Comparison of the Effects of Dextromethorphan, Dextrorphan, and Levorphanol on the Hypothalamo-Pituitary-Adrenal Axis

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ABSTRACT

Dextromethorphan is a weak noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist. It is metabolized in vivo to dextrorphan, a more potent noncompetitive NMDA antagonist that is the dextrorotatory enantiomer of the opioid agonist levorphanol. The present study characterized the effects of the acute administration of dextromethorphan, dextrorphan, and levorphanol on the hypothalamo-pituitary-adrenal (HPA) axis in the rat and tested the involvement of opioid receptors in the responses produced by dextrorphan and levorphanol. Although both dextromethorphan and dextrorphan increased plasma levels of adrenocorticotropic hormone (ACTH) and corticosterone, the dextromethorphan-induced responses occurred more rapidly than the dextrorphan-induced responses. The analysis of plasma levels of dextrorphan produced after the administration of dextromethorphan indicates that the concentration of dextrorphan formed was too low to be pharmacologically relevant, suggesting that at least some of the effects on the HPA axis are due to the parent compound, and not the metabolite. Naloxone (2 mg/kg) had no effect on the dextrorphan-induced increases in plasma levels of ACTH and corticosterone, but it blocked the levorphanol-induced increases. These results support the hypothesis that dextromethorphan has pharmacological activity aside from its biotransformation to dextrorphan and demonstrate that the effects of dextrorphan are not mediated by opioid receptors.

Dextromethorphan is an antitussive that has been proposed to have potential utility in the treatment of various neurological disorders (Steinberg et al., 1996). Moreover, it has been suggested to be useful in attenuating tolerance to opioids, reducing opioid withdrawal, and inhibiting the reinforcing properties of a variety of abused drugs (Elliot et al., 1994; Herman et al., 1995; Jun and Schindler, 2000; Soyka et al., 2000). Aside from its antitussive effects, dextromethorphan is essentially devoid of other opioid-type effects (Benson et al., 1953; Pert and Snyder, 1973); however, it interacts at nonopioid sites and possesses other pharmacological activity. For example, dextromethorphan is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist (Church et al., 1985; Church et al., 1989; Franklin and Murray, 1992). In rats and monkeys, dextromethorphan produces discriminate stimuli that generalize to phencyclidine (PCP) and other noncompetitive NMDA receptor antagonists (Holtzman, 1994; Nicholson et al., 1999). Like other noncompetitive NMDA receptor antagonists, such as PCP, dextromethor-

phan produces ataxia, and stereotypy in rats (Székely et al., 1991; Ishmael et al., 1998) and psychotomimetic and ethanol-like effects and is subject to abuse in humans (Jasinski et al., 1971; Fleming, 1986; Orrell and Campbell, 1986; Mortimer et al., 1989; Bem and Peck, 1992; Steinberg et al., 1996; Soyka et al., 2000). Dextromethorphan also binds with high affinity to other sites (Musacchio et al., 1988), including sigma binding sites (Musacchio et al., 1989; Rothman et al., 1991), nicotinic receptors (Hernandez et al., 2000), and calcium channels (Netzer et al., 1993). It has been suggested that the discriminative stimulus effects of dextromethorphan more closely resemble the effects of drugs that interact at sigma receptors compared with other sites (Gavend et al., 1995). Determining the specific mechanisms underlying the pharmacological effects of dextromethorphan in vivo is complicated because it is *O*-demethylated to produce dextrorphan (Mortimer et al., 1989). Dextrorphan, a more potent NMDA receptor antagonist (Church et al., 1985, 1989; Franklin and Murray, 1992), also produces PCP-like behavioral effects (Székely et al., 1991; Ishmael et al., 1998). Thus, some of the pharmacological effects of dextromethorphan in vivo might be due to its conversion to dextrorphan.

Aside from producing profound behavioral effects, noncompetitive NMDA antagonists such as PCP, dizolcipine, dexox-

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ABBREVIATIONS: NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine; HPA, hypothalamo-pituitary-adrenal; ACTH, adrenocorticotropic hormone.

adrol, and (+)-*N*-allylnormetazocine stimulate the hypothalamo-pituitary-adrenal (HPA) axis in the rat (Pechnick et al., 1989a, 1990; Iyengar et al., 1990; Pechnick and Poland, 1994). This response is centrally mediated and not due to direct stimulatory effects at the level of the pituitary or adrenal gland (Pechnick et al., 1990). Opioid agonists also stimulate the HPA axis in the rat by interacting with central opioid target sites (Pechnick, 1993). Dextrorphan is the dextrorotatory enantiomer of the opioid agonist levorphanol, but it has a 4000-fold lower affinity than levorphanol for opioid binding sites (Pert and Snyder, 1973). It is conceivable that responses produced by high doses of dextrorphan could involve opioid receptors.

The purpose of the present study was 3-fold: first, to characterize the effects of dextromethorphan on plasma levels of ACTH and corticosterone in the rat; second, to compare and contrast the effects of dextromethorphan, dextrorphan, and levorphanol; and third, to test for the involvement of opioid receptors in the response. To determine the extent and relevancy of in vivo conversion of dextromethorphan to dextrorphan, plasma levels of dextromethorphan and dextrorphan were measured by high-performance liquid chromatography.

Materials and Methods

Experimental Animals. Male Sprague-Dawley-derived rats (Charles River Breeding Laboratories, Wilmington, MA) were used for all experiments. They were housed five per cage under a 12/12-h light/dark cycle (lights on from 7:00 AM to 7:00 PM) at a temperature of 21–22°C for 14 days before drug administration. Food and water were available ad libitum. The rats were handled daily for 5 days before testing to habituate them to the experimental procedure and reduce stress-induced changes in hormone secretion. All plasma samples were obtained between 11:00 AM and 1:00 PM, and all subjects were randomly assigned to treatment groups. The studies were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

Drugs. Dextromethorphan hydrobromide was purchased from Sigma/RBI (Natick, MA), and dextrorphan tartrate, levorphanol tartrate, and naloxone hydrochloride were supplied by the National Institute on Drug Abuse. All drugs were dissolved in saline and injected s.c. in a volume of 1.0 ml/kg.

Drug Administration. To determine the time course of the effects of dextromethorphan and dextrorphan on the HPA axis, groups of rats were injected s.c. with saline (0.9%), dextromethorphan (30.0 mg/kg), or dextrorphan (30.0 mg/kg) and returned to their home cages. The rats were sacrificed by decapitation 30, 60, or 120 min later, and trunk blood was collected into chilled tubes containing disodium EDTA (5.0 mg), sodium azide (0.081 mg), and aprotinin (500 kallikrein units). The blood was immediately centrifuged under refrigeration at 500*g* for 12 min, and the plasma stored at −70°C for subsequent determination of plasma levels of ACTH and corticosterone. For the dose-response study, rats were injected with saline, dextromethorphan (3.0, 10.0, or 30.0 mg/kg), dextrorphan (3.0, 10.0, or 30.0 mg/kg), or levorphanol (1.0, 3.0, or 10.0 mg/kg) and returned to their home cages. Sixty minutes later the rats were sacrificed by decapitation and trunk blood was collected for subsequent determination of plasma levels of ACTH and corticosterone. In this experiment, plasma also was retained for the measurement of dextromethorphan and dextrorphan. A final study was conducted to determine the involvement of opioid receptors in the effects of dextrorphan and levorphanol on the HPA axis. Rats were injected s.c. with saline or naloxone (2.0 mg/kg), immediately followed by a second s.c. injection of either saline, dextrorphan (30.0 mg/kg), or levorphanol (3.0 mg/kg). Blood samples were obtained 60 min later as described above.

Radioimmunoassays. Plasma levels of ACTH and corticosterone were measured by RIA as described previously (Pechnick et al., 1990) by using the INCSTAR (Stillwater, MN) antibody for ACTH and corticosterone antiserum (ICN Biomedicals, Irvine, CA). The reference standard for the ACTH assay was $ACTH_{1-39}$, and the limits of sensitivity for the two assays were ACTH, 40.0 pg/ml, and corticosterone, 2.0 ng/ml. As determined by low, medium and high plasma pool replicates, the maximum inter- and intra-assay coefficients of variation for ACTH and corticosterone assays are 19 and 12%, and 14 and 10%, respectively.

Determination of Plasma Levels of Dextromethorphan and Dextrorphan. Plasma levels of dextromethorphan and dextrorphan were measured by high-performance liquid chromatography. Plasma (0.1 ml) was mixed with 0.9 ml of 0.25 M sodium carbonate and 10 ml of toluene and shaken for 20 min. After centrifugation at 250*g* for 15 min, the bottom aqueous layer was frozen on dry ice and the organic layer was poured off into tubes containing 0.5 ml of 0.1 M HCl, shaken for 5 min, and centrifuged for 5 min at 250*g*. The aqueous layer was frozen on dry ice and the organic layer was discarded. Compounds were separated on a high-performance liquid chromatography system using a cyanopropyl column (Axxiom CNP, 4.5 × 150-mm column, 5-μm particle size). The mobile phase consisted of an aqueous phase (25 mM citric acid, 25 mM acetic acid, 10 mM triethylamine, and 0.1 mM EDTA) with a pH of 4.8 mixed with acetonitrile (30%). The flow rate of the mobile phase was 1 ml/min. The fluorescence detector (RF-551; Shimadzu, Kyoto, Japan) was set to 227-nm excitation and 308-nm emission. External standards for dextromethorphan and dextrorphan ranged from 10 to 10,000 ng/ml. Drug concentrations were determined from log (concentration) − log (peak height) regressions lines. The sensitivity of the system was 25 ng/ml plasma.

Data Analysis. The time course data were analyzed by two-way analysis of variance, followed by one-way analysis of variance at each postinjection time point. The dose-response and naloxone interaction experiments were analyzed by one-way analysis of variance. Analyses that yielded significant treatment effects were further analyzed by Dunnett's test for comparison of the drug-treated groups with the saline controls, Scheffé's test for comparisons between specific treatment groups, or Student's *t* test to compare specific treatment groups across time points. Because the ACTH data displayed heterogeneity of variance across the experimental groups, and the data were not normally distributed, these data were analyzed using log-transformed values, whereas the corticosterone data were analyzed using the raw values. The data are expressed as the means ± the standard errors of the mean, and for all comparisons a criterion of $p < 0.05$ was used for the rejection of the null hypothesis.

Results

In the time course study, the acute administration of dextromethorphan and dextrorphan increased plasma levels of both ACTH (Fig. 1A). Two-way analysis of variance of the ACTH time-course data showed significant treatment [$F_{(2,76)} = 32.26$; $p < 0.0001$], time [$F_{(2,76)} = 18.84$; $p < 0.0001$], and interaction effects [$F_{(4,76)} = 8.25$; $p < 0.0001$]. Thirty minutes after administration both dextromethorphan and dextrorphan significantly increased plasma ACTH levels, but the response produced by dextromethorphan was significantly greater than that produced by dextrorphan. Both drugs produced equivalent increases in plasma ACTH 60 min after drug administration; however, the dextromethorphan-induced increase was significantly less at this time point compared with the response 30 min after drug administration. Plasma levels of ACTH in either treatment group were not significantly different from saline-treated subjects 120 min after drug administration.
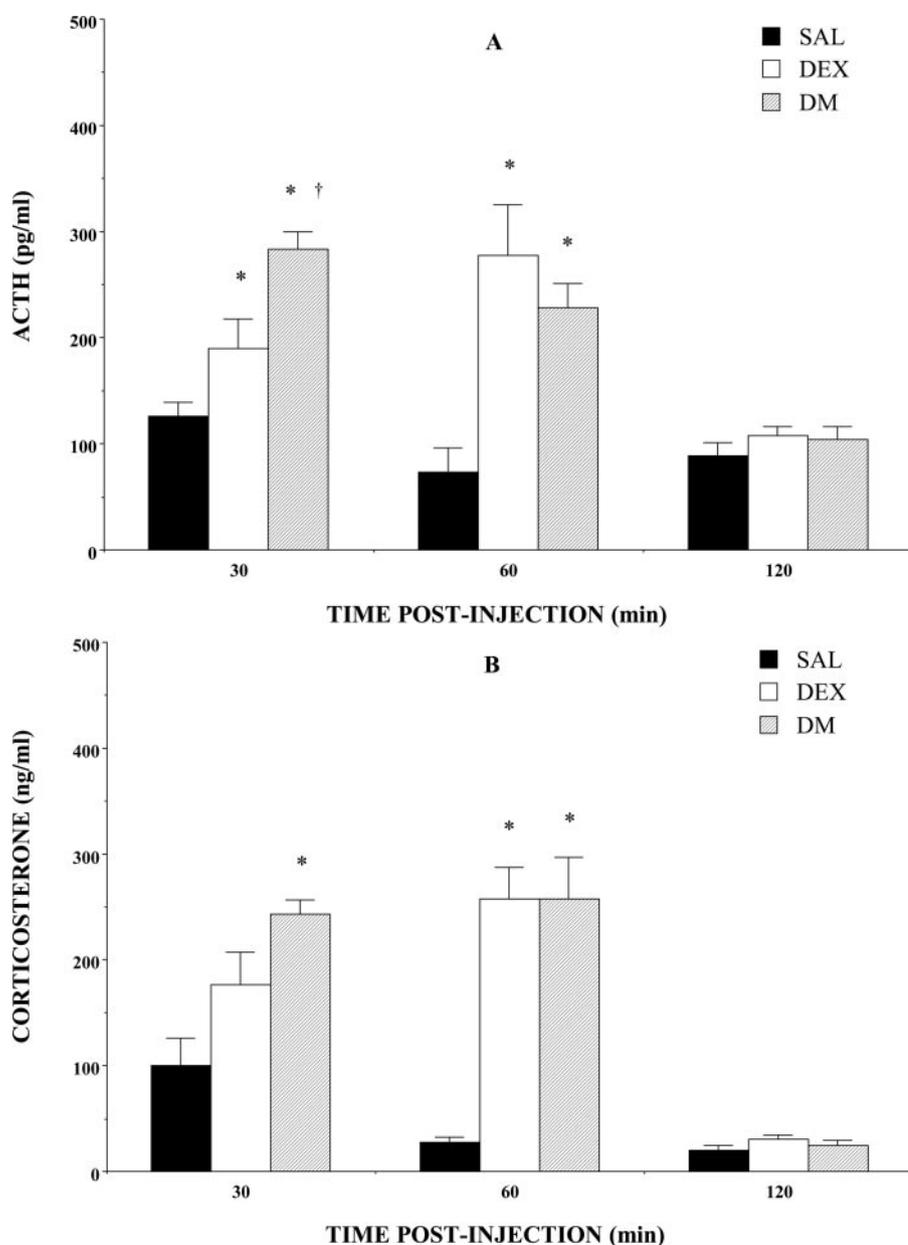
Fig. 1. A and B, effects of dextromethorphan (DM; 30.0 mg/kg) and dextrorphan (DEX; 30.0 mg/kg) on plasma levels of ACTH (A) and corticosterone (B). Values represent the means + the standard errors of the mean (n = 8–10). *, $p <$ 0.05 compared with saline-treated controls; †, $p <$ 0.05 compared with dextrorphan-treated subjects.

The acute administration of both drugs also increased plasma levels of corticosterone (Fig. 1B); there were significant treatment [$F_{(2,76)}$ = 29.20; $p <$ 0.0001], time [$F_{(2,76)}$ = 48.74; $p <$ 0.0001], and interaction effects [$F_{(4,76)}$ = 9.68; $p <$ 0.0001]. Only dextromethorphan significantly increased plasma corticosterone levels 30 min after drug administration, whereas both dextromethorphan and dextrorphan produced significant increases at the 60-min time point. Plasma corticosterone levels were not significantly different from saline-treated subjects 120 min after drug administration.

In the dose-response study, 60 min after drug administration, dextromethorphan (3.0–30.0 mg/kg) significantly affected plasma levels of ACTH [Fig. 2A; treatment $F_{(3,36)}$ = 0.24; $p <$ 0.03] and corticosterone [Fig. 2B; treatment $F_{(3,36)}$ = 65.68; $p <$ 0.0001]. However, in both cases only the highest dose produced significant increases. The highest dose of dextrorphan (30.0 mg/kg) also caused significant increases in the plasma levels of both ACTH [Fig. 3A; treatment $F_{(3,29)}$ = 7.83; $p <$ 0.0006] and corticosterone [Fig. 3B;

treatment $F_{(3,29)}$ = 20.26; $p <$ 0.001]. Levorphanol stimulated the HPA axis but was more potent than dextrorphan or dextromethorphan; the two highest doses (3.0 and 10.0 mg/kg) increased plasma levels of increased plasma levels of ACTH [Fig. 4A; treatment $F_{(3,36)}$ = 23.02; $p <$ 0.0001] and corticosterone [Fig. 4B; treatment $F_{(3,36)}$ = 20.35; $p <$ 0.0001]. The two highest doses seemed to produce maximal increases in plasma levels of both ACTH and corticosterone.

In the rats that received dextromethorphan (30 mg/kg s.c.), 60 min after drug administration the mean plasma level of dextromethorphan was 5.8 ± 0.35 nmol/ml (n = 20), whereas the mean plasma level of dextrorphan was 200.0 ± 42.0 pmol/ml (n = 20), giving a ratio of dextromethorphan to dextrorphan of approximately 1 to 0.034. In rats that received dextrorphan (30 mg/kg s.c.), the mean plasma level of dextrorphan 60 min after drug administration was 4.9 ± 0.7 nmol/ml (n = 19). This was more that 24-fold higher than the plasma concentration of dextrorphan found after the administration of dextromethorphan.
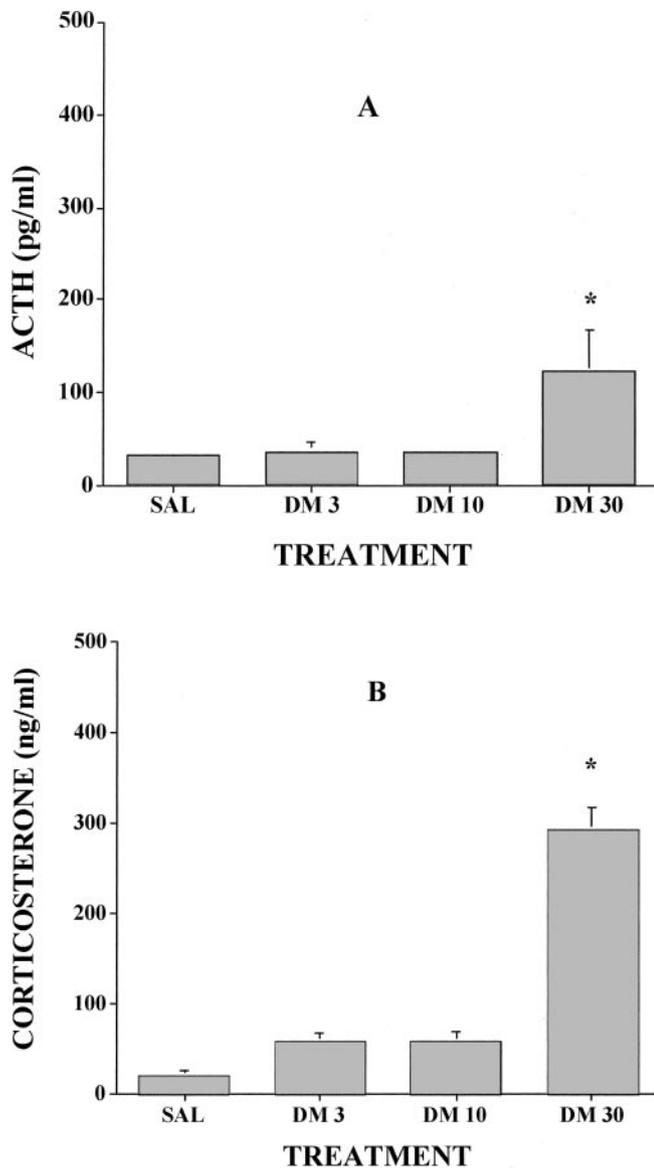
Fig. 2. A and B, effects of dextromethorphan (DM; 3.0, 10.0, or 30.0 mg/kg) on plasma levels of ACTH (A) and corticosterone (B) 60 min after s.c. injection. Values represent the means + the standard errors of the mean ($n = 7–10$). $*$, $p < 0.05$ compared with saline-treated controls.

The last experiment tested whether the opioid antagonist naloxone could attenuate the stimulatory effects of dextrorphan and levorphanol on the HPA axis. There were significant treatment effects with regard to plasma ACTH [treatment $F(5,48) = 18.38$; $p = 0.0001$] and plasma corticosterone levels [treatment $F(4,48) = 39.40$; $p = 0.0001$]. Naloxone (2.0 mg/kg) given alone had no effect on plasma levels of either ACTH or corticosterone (Fig. 5, A and B). The increases in plasma levels of ACTH and corticosterone produced by dextrorphan (30.0 mg/kg) were not reduced by naloxone; however, naloxone pretreatment blocked the levorphanol-induced (3.0 mg/kg) increases in plasma levels of both ACTH and corticosterone.

Discussion

The results of the present study show that both dextromethorphan and dextrorphan stimulate the HPA axis in the rat; however, the time course of the responses produced by the two drugs was not identical. Significant increases in plasma ACTH levels were observed 30 min after the administration of either dextromethorphan or dextrorphan, whereas only dextromethorphan produced a significant increase in plasma corticosterone at this time point. Moreover, the dextromethorphan-induced increase in plasma ACTH was maximal 30 min after drug administration. In contrast, the dextrorphan-induced increases in both ACTH and corticosterone peaked at the 60-min time point. Thus, the dextromethorphan-induced stimulation of the HPA axis occurred more rapidly and reached a maximum at an earlier time point than the dextrorphan-induced responses. In an earlier study Eisenberg and Sparber (1979) did not find that dextrorphan increased plasma levels of corticosterone, but the dose used in their study (1 mg/kg) was far lower than the dose that caused a significant increase in the present experiment (i.e., 30 mg/kg). To our knowledge this is the first report to show its effects in the rat, but dextromethorphan has been found to increase plasma cortisol levels in human subjects (Soyka et al., 2000).

The finding that dextromethorphan and dextrorphan can stimulate the HPA axis is consistent with the reports that other noncompetitive NMDA receptor antagonists, such as PCP, dizolcipine, dexoxadrol, and (+)-N-allylnormetazocine, also stimulate the HPA axis in the rat (Pechnick et al., 1989a, 1990; Iyengar et al., 1990; Pechnick and Poland, 1994). Dextrorphan has a higher affinity for the noncompetitive binding domain of the NMDA receptor (Franklin and Murray, 1992), and electrophysiological data show that dextrorphan is a more potent NMDA receptor antagonist than dextromethorphan both in vitro (Church et al., 1985) and after in vivo administration (Church et al., 1989; Ishmael et al., 1998). It was not possible to determine relative potencies with respect to stimulation of the HPA axis because the effects of the two drugs peak at different time points after drug administration, and the dose-response study was conducted at a single time point. Moreover, the differences in potency might be obscured by other variables, such as more rapid uptake, producing larger, more abrupt responses. However, the differences in potency between the two compounds do not seem to be large. This suggests that sites of action in addition to NMDA receptors might be involved.

In addition to acting as a noncompetitive NMDA receptor antagonists, dextromethorphan and dextrorphan also have other activity and interact with other binding sites. The finding that the effects of dextrorphan were not reduced by pretreatment with naloxone indicates that opioid mechanisms are not involved in its effects on the HPA axis at the doses tested. Both dextromethorphan and dextrorphan inhibit calcium flux (Carpenter et al., 1988), although with respect to dextromethorphan, it is 100-fold less potent as a calcium channel blocker compared with its activity as an NMDA receptor antagonist (Netzer et al., 1993). Both dextromethorphan and dextrorphan also bind to high-affinity dextromethorphan and sigma binding sites (Musacchio et al., 1988; Rothman et al., 1991), which might be separate or related entities (Musacchio et al., 1989). Although the exact consequences of interacting with these other binding sites are unknown, some sigma receptor ligands can stimulate the HPA axis in the rat (Iyengar et al., 1990; Pechnick and Poland, 1994).
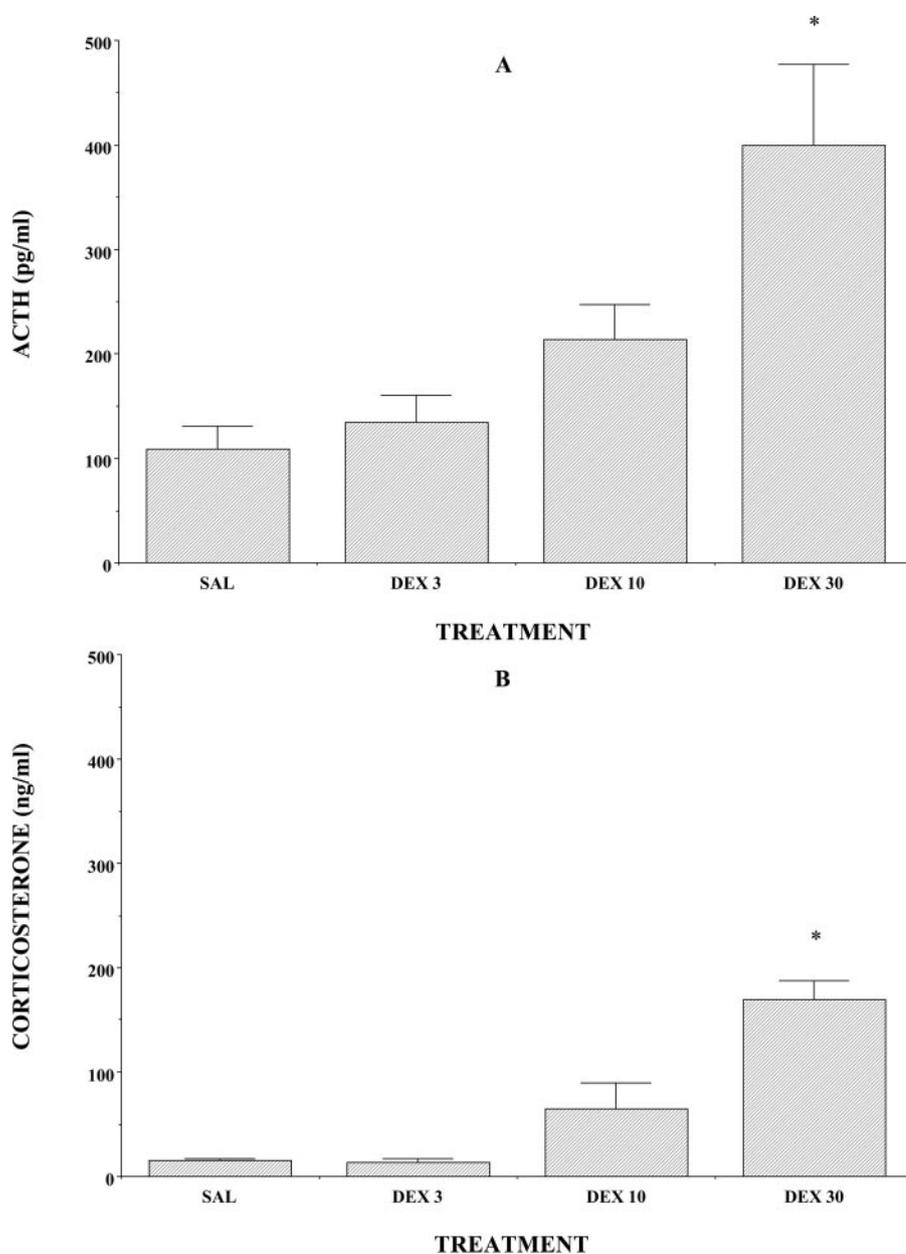
Fig. 3. A and B, effects of dextrorphan (DEX; 3.0, 10.0, or 30.0 mg/kg) on plasma levels of ACTH (A) and corticosterone (B) 60 min after s.c. injection. Values represent the means + the standard errors of the mean (n = 7–9). *, $p < 0.05$ compared with saline-treated controls.

In agreement with a previous report (Eisenberg and Sparber, 1979), levorphanol, the levorotatory enantiomer of dextrorphan, also stimulated the HPA axis. Levorphanol has a 4000-fold higher affinity than dextrorphan for opioid binding sites (Pert and Snyder, 1973). This stereospecificity is supported by the finding that levorphanol is a potent opioid analgesic, whereas dextrorphan has negligible analgesic activity (Benson et al., 1953). Many opioid agonists stimulate the HPA axis in the rat by interacting with central opioid target sites (Pechnick, 1993). The effects of levorphanol on the HPA axis were completely blocked by pretreatment with naloxone, demonstrating that this response is mediated by opioid receptors. However, levorphanol also is a noncompetitive NMDA receptor antagonist (Church et al., 1985). The effects of other noncompetitive NMDA receptor antagonists, such as PCP and (+)–N-allylnormetazocine, are not blocked by naloxone (Pechnick et al., 1989b; Iyengar et al., 1990). It is surprising that some component of the levorphanol-induced

stimulation of the HPA axis was not naloxone-resistant. However, levorphanol is a weak NMDA receptor antagonist (Church et al., 1985; Franklin and Murray, 1992), and at doses tested NMDA antagonist activity might make a minor contribution to the response.

Although dextromethorphan is O-demethylated in vivo to produce dextrorphan, the data do not support the hypothesis that the pharmacological activity of dextromethorphan is a consequence of the formation of this metabolite. First, the effects of dextromethorphan occurred more rapidly and reached a maximum at an earlier time point than the dextrorphan-induced responses. This suggests that at least some of the effects on the HPA axis were due to the parent compound, and not the metabolite. Second, that data indicate that the concentration of dextrorphan formed from dextromethorphan most likely was too low to be pharmacologically relevant. Sixty minutes after drug administration, the mean plasma level of dextrorphan was approximately 3% of the
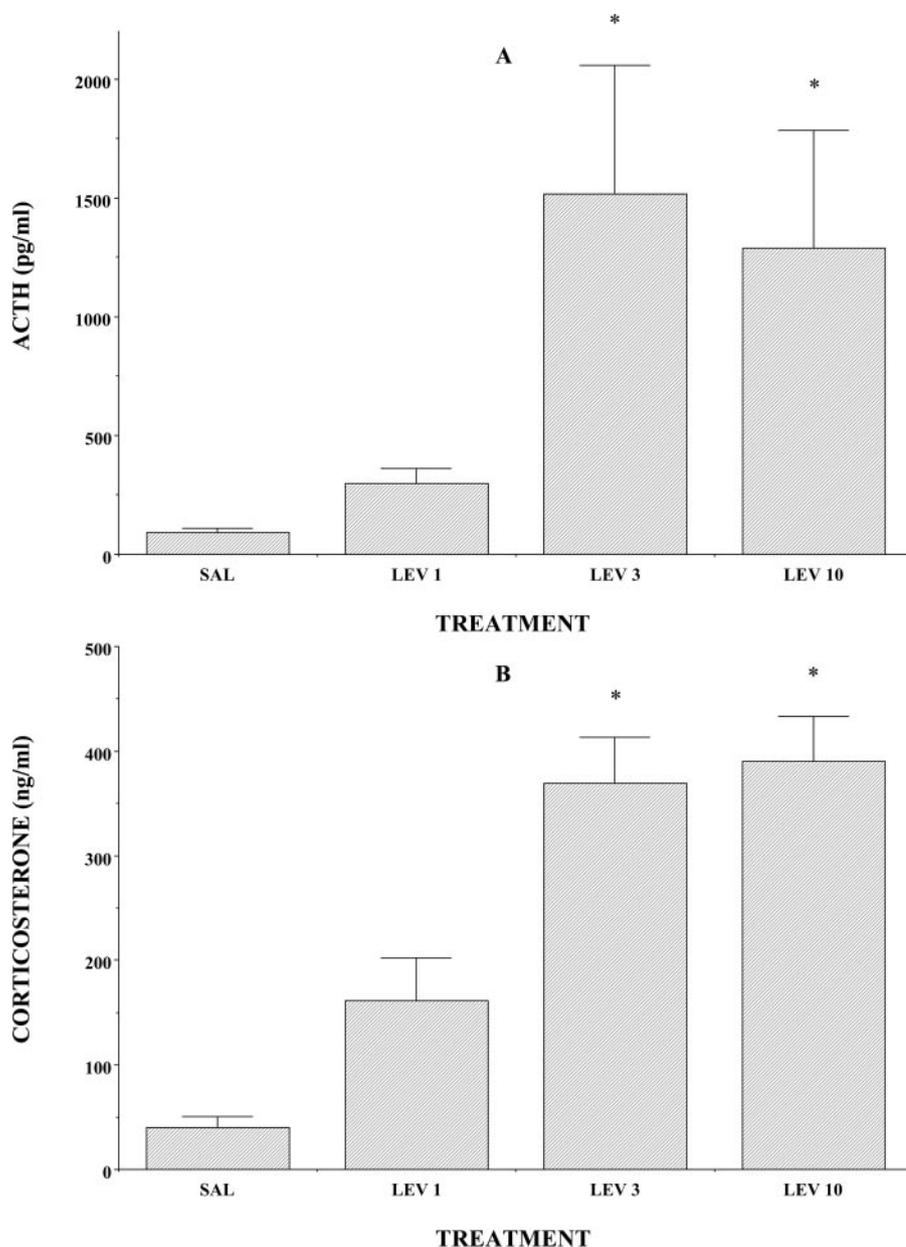
Fig. 4. A and B, effects of levorphanol (LEV; 1.0, 3.0, or 10.0 mg/kg) on plasma levels of ACTH (A) and corticosterone (B) 60 min after s.c. injection. Values represent the means + the standard errors of the mean ($n = 10$). *, $p < 0.05$ compared with saline-treated controls.

plasma level of dextromethorphan. Moreover, the plasma concentration of dextrorphan found after the administration of a dose of dextrorphan that caused a significant rise in plasma ACTH was approximately 24-fold higher than the plasma concentration of dextrorphan found after dextromethorphan administration. Although not determined in the present study, the brain levels of dextrorphan might have been even lower due to the higher lipophilicity of dextromethorphan. Supporting this supposition, Wu et al. (1995) have found that after the s.c. administration of the same dose of dextromethorphan (30.0 mg/kg), the brain/plasma ratio of dextromethorphan was 15.5, whereas the brain/plasma ratio of dextrorphan was 5.0 at the time of peak plasma concentration. It should be noted that plasma levels of the drugs were measured at only one time point, and it is possible that higher concentrations of dextrorphan might have occurred at earlier time points. Moreover, dextromethorphan might be metabolized to dextrorphan within the brain and could possibly reach concentrations much higher than found in the plasma.

The data from the present study strongly suggest that dextromethorphan has pharmacological activity in addition to its biotransformation to dextrorphan. Several studies support this hypothesis. Dark Agouti rats cannot convert dextromethorphan to dextrorphan because they lack CYP2D1, the enzyme responsible for the O-demethylation of dextromethorphan to dextrorphan in rats. Therefore, any effects produced by dextromethorphan are not a consequence of its conversion to dextrorphan. Comparing dark Agouti to Sprague-Dawley rats, Ishmael et al., (1998) found no differences between dextromethorphan and dextrorphan in the time to peak effect or potency. Furthermore, neither the discriminative stimulus (Gavend et al., 1995) nor the anticonvulsant (Kim et al., 2003) effects of dextromethorphan seem to result primarily from its metabolism to dextrorphan. Although some studies have found no difference between the
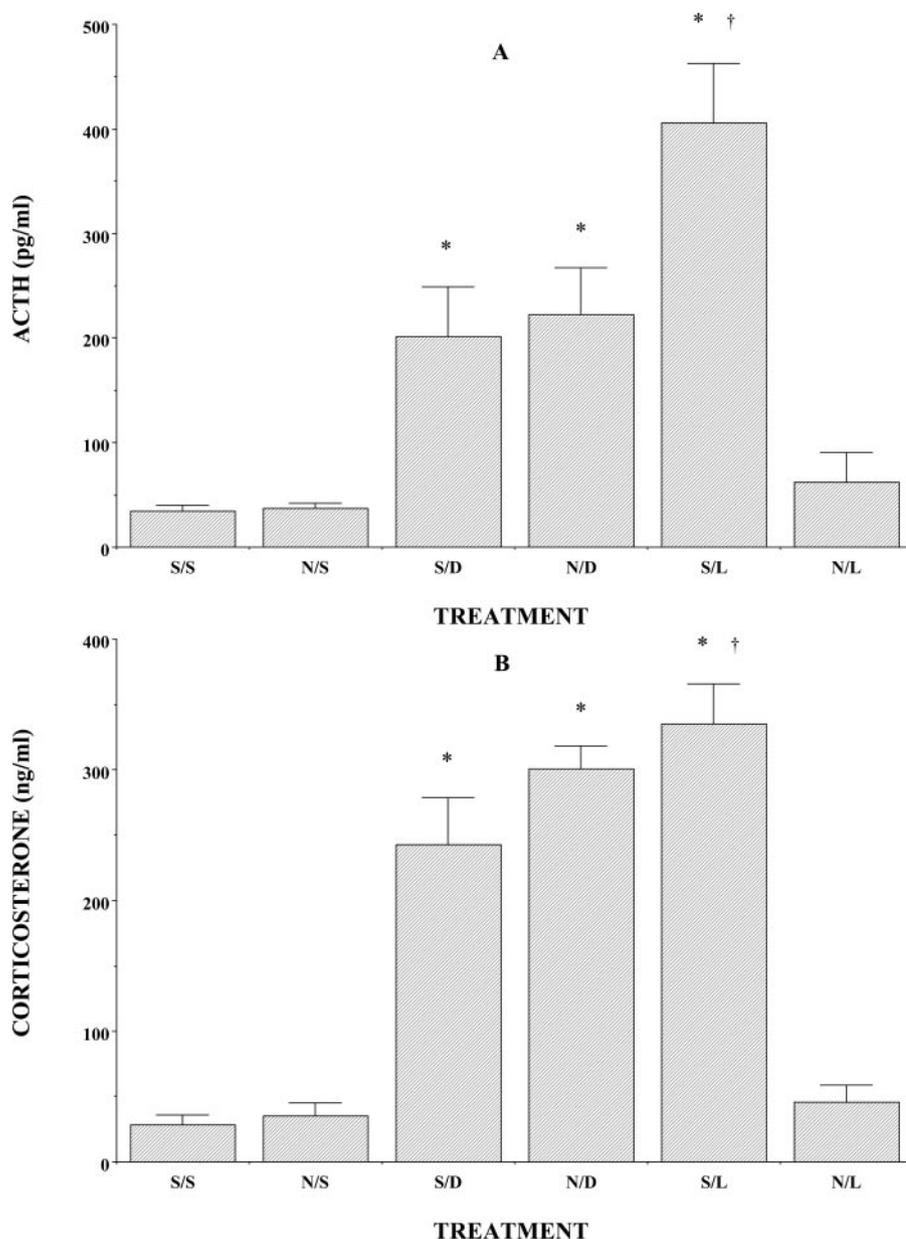
Fig. 5. A and B, effects of pretreatment with saline (S) or naloxone (N; 2.0 mg/kg) on plasma levels of ACTH (A) and corticosterone (B) 60 min after s.c. injection of S, dextrorphan (D; 30.0 mg/kg), or levorphanol (L; 3.0 mg/kg). Values represent the means + the standard errors of the mean (n = 8–10). ∗, $p < 0.05$ compared with saline/saline- or naloxone/saline-treated subjects; †, $p < 0.05$ compared with naloxone/levorphanol-treated subjects.

behavioral syndromes produced by dextromethorphan and dextrorphan (Ishmael et al., 1998), others have found different behavioral profiles (Dematteis et al., 1998). The nature and the clinical relevance of the non-NMDA receptor-mediated effects of dextromethorphan are unknown.

NMDA antagonists have been suggested be useful in the treatment of various neurological disorders (Choi et al., 1987; Steinberg et al., 1996), and they are in various stages of clinical testing (Muir and Lees, 1995). They also might have utility in attenuating tolerance to opioids, reducing opioid withdrawal and inhibiting the reinforcing properties of a variety of abused drugs (Elliot et al., 1994; Herman et al., 1995; Jun and Schindler, 2000; Soyka et al., 2000). Given that fact that dextromethorphan is a weaker NMDA receptor antagonist than dextrorphan (Church et al., 1985, 1989; Ishmael et al., 1998), dextromethorphan might be efficacious because it acts as a prodrug (Choi et al., 1987). Humans can be categorized as being "poor" or "extensive" metabolizers of dextromethorphan (Schmid et al., 1985), with the latter

group rapidly converting dextromethorphan to dextrorphan. Because noncompetitive NMDA receptor antagonists can produce psychotomimetic effects in humans, it is possible that extensive metabolizers of dextromethorphan might be more prone to develop adverse behavioral reactions after drug administration, and preclude the use of dextromethorphan in all but the most dire circumstances. Furthermore, the abuse of dextromethorphan also might be linked to individual differences in the rate and extent of metabolism of dextromethorphan to dextrorphan. Zawertailo et al. (1998) have suggested that poor metabolizers might be less likely to abuse dextromethorphan. Thus, the issues of the biotransformation of dextromethorphan to dextrorphan, as well as the relative pharmacological activity of dextromethorphan compared with dextrorphan, might have clinical relevance.

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