessions, completion of a FR on either lever resulted in the delivery of food reinforcement. Training continued under the double alternation of PCP and saline injections. The subjects were tested on qualifying test days with different doses of DXM (3–56 mg/kg, i.p.) or DXO (2.2–40.9 mg/kg, i.p.) given 30 min prior to the session. Doses were generally tested in ascending order across the different test days. The DXO doses were chosen to provide molar equivalent doses with DXM (8.5, 28, 85 and 159 μ mole/kg). Control tests with PCP and saline were done prior to and after each dose–response curve determination. In addition, the same subjects were tested with 30 mg/kg DXM and 40.9 mg/kg DXO, administered at different times (5, 10, 15 and 30 min) before session initiation. Injection volumes were 2.0

ml/kg for the 21.9-mg/kg dose of dextrorphan and 1.9 ml/kg for the 56-mg dose of DXM; all other injection volumes were 1 ml/kg.

Data from test sessions were analyzed by determining the mean percentage of responses on the PCP-associated lever and the overall mean response rate for all subjects. Data from sessions in which responding was less than 0.05 responses/s were excluded from determination of the mean percentage PCP-lever responding. Full substitution for PCP required greater than 80% PCP-lever responding, while partial substitution was defined as producing between 20% and 80% PCP-lever responding. To compare the relative potencies of the test drugs, the ED_{50} estimates for generalization from PCP (the dose resulting in 50% substitution for the PCP training dose) and response-rate effects (the dose estimated to cause a 50% decrease in rates of responding relative to control rates) were calculated using linear regression analysis of the linear portions of the dose–response curves. Control response rates were calculated for each subject as the average of the rates of responding on saline control tests which preceded and followed each dose–response curve determination.

Drug discrimination in rhesus monkeys

The subjects were four adult male rhesus monkeys (*Macaca mulatta*) (9.5–11 kg) with extensive experience in PCP discrimination studies (Balster et al. 1995). The monkeys were individually housed with ad libitum access to water and with restricted feeding of Purina Monkey Chow and food supplements. All monkeys participated in an IACUC-approved environmental enrichment program. Using the pole-and-collar technique, the monkeys were placed in restraint chairs and brought to the laboratory. Injections were given i.m. and the chaired monkeys were placed in a darkened test chamber equipped with two response levers, a centrally located food trough, stimulus lights and a ventilation fan. Daily (Monday–Friday) 20-min food availability was signaled by the illumination of the three stimulus lights located above each response lever.

The monkeys had been trained to discriminate injections of 0.1 mg/kg PCP (0.08 mg/kg for M1146) from sham injections given i.m. 10 min pre-session under a FR 50 schedule of food presentation. Each correct FR completed resulted in the delivery of two 1-g food pellets and a 20-s time-out, during which the lights were extinguished. PCP and sham training sessions continued under a double alternation schedule throughout the testing period. Test sessions were scheduled for Tuesday and Friday if the following criteria were met on the four most recent training sessions: (1) first FR completed on the correct lever; and (2) $\geq 85\%$ correct-lever responding. During the 20-min test sessions, FRs completed on either lever were reinforced.

The monkeys were tested with 0.02–0.18 mg/kg PCP, i.m., given 10 min prior to the session. DXO (0.25–8.0 mg/kg, i.m.) was also administered 10 min prior to the session. DXM (0.3–10 mg/kg, i.m.) was injected 30 min prior to the beginning of the session. Due to the extended pretreatment time, DXM injections were administered in the home cage and 0.05 ml/kg saline was given i.m. 10 min prior to the session to replicate training conditions. In most cases, drug doses were administered in ascending order across test sessions. Control tests were conducted with the training dose of PCP and 0.05 ml/kg saline before and after each dose–effect curve determination. The percentage PCP-lever responding and the rate of responding (responses/s) data were examined in evaluating the test drugs for generalization from the PCP training dose on an individual animal basis. The PCP-lever responding data were not included in the evaluation if the subject failed to successfully complete one FR. The ED_{50} estimates for PCP and DXO were calculated based on the means of all the subjects in a manner similar to the analysis of the rat data.

Self-administration studies

The subjects were one female (6.9 kg; M1227) and seven male (9.5–10.9 kg) rhesus monkeys. Subjects had previously been in-

cluded in PCP (all monkeys) and cocaine (M1145) self-administration studies. The subjects were individually housed in experimental cubicles (1 m³) with unlimited access to water. Food (Purina Monkey Chow) was provided in quantities sufficient to maintain constant body weights. All monkeys participated in an IACUC-approved environmental enrichment program. The jugular or femoral veins of seven of the subjects were catheterized with silicone i.v. catheters under an anesthetic protocol described previously (Nicholson et al. 1998). Subject M1145 was prepared with a renathane RenaPulse step-down catheter (0.06 cm i.d., Braintree Scientific, Inc., Braintree, Mass.) implanted in a brachial vein under the same anesthetic protocol. Catheters traveled subcutaneously from the catheterized vein and exited in the mid-scapular area. Each subject was fitted with a stainless steel harness and a spring arm attached to the rear of the cubicle, providing protection for the indwelling catheter while allowing relatively unrestricted movement in the cage. Subjects also often wore shirts (Alice King Chatham, Medical Arts, Hawthorne, Calif.) over the harness to provide further catheter protection. The catheters traveled through the spring arms to peristaltic infusion pumps (Cole-Parmer, Chicago, Ill.). Two response levers were mounted on the inside of the cubicle's clear polycarbonate door. Three stimulus lights (red light between two white lights) were located approximately 10 cm above each lever. The activation of stimulus lights and infusion pumps as well as recording of lever responses was accomplished using a PDP-11-based computer system utilizing a SKED interface and SKED-11 software (State Systems, Kalamazoo, Mich.).

The eight monkeys were trained to lever press for 3 μ g/kg/infusion (M1102 and M1106) or 10 μ g/kg/infusion PCP under FR schedules. The maintenance dose of PCP and the FR value for each subject were selected to obtain a clear difference between infusion rates maintained by PCP and saline. One-hour sessions were conducted daily (7 days/week). Illumination of the white lights over the left lever indicated the beginning of the session. Upon completion of FR 10, 50 (M1244) or 100 (M1227), a 10-s duration, 1-ml infusion of saline or drug solution was delivered. During the infusion, the white lights were extinguished, the red light illuminated and responses were recorded but did not count towards completion of the FR requirement. Substitution of saline or test drug solutions for PCP occurred following three consecutive baseline sessions in which the number of PCP infusions did not vary by more than 20% from the mean for those sessions. Each saline and test drug substitution was for four consecutive sessions and was preceded and followed by a minimum of three PCP baseline sessions. Two saline substitution series were done for each dose–response curve determination, one before and one after its completion. DXM (10, 30, 100, 300, 560 and 1000 μ g/kg/infusion) was tested in six monkeys. In addition, the 100 μ g/kg/infusion dose was retested in M1106 and M1077 and the 300 μ g/kg/infusion dose was retested in M1102. For DXO, 10, 30 and 100 μ g/kg/infusion doses were tested in four subjects and retesting of the 30 μ g/kg/infusion and the 100 μ g/kg/infusion doses for M1246 was also done. For both drugs, the dose–response curve determination included at least one dose that produced observable behavioral effects.

The number of infusions during the last three sessions of each DXM and DXO substitution series were used in data analyses. The baseline rate of PCP self-administration was based on the data from the last three PCP sessions preceding each substitution series. Saline data were evaluated both for each individual substitution series, using data from the last three sessions, and as combined data from the last 3 days of the saline substitution series before and after the dose–response curves ($n=6$). For a drug to be considered a positive reinforcer, the mean number of test-drug infusions must have exceeded the mean of the combined saline data by at least two standard deviations.

Drugs

PCP HCl, obtained from the National Institute on Drug Abuse (Rockville, Md.), was dissolved in physiological saline (0.9%).

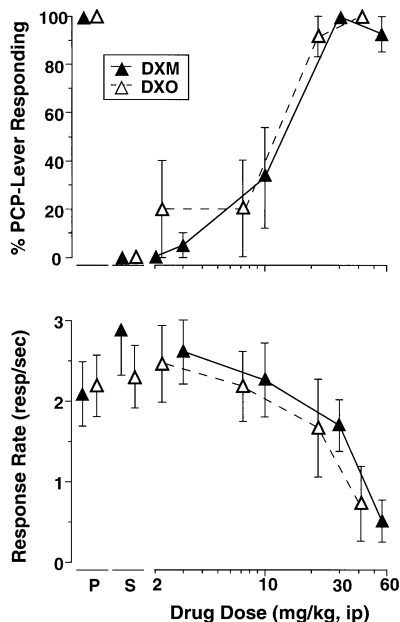


Fig. 1 Effects of dextromethorphan (*DXM*) and dextrorphan (*DXO*) in rats trained to discriminate 1.25 mg/kg phencyclidine (*PCP*) from saline. Shown in the *upper panel* is mean (\pm SE) percentage PCP-lever responding and, in the *lower panel*, mean (\pm SE) rates of responding. Values above *P* and *S* are the results of control tests with 1.25 mg/kg PCP and saline, respectively, conducted before testing *DXM* (\blacktriangle) and *DXO* (\triangle). Mean percentage PCP-lever responding was based on three of five rats for the *DXO* dose of 40.9 mg/kg, and on four of six rats for the *DXM* dose of 56 mg/kg. All other data points are averages of five (*DXO*) or six (*DXM*) rats

Dextrorphan (free base) for the rat study was obtained from Hoffman LaRoche (Nutley, N.J.) and was dissolved in 0.1 M HCl to produce a stock solution, then buffered to a neutral pH. It was then diluted in physiological saline (0.9%) to achieve the desired final concentration. Dextromethorphan HBr for the rat study was obtained from AH Robins (Richmond, Va.) and was dissolved in distilled water for a stock concentration of 30 mg/ml. For the monkey studies, dextrorphan tartrate was obtained from RBI (Natick, Mass.) and dextromethorphan HBr from Sigma Chemical Co. (St. Louis, Mo.). Both were dissolved in small amounts of distilled water and then diluted in physiological saline (0.9%) to achieve the desired final concentration. Doses expressed as milligrams or micrograms per kilogram were calculated on the form of drugs described above.

Results

Drug discrimination studies

The results of substitution tests with *DXO* and *DXM* in *PCP*-trained rats are shown in Fig. 1. Control tests with *PCP* or saline resulted in more than 95% and less than 5% *PCP*-lever responding, respectively, demonstrating stimulus control of responding over the course of the study. *DXM* and *DXO* both produced dose-dependent substitution for the training dose of *PCP*. For *DXO*, full substitution occurred at the 21.9-mg/kg dose, producing on average 91.5% *PCP*-lever responding without con-

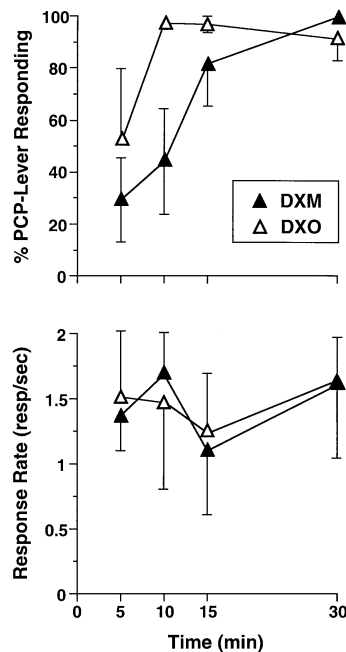


Fig. 2 Effects of dextromethorphan (*DXM*) and dextrorphan (*DXO*) in rats trained to discriminate 1.25 mg/kg phencyclidine (*PCP*) from saline when administered at various times pre-session. Shown in the *upper panel* is mean (\pm SE) percentage PCP-lever responding and, in the *lower panel*, mean (\pm SE) rates of responding. Mean percentage PCP-lever responding was based on three of five rats for the *DXO* dose of 21.9 mg/kg, and on four of six rats for the *DXM* dose of 56 mg/kg. All other data points are averages of five (*DXO*) or six (*DXM*) rats

comitant response-rate suppression. On an individual animal basis (data not shown), five of six subjects showed full substitution with *DXO* at one or more doses tested. One subject demonstrated only partial substitution (57%), even at response-rate decreasing doses. Similarly, *DXM* produced full substitution for *PCP* in rats, with all subjects showing full substitution at one or more doses that did not suppress rates of responding to less than 50% of saline control levels.

Figure 2 presents the results of a time-course evaluation of the effects of 30 mg/kg *DXM* and 21.9 mg/kg *DXO*, equivalent to 85 μ mole/kg for each drug, on both behavioral measures. These doses had been shown to produce full substitution for *PCP* in the initial dose-effect curve determination. These doses of *DXO* and *DXM* again fully substituted for *PCP* at one or more of the pretreatment times tested. *DXO* had a rapid onset of effects with substitution occurring in half the subjects at the shortest pretreatment time tested (5 min). For the 10-min pretreatment time, all subjects responded almost exclusively on the *PCP*-associated lever. *DXM* produced 81% *PCP*-lever responding following a 15-min pretreatment time, but a 30-min pretreatment time was necessary to see more than 99% *PCP*-lever selection in all subjects. These doses of *DXM* and *DXO* had minimal effects on rates of responding, although there was a mild decrease in rates seen during the 15-min pretreatment test session for both drugs.

Table 1 Potency of dextromethorphan (DXM) and dextrorphan (DXO) to produce PCP-like discriminative stimulus effects and response-rate decreasing effects in rats. *NA* not available, ED_{50} dose resulting in 50% response

Drug	PCP-like discriminative stimulus effects ^a		Response-rate decreasing effects ^b	
	ED_{50} (mg/kg) (95% C.L.)	ED_{50} (μ mole/kg) (95% C.L.)	ED_{50} (mg/kg) (95% C.L.)	ED_{50} (μ mole/kg) (95% C.L.)
PCP	0.7 ^c (0.6–0.8)	2.5 ^c (2.1–2.8)	NA	NA
DXM	11 (7–16)	30 (20–46)	50 (8.0–309)	141 (23–878)
DXO	11 (7–20)	44 (26–78)	28 (12–66)	110 (47–254)

^a ED_{50} (95% confidence limits) for substitution for the PCP training dose

^b ED_{50} (95% confidence limits) for decreases in rates of responding relative to saline control test sessions

^cValue from Willetts and Balster 1988b

Fig. 3 Effects of phencyclidine (PCP), dextromethorphan and dextrorphan in four rhesus monkeys trained to discriminate 0.1 mg/kg PCP (0.08 mg/kg for M1146) from sham injection. Individual subject data are shown with percentage PCP-lever responding in the upper panels and rates of responding in the lower panels. Shown above *P* and *S* are the results of control tests with the PCP training dose and 0.05 ml/kg saline conducted before each dose-effect curve determination. Note scaling differences in the ordinates for response-rate effects

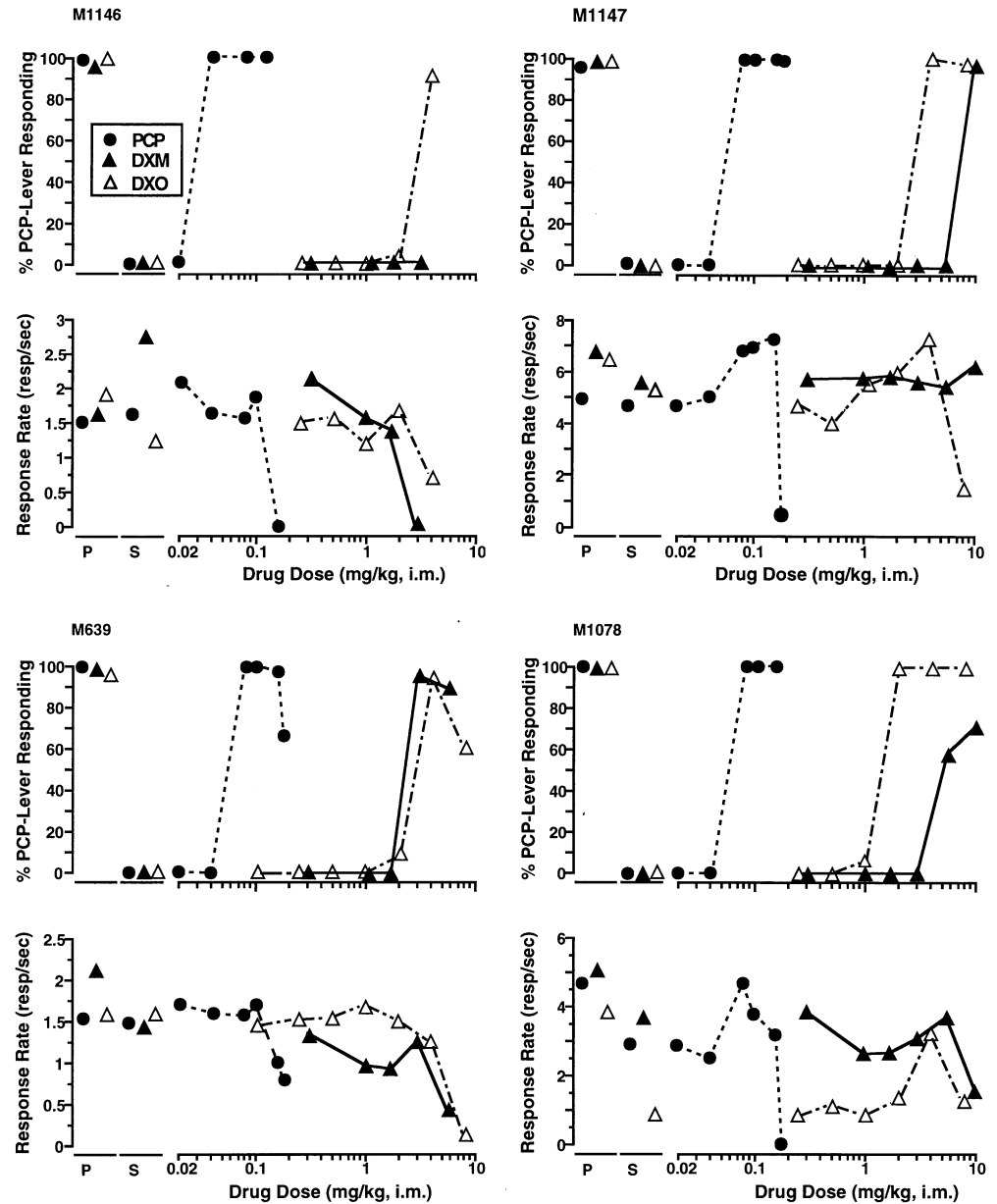


Table 1 presents a comparison of the relative potencies of DXO and DXM to produce PCP-like behavioral effects in rats. The similar ED_{50} estimates suggest that DXM and DXO were equipotent in producing PCP-like discriminative stimulus effects as well as suppression of

response rates. The potency ratios of DXM to DXO ranged from 0.9 to 1.8 which, in consideration of the variability, are consistent with the conclusion that no significant difference in potency between the two drugs was found in this study.

Figure 3 presents results from substitution tests with various doses of PCP, DXO and DXM for each of four PCP-trained monkeys. Control tests with the training dose of PCP and saline resulted in more than 97% and virtually 0% PCP-lever responding, respectively, over the course of this study. PCP produced a dose-dependent substitution for the PCP training dose. Response-rate increasing effects produced by PCP were evident on control tests with PCP and at intermediate doses of PCP in the dose-response determination for two of the monkeys (M1147 and M1078). Response rates were significantly decreased in all four monkeys at PCP doses higher than those needed to produce complete substitution.

DXO dose-dependently generalized from PCP in all four monkeys with one or more doses producing 90% or greater PCP-lever selection without reducing rates of responding below 50% of saline control test levels. As with PCP, response-rate increasing effects relative to saline were produced by one or more intermediate doses of DXO in monkeys M1147 and M1078. Monkey M1146 demonstrated signs of strong intoxication at the 4 mg/kg doses of DXO and, therefore, was not tested at the highest dose. The 8 mg/kg dose produced moderate sedation with varying degrees of ataxia in the other three monkeys. For M1078, response rates during determination of the DXO dose-response curve were generally much lower than during the PCP and DXM dose-response curve determinations. Low rates were also seen for the related control test sessions and on training days during this period and were not specifically associated with DXO administration. In three of the monkeys, DXM produced partial (58% for M1078) to full (>95% for M1147 and M639) substitution for PCP at doses that did not suppress rates of responding. Increasing the dose for M1078 to a level that did produce a decreased response rate failed to significantly increase the percentage PCP-lever responding. For M1146, DXM administration occasioned no responding on the PCP-associated lever, even at doses that resulted in a decrease in rates of responding and visible signs of intoxication. PCP (ED_{50} =0.05 mg/kg; 95% C.L. 0.03–0.06) was over 40 times more potent than DXO (ED_{50} =2.2 mg/kg; 95% C.L. 1.6–3.1) in producing PCP-like discriminative stimulus effects. Similarly, the potency of PCP (ED_{50} =0.16 mg/kg; 95% C.L. 0.08–0.33) for suppressing rates of responding was over 90-fold more potent than DXO (ED_{50} =15 mg/kg; 95% C.L. 8.0–30). These ratios are much larger than would be predicted based on the relative affinities of PCP (k_i =45 nM) and DXO (k_i =170 nM) for the PCP-site, which suggest a potency ratio of approximately 4 to 1. The variability of DXM results precluded calculating potency estimates for this drug.

Self-administration study

Figure 4 and Figure 5 show the mean number of infusions per session for PCP baseline conditions, for the saline substitution series prior to the dose-response curve

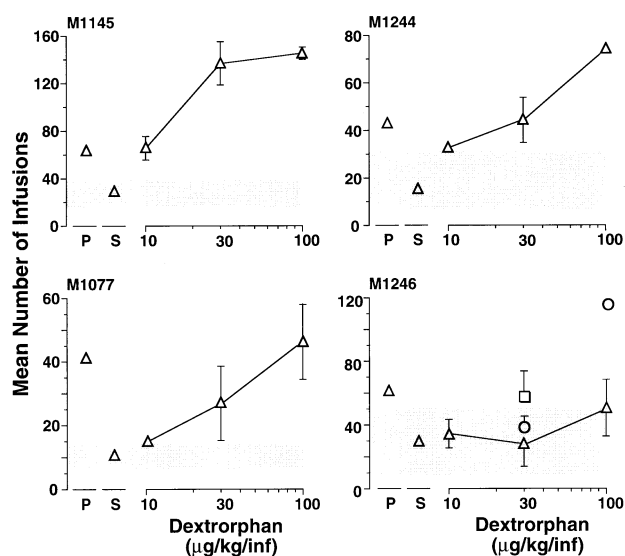


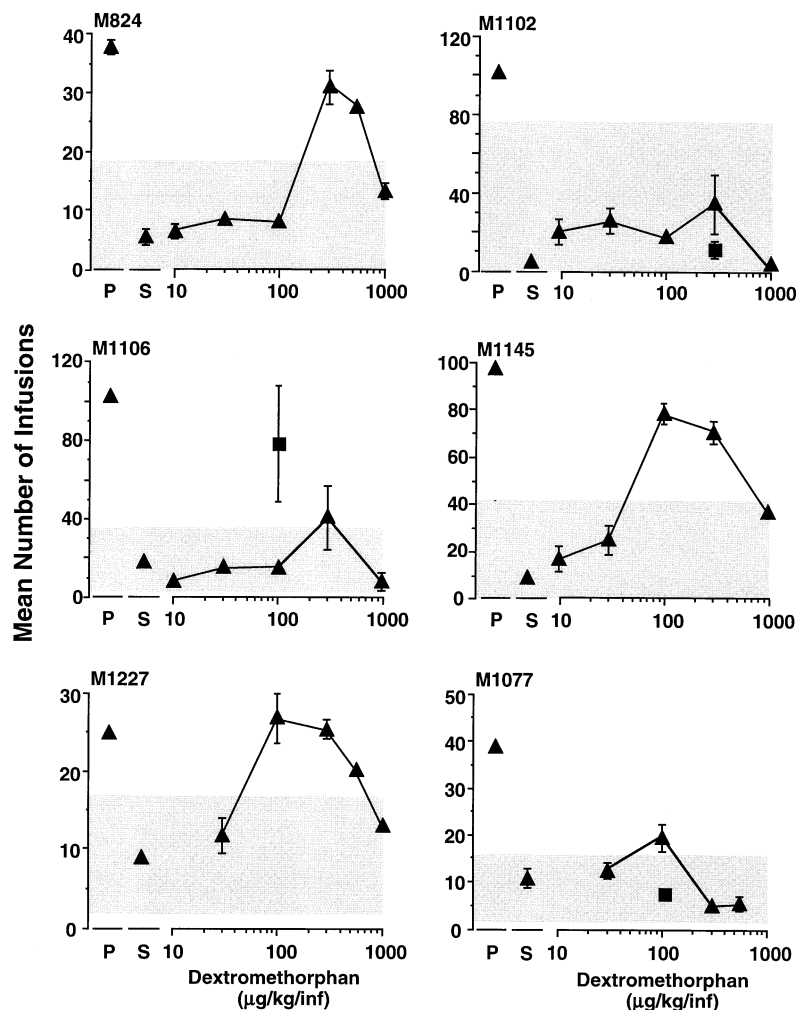
Fig. 4 Results of i.v. self-administration study with dextrophan (DXO) in four rhesus monkeys. Shown are the mean (\pm SE) number of infusions of phencyclidine (P) during baseline conditions, saline (S) infusions during the substitution preceding the dose-response curve determination and results for three test doses of DXO in rhesus monkeys trained to self-administer 10 μ g/kg/infusion of PCP under FR schedules of reinforcement. The *open circle* and *square* represent results of retesting the 30 μ g/kg/infusion and 100 μ g/kg/infusion doses of DXO in M1246. The *shaded area* encompasses two standard deviations of the mean number of saline infusions during the saline substitution series before and after testing of DXO. Note scaling differences in the ordinates

determinations and for tests with various doses of DXM and DXO. The shading indicates the range of infusion numbers that fall within two standard deviations (SD) of the mean number of saline infusions from the last 3 days of the saline substitution series before and after determination of each dose-effect curve determination. For all subjects, the mean number of infusions for individual saline substitution tests were within the 2 SD range, as illustrated by the saline data points shown in the figures. In all of the subjects, the number of PCP infusions self-administered during baseline sessions was significantly (>2 SD) higher than the overall mean number of saline infusions, showing that PCP was serving as a positive reinforcer in these subjects (Fig. 4 and Fig. 5).

For all four monkeys, at least one dose of DXO resulted in infusion numbers significantly greater than the mean number of saline infusions (Fig. 4). For three of the monkeys (M1145, M1244 and M1246), maximal levels of DXO self-administration exceeded those for the PCP baseline dose. Initially, M1246 failed to self-administer DXO above saline levels. Due to variability noted in responding for DXO, several doses were retested in this subject. This resulted in a moderate increase in infusion rates for the 30 μ g/kg dose and a large increase for the 100 μ g/kg dose, the latter resulting in very consistent responding and a mean infusion rate approximately twice that for the PCP maintenance dose.

In five of the six subjects, one or more doses of DXM resulted in mean infusion levels greater than 2 SD above

Fig. 5 Results of i.v. self-administration study with dextromethorphan (DXM) in six rhesus monkeys. Shown are the mean (\pm SE) number of infusions of phencyclidine (P) during baseline conditions, saline (S) during the substitution series preceding the dose-response curve determination and results for test doses of DXM in rhesus monkeys trained to self-administer PCP (3 μ g/kg/infusion or 10 μ g/kg/infusion) under FR schedules of reinforcement. The closed square represents results of retesting the 100 μ g/kg/infusion dose in M1102 and M1106 as well as the 300 μ g/kg/infusion dose in M1077. The shaded area encompasses two standard deviations of the mean number of saline infusions during the saline substitution series before and after testing of DXM. Note scaling differences in the ordinates



the mean for saline self-administration (Fig. 5). The peak number of DXM infusions self-administered approximated that for PCP in four of the monkeys (M1106, M1145, M1227 and M824). For M1077, the number of DXM infusions was not much greater than for saline. For M1102, no dose of DXM maintained infusion rates greater than those for saline, nor was there any evidence of a dose-response relationship. For both M1077 and M1102, testing with the dose resulting in maximal infusion rates was repeated to determine the reliability of these results. For both subjects, the repeated tests resulted in even lower overall rates of self-administration. For M1106, the 300 μ g/kg/infusion dose produced highly variable results from day to day, suggesting that the monkey may have accumulated drug over the test days causing responding to decrease over the 4-day test. Therefore, the next lowest dose (100 μ g/kg/infusion) was retested. Re-exposure to this intermediate dose did result in a large increase in rates of DXM self-administration with the mean number of infusions per session being well above the saline range.

Discussion

In the first study, the effects of the NMDA channel blockers, DXO and DXM, were compared with those of PCP in drug discrimination studies in rats and rhesus monkeys. DXO fully substituted for PCP in both rats and monkeys. As with PCP, full substitution with DXO occurred at doses below those needed to decrease rates of responding. Also, in the two monkeys in which PCP produced response-rate increases, DXO did also. The results observed with DXO were typical for high affinity PCP-like antagonists, such as dizocilpine and (+)-*N*-allylnormetazocine (Brady et al. 1982a; Beardsley et al. 1990), and also generally consistent with previous studies in various species comparing the discriminative stimulus effects of DXO to those of PCP-like noncompetitive antagonists (Holtzman 1980, 1982, 1994; Herling et al. 1981; France et al. 1991). There is good evidence that binding to the PCP-associated site is predictive of PCP-like discriminative stimulus effects (Jackson and Sanger 1988; Balster 1991a).

As with DXO, DXM produced full substitution for PCP in the rats. However, the results with DXM in PCP-

trained monkeys were not the same as those obtained with DXO, with DXM producing either no or partial substitution for PCP in one-half of the subjects. These results are consistent with previous results in squirrel monkeys trained to discriminate PCP from saline (Holtzman 1982), where DXO produced full substitution while DXM produced only partial substitution for the training drug. However, previous studies with DXM in ketamine- and dizocilpine-trained rhesus monkeys failed to show even partial generalization from the training drug (Herling et al. 1981; France et al. 1991). The inconsistent results with DXM are also similar to results produced by other low-affinity channel blockers, such as remacemide, AR-R 12495 and AR-R 16283 (Grant et al. 1996; Nicholson 1998). Additionally, while full substitution of DXM for PCP in rats has been reported before, it is greatest under conditions favorable for DXM metabolism to DXO. That is, when DXM is administered i.p. a minimum of 30 min pre-session, full substitution is obtained. When it is administered s.c. or the pretreatment time shortened, the findings in rats are more similar to the current results in monkeys, with DXM producing, at most, partial substitution for PCP (Holtzman 1980, 1994; Grant et al. 1996).

In the self-administration study, DXO clearly functioned as a positive reinforcer. Infusion numbers significantly above saline levels were obtained for at least one dose of DXO in all four monkeys. Additional evidence that DXO was serving as a reinforcer is demonstrated by the orderly dose-related changes. The positive results with DXO are typical findings for NMDA channel blockers. Under test conditions very similar to those used in this experiment, PCP, dizocilpine, ketamine, (+)-*N*-allylnormetazocine, dexoxadrol and etoxadrol have all been reliably shown to have reinforcing properties in rhesus monkeys (Brady et al. 1982b; Slifer and Balster 1983; Beardsley et al. 1990).

DXM demonstrated reinforcing effects in five of six monkeys that self-administered DXM at levels above those for saline, with the maximal number of infusions approximating those for PCP baseline sessions for one or more doses in four of the subjects. In addition, the dose-response curve for DXM in these monkeys formed the inverted U-shape normally produced by drugs functioning as reinforcers (Young and Herling 1986). It appears that DXM served only as a weak reinforcer for monkey M1077. Initial testing with the 100 µg/kg/infusion dose of DXM in this subject produced levels of responding just above saline levels and well below PCP control levels. When retested, this same dose failed to maintain self-administration above saline levels. Overall, these results are similar to those for another low-affinity channel blocker, memantine, which also maintained somewhat lower rates of self-administration than PCP in PCP-experienced monkeys (Nicholson et al. 1998).

Metabolism of DXM may have played an important role in its behavioral effects demonstrated in this study. The potency of DXM and DXO in *in vitro* studies is correlated with their relative affinity for the channel site, i.e.

DXO is typically about five- to tenfold more potent than DXM (Church et al. 1985, 1991; Parsons et al. 1995). In many *in vivo* studies, however, DXM is more potent than would be predicted, with DXM and DXO frequently being equipotent (Leander et al. 1988; Ferkany et al. 1988; Chapman and Meldrum 1989). In humans, DXO represents over 70% of the drug product after DXM metabolism by cytochrome *P*₄₅₀ 2D6 enzymes in the liver (Ramachander et al. 1977; Aylward et al. 1984). The conversion of DXM to DXO also occurs in rats and non-human primates through the action of comparable hepatic enzymes (Jacqz-Aigrain et al. 1991; Otton et al. 1992). The relevance of this high degree of metabolism of DXM is that the primary metabolite, DXO, may be responsible for some or all of the PCP-like effects produced following DXM administration.

The current drug discrimination study in rats used i.p. drug administration. In the time-course study (Fig. 2), the peak level of substitution for PCP by DXO occurred 10 min post-injection, whereas for DXM peak substitution occurred 30 min post-injection. The delayed onset of DXM effects is consistent with the hypothesis that metabolic conversion to DXO plays a role in DXM's PCP-like effects. Metabolism studies in rats have demonstrated that, within 30 min of i.p. DXM administration, conjugated DXO was the major component present in the plasma (Wu et al. 1995). This extensive and rapid metabolism seen following i.p. administration is due to first-pass metabolism in the liver subsequent to absorption into the hepatic portal vessels. Additionally, because DXM has a five- to tenfold lower affinity for the NMDA channel site than DXO, the equal potency seen (Table 1) in producing both response-rate suppression and PCP substitution are added evidence that DXM metabolism was a major factor in the resultant rat data. This concurs with the findings by Holtzman (1994) in a study comparing the effects of DXM administered s.c. versus i.p. in PCP-trained rats. Administration via the s.c. route prevents first-pass metabolism of DXM by the liver and purportedly favors the expression of DXM versus DXO behavioral effects (Wu et al. 1995). Holtzman demonstrated that DXM given s.c. substituted for PCP, but only partially, whereas 30 min after i.p. administration, DXM fully substituted for PCP, most likely due to the formation of DXO.

The conditions in the monkey study were more analogous to the s.c. route in the Holtzman study since i.m. injections should also circumvent the first-pass effect. Indeed, substitution for PCP was not as complete and unequivocal in the monkeys as in the rats. This may be because the DXM was not as rapidly and readily converted to DXO in the monkeys. A separate study in these monkeys demonstrated that, after i.m. injection of DXM, conjugated DXO was not the primary plasma component until 120 min post-injection (Dr. D. Wu personal communication). Additionally, the study found that the DXO formed from DXM in nonhuman primates was more highly conjugated than in humans, thus decreasing the proportion of DXO which would be available to access

the central nervous system in these monkeys (Otton et al. 1996). Therefore, the results in the rhesus monkey drug-discrimination study may reflect the direct effects of DXM and its low-affinity interaction with the NMDA receptor channel, and are less likely than in the rat to be due to the effects of DXO.

Metabolism of DXM may also have played a role in determining its reinforcing properties, since its metabolite, DXO, has been shown to function as an effective reinforcer in this and other (Young and Woods 1981) self-administration studies. Previous studies have demonstrated that differences in biodisposition can affect self-administration behavior between drugs with similar pharmacological effects (Winger et al. 1975; Morse 1976; Meisch 1987). Drugs with a slow onset of action introduce a delay of reinforcement, and even short delays can result in reduced rates of self-administration (Stretch et al. 1976; Beardsley and Balster 1993). In the current self-administration study, if DXM had to be converted to DXO first and it was the DXO which served to reinforce lever pressing behavior, this would impose a delay of reinforcement and weaken the reinforcing effects of DXM. This could account for the somewhat more variable rates of DXM than DXO self-administration. However, the finding that robust DXM self-administration was obtained in four of six monkeys provides evidence that DXM itself may have some reinforcing effects. In addition, evaluation of the infusion numbers over the course of the sessions (data not shown) shows that a significant portion of the infusions were obtained within the first half of the session, before significant conversion to DXO is likely to occur. Genetic polymorphism affecting the activity of the cytochrome P_{450} 2D6 enzyme is seen in humans, with approximately 10% of the population being classified as "poor metabolizers" (Lennard 1990). It is possible that individual differences seen among monkeys for both discriminative stimulus and reinforcing effects of DXM may be caused by a similar genetic polymorphism affecting DXM metabolism.

As discussed above, DXM had a somewhat lower potential to produce PCP-like and reinforcing effects than PCP and DXO. In other studies, DXM shows a higher therapeutic index of beneficial effects relative to motor and other side effects than typical PCP-site antagonists (Leander et al. 1988; Rogawski 1992; Steinberg et al. 1993). One of the most likely explanations for this diminished potential for DXM to produce these PCP-like effects is its lower affinity for the channel site than that of PCP and DXO. This lower affinity results in a much faster dissociation rate, which in turn results in a shorter duration of blockade, for compounds such as DXM, memantine and remacemide, while high-affinity compounds, such as PCP and DXO, bind more tenaciously (Parsons et al. 1993; Church et al. 1994). Additionally, studies have shown that differences exist in the NMDA receptor populations that are blocked by typical PCP-site antagonists relative to DXM and other low-affinity channel blockers. In autoradiographic binding studies (Porter

and Greenamyre 1995), analyses of alterations in NMDA-stimulated neurotransmitter release (Nankai et al. 1998) and activity in specific subunit containing recombinant NMDA receptors (Monaghan and Larsen 1997), DXM has been shown to differ from typical PCP-site NMDA antagonists. These findings suggest that differences in binding profiles play a role in the behavioral effects produced by different channel blockers and may determine the degree of PCP-like effects produced.

Overall, the current studies show that DXO produces PCP-like discriminative stimulus effects in rats and monkeys and reliably serves as a positive reinforcer in rhesus monkeys. DXM also produced PCP-like discriminative stimulus effects in rats but less consistently produced PCP-like discriminative stimulus effects and reinforcing effects in rhesus monkeys. The potency and time-course results in rats provide support for the proposal that conversion of DXM to DXO, at least after i.p. administration, plays an important role in producing DXM's PCP-like effects. The more variable behavioral results with DXM in rhesus monkeys may be due to its less rapid conversion to DXO subsequent to i.m. administration as well as lower levels of production of the unconjugated form of DXO. DXM clearly has the potential to produce typical PCP-like NMDA antagonist behavioral effects in this species, but whether this occurs appears to depend on the subject and on the exact testing conditions. For many of the same reasons that DXM produces somewhat variable effects in animals, it may also do so in humans, suggesting that individual differences and circumstances of use may determine vulnerability to abuse and the likelihood of side effects typically associated with NMDA channel blockers.

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