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Comparative effects of dextromethorphan and dextrorphan on morphine, methamphetamine, and nicotine self-administration in rats

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Abstract

The effects of dextromethorphan and its metabolite dextrorphan on morphine, methamphetamine and nicotine self-administration and on responding for a nondrug reinforcer (water) were assessed in rats. Both dextromethorphan and dextrorphan decreased morphine self-administration at 10–30 mg/kg, s.c., decreased methamphetamine self-administration at 20 and 30 mg/kg, s.c., and decreased nicotine self-administration at 5–30 mg/kg, s.c.; doses of both drugs less than 40 mg/kg, s.c. did not affect responding for water. The equal potencies of dextromethorphan and dextrorphan suggest mediation of these effects by a non-NMDA receptor mechanism, possibly involving blockade of $\alpha 3\beta 4$ nicotinic receptors. The results also suggest that dextromethorphan should be tested extensively as a potential treatment for diverse populations of drug-abusing patients.

Keywords: Dextromethorphan; Dextrorphan; Morphine; Methamphetamine; Nicotine; Drug addiction

1. Introduction

Dextromethorphan, the active ingredient in most over-the-counter cough medicines, has a complex pharmacology that has led investigators to suggest several other potential uses for this agent. Although structurally related to the morphinan opioid levorphanol, dextromethorphan has little or no opioid activity but binds with high affinity to a site associated with σ receptors (Klein and Musacchio, 1989) and with lower affinity to the PCP (phencyclidine) site of the NMDA receptor (Murray and Leid, 1984; Ebert et al., 1998). Most recently, dextromethorphan has been shown to be a noncompetitive antagonist at $\alpha 3\beta 4$ nicotinic receptors (Hernandez et al., 2000). Furthermore, dextromethorphan's major metabolite, dextrorphan, has a low affinity at the σ-like site but an approximately 10-fold higher affinity than dextromethorphan at the PCP site (Franklin and Murray, 1992). Dextrorphan is approximately three times less potent than dextromethorphan at $\alpha 3\beta 4$ nicotinic receptors (Hernandez et al., 2000). Dextromethorphan has been proposed as a treatment for Huntington's (Walker and Hunt, 1989) and Parkinson's (Montastruc et al., 1994) diseases, stroke and ischemia (Moses and Choi, 1991; Steinberg et al., 1993), seizure disorders (Fisher et al., 1990), and cocaine dependence (Pulvirenti et al., 1997). The rationale for these uses is based primarily on the NMDA receptor antagonist effects of dextromethorphan and dextrorphan, in relationship to the pervasive role of glutamate in modulating changes in cell excitability that are involved in neurotoxic and neurodegenerative processes, seizures, and the reinforcing actions of stimulant drugs.

Because dextromethorphan is metabolized to dextrorphan, the relative extent to which dextromethorphan or dextrorphan mediates the effects of dextromethorphan is not always clear. This in turn has a bearing on the mechanism of action of dextromethorphan in view of the different affinities of dextromethorphan and dextrorphan for various receptor sites. Furthermore, the route of administration of dextromethorphan can have a substantial influence on the metabolism of dextromethorphan. In rats, approximately three times as much dextrorphan is formed after intraperitoneal (i.p.) administration as after subcutaneous (s.c.) administration of dextromethorphan; and peak brain concentrations of dextrorphan are fivefold higher after i.p. than after s.c. administration of dextromethorphan (Wu et al., 1995). Indeed, from the available evidence (Holtzman, 1994; Nicholson et al., 1999; Szekely et al., 1991; Wu et al., 1995), it appears that, when administered i.p., most of the effects of dextromethorphan are mediated

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by dextrorphan, whereas when administered s.c., the effects of dextromethorphan are mediated almost entirely by dextromethorphan itself.

Studies comparing dextromethorphan and dextrorphan have generally found that, consistent with their binding affinities, dextrorphan is much more potent than dextromethorphan in behavioral paradigms that are sensitive to PCP-like or NMDA receptor antagonist effects (Holtzman, 1994; Nicholson et al., 1999; Szekely et al., 1991). In other instances, particularly when dextromethorphan has been studied by itself, the mechanism of its behavioral effects has been much less certain. The effects of dextromethorphan on cocaine self-administration (Pulvirenti et al., 1997), for example, have been attributed to NMDA receptor antagonism, although there is no compelling evidence that this is actually the mechanism involved. In the present study, the effects of dextromethorphan and dextrorphan, administered s.c., on morphine, methamphetamine and nicotine self-administration as well as on responding for a nondrug reinforcer (water), were determined. Our goal was to learn if dextromethorphan's reported effects on cocaine self-administration extended to other drugs of abuse and, by comparing dextromethorphan and dextrorphan, to assess whether an NMDA receptor antagonist action was a likely mechanism mediating such effects.

2. Materials and methods

2.1. Chemicals

Dextromethorphan hydrobromide and dextrorphan tartrate (Sigma/RBI, St. Louis, MO) were dissolved in saline and injected subcutaneously.

2.2. Animals

Naïve female Long–Evans derived rats (250 g; Charles River, NY) were maintained on a normal 12-h light cycle (lights on at 7:00 a.m., lights off at 7:00 p.m.). For all experiments the "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed.

2.3. Self-administration procedure

The intravenous self-administration procedure has been described previously (e.g., Glick et al., 1996, 2000). Briefly, responses on either of two levers (mounted 15 cm apart on the front wall of each operant test cage) were recorded on an IBM-compatible computer with a Med Associates interface. The intravenous self-administration system consisted of polyethylene–silicone cannulas constructed according to the design of Weeks (1972), Instech harnesses and swivels, and Harvard Apparatus infusion pumps (#55-2222). Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks (1972). Self-administration testing began with a 16-h nocturnal session followed by daily 1-h sessions, 5 days (Monday–Friday) a week. A lever-press response produced a 10-μl infusion of drug solution (0.01 mg of morphine sulfate) in about 0.2 s, or a 50-μl infusion of drug solution (0.01 mg of nicotine hydrogen bitartrate or 0.025 mg of methamphetamine sulfate) in about 1 s. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine or nicotine (0.014 mg/kg free base) or 0.1 mg/kg of methamphetamine. One noncontingent drug infusion was administered at the beginning of each session. Experiments to assess the effects of dextromethorphan and dextrorphan were begun when baseline self-administration rates stabilized (≤ 10% variation from 1 day to the next across 5 days), usually after 2 weeks of testing. In order to provide an indication of the specificity of treatment effects on drug self-administration, dextromethorphan and dextrorphan were also administered to other rats bar-pressing for water (0.01 ml orally) on a comparable schedule (continuous reinforcement; 1-h sessions).

3. Results

Figs. 1–4 show the effects of dextromethorphan and dextrorphan on morphine, methamphetamine and nicotine self-administration and on responding for water, respec-

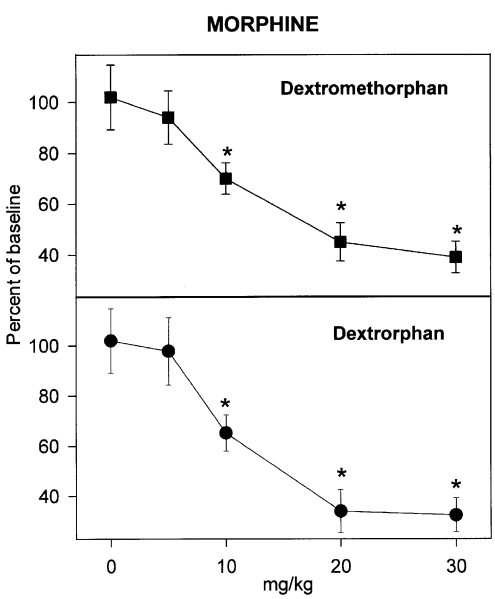

Fig. 1. Effects of dextromethorphan and dextrorphan on morphine self-administration. Baseline morphine infusions averaged (±S.E.M.) 35.5 ± 3.0 and 39.3 ± 3.5 in the dextromethorphan and dextrorphan groups, respectively. Each data point represents the mean (±S.E.M.) percent of baseline of 5–6 rats. * Significant differences between drug and vehicle (ANOVA, $P < 0.00005$ for both dextromethorphan and dextrorphan; post-hoc Newman–Keuls, $P < 0.05$–0.001).

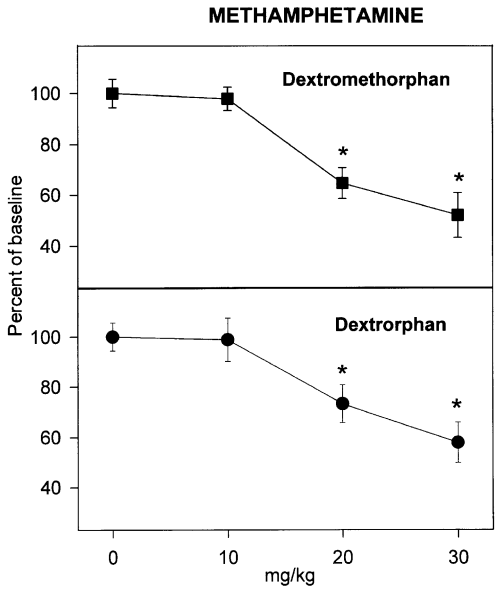

Fig. 2. Effects of dextromethorphan and dextrorphan on methamphetamine self-administration. Baseline methamphetamine infusions averaged (±S.E.M.) 22.8±2.6 and 22.6±2.3 in the dextromethorphan and dextrorphan groups, respectively. Each data point represents the mean (±S.E.M.) percent of baseline of 4–7 rats. * Significant differences between drug and vehicle (ANOVA, $P < 0.0004$ and 0.003 for dextromethorphan and dextrorphan, respectively; post-hoc Newman–Keuls, $P < 0.05$–0.01].

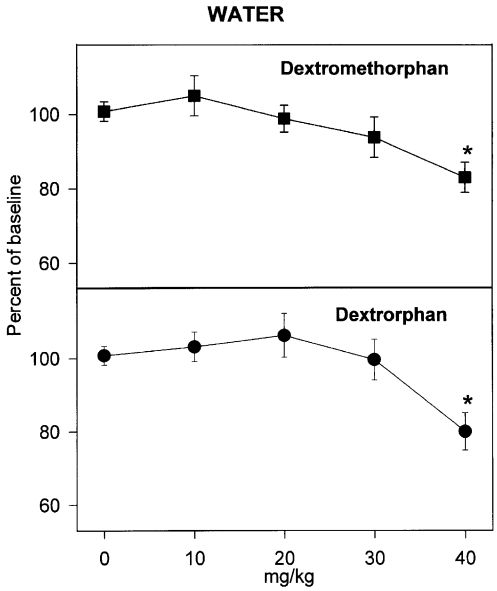

Fig. 4. Effects of dextromethorphan and dextrorphan on responding for water. Baseline rates of responding averaged (±S.E.M.) 838.4±28.8 and 854.5±30.1 in the dextromethorphan and dextrorphan groups, respectively. Each data point represents the mean (±S.E.M.) percent of baseline of 4–6 rats. * Significant differences between drug and vehicle (ANOVA, $P < 0.05$ and 0.02 for dextromethorphan and dextrorphan, respectively; post-hoc Newman–Keuls, $P < 0.05$).

tively. There were significant effects of dextromethorphan and dextrorphan in all four paradigms (for both dextromethorphan and dextrorphan, the significance of ANOVAs ranged from $P < 0.05$ for water to $P < 0.00001$ for nicotine). Post-hoc Newman–Keuls tests showed significant ($P < 0.05$–0.0001) effects of both dextromethorphan and dextrorphan at 10–30 mg/kg on morphine self-administration, at 20 and 30 mg/kg on methamphetamine self-administration, at 5–30 mg/kg on nicotine self-administration, and at 40 mg/kg on responding for water. There were no significant differences between the effects of dextromethorphan and dextrorphan. Calculation of ED50s confirmed this conclusion: using a criterion of a 25% decrease in self-administration rates, the ED50s for dextromethorphan and dextrorphan were, respectively, 10 and 8.7 mg/kg on morphine self-administration, 5 and 5 mg/kg on nicotine self-administration, 18.3 and 20 mg/kg on methamphetamine self-administration, and > 40 and 40 mg/kg on responding for water.

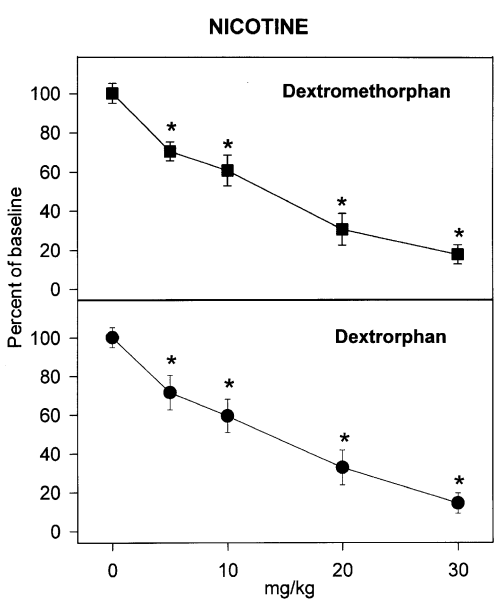

Fig. 3. Effects of dextromethorphan and dextrorphan on nicotine self-administration. Baseline nicotine infusions averaged (±S.E.M.) 26.3±2.3 and 24.6±2.4 in the dextromethorphan and dextrorphan groups, respectively. Each data point represents the mean (±S.E.M.) percent of baseline of 4–6 rats. * Significant differences between drug and vehicle (ANOVA, $P < 0.00001$ for both dextromethorphan and dextrorphan; post-hoc Newman–Keuls, $P < 0.01$–0.0001).

4. Discussion

Dextromethorphan and dextrorphan had pronounced and selective effects on drug self-administration: both agents decreased morphine, methamphetamine and nicotine intake at doses (≤ 30 mg/kg) that were ineffective on responding for water. As these studies were nearing completion, Jun and Schindler (2000) published a report showing, similarly, that dextromethorphan (25 mg/kg, i.p.) decreased methamphetamine self-administration in rats but did not affect responding for a food reward. Thus, the present findings, together with the results of Pulvirenti et

al. (1997) and Jun and Schindler (2000), suggest that dextromethorphan, widely available as an over-the-counter cough remedy for many years, may be useful in treating multiple forms of drug abuse.

Jun and Schindler (2000), like Pulvirenti et al. (1997), attributed their results to the NMDA receptor antagonist activity of dextromethorphan. However, the present data suggest an alternative interpretation. That is, dextromethorphan and dextrorphan were equally potent in the present study; if NMDA receptor antagonism was the sole mechanism responsible for dextromethorphan's effects, dextrorphan should have been several times more potent than dextromethorphan (Dematteis et al., 1998), especially when administered by the s.c. route (Holtzman, 1994; Nicholson et al., 1999; Szekely et al., 1991; Wu et al., 1995). Dextromethorphan and dextrorphan have much more comparable potencies at the $\alpha 3\beta 4$ nicotinic receptor (Hernandez et al., 2000), and it is possible that this site has a more prominent role in determining the effects of dextromethorphan and dextrorphan on drug self-administration. Indeed, consistent with a nicotinic antagonist action, both dextromethorphan and dextrorphan were more potent and more effective in decreasing nicotine self-administration than in decreasing morphine or methamphetamine self-administration. Recent findings with the nonspecific nicotinic antagonist mecamylamine provide further evidence that nicotinic mechanisms might modulate the abuse of drugs other than nicotine. Mecamylamine was recently reported to decrease craving for cocaine in humans (Reid et al., 1999) and to reduce cocaine self-administration in rats (Levin et al., 2000).

The results of short-term and limited clinical trials with heroin addicts have indicated that treatment with dextromethorphan may reduce heroin intake (Koyuncuoglu, 1995), craving (Koyuncuoglu and Saydam, 1990), and signs of withdrawal (Koyuncuoglu and Saydam, 1990; Koyuncuoglu, 1995). The results of the present study suggest that dextromethorphan should be tested more extensively in diverse populations of drug-abusing patients.

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