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 ($K_i = 12–57 \text{ nM}$) to a site associated with sigma-site ligands and with low affinity ($K_i = 0.51–2.5 \text{ µM}$) 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 ($K_i = 23–170 \text{ nM}$) (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).
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 (Willett et al. 1990; Balster and Willett 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 Willett 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 (Bradly 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 (Willett 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 µmole/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