British Journal of Pharmacology (2005) 144, 400–404
www.nature.com/bjp

Dextromethorphan differentially affects opioid antinociception in rats

[1]Shiou-Lan Chen, [2]Eagle Yi-Kung Huang, [1]Lok-Hi Chow & *,[2]Pao-Luh Tao

[1]Graduate Institute of Medical Science, National Defense Medical Center, 161 Minchuan East Road, Sec. 6 Taipei, Taiwan, Republic of China and [2]Department of Pharmacology, National Defense Medical Center, 161 Minchuan East Road, Sec. 6 Taipei, Taiwan, Republic of China

1 Opioid drugs such as morphine and meperidine are widely used in clinical pain management, although they can cause some adverse effects. A number of studies indicate that *N*-methyl-D-aspartate (NMDA) receptors may play a role in the mechanism of morphine analgesia, tolerance and dependence. Being an antitussive with NMDA antagonist properties, dextromethorphan (DM) may have some therapeutic benefits when coadministered with morphine. In the present study, we investigated the effects of DM on the antinociceptive effects of different opioids. We also investigated the possible pharmacokinetic mechanisms involved.

2 The antinociceptive effects of the μ-opioid receptor agonists morphine (5 mg kg^{-1}, s.c.), meperidine (25 mg kg^{-1}, s.c.) and codeine (25 mg kg^{-1}, s.c.), and the κ-opioid agonists nalbuphine (8 mg kg^{-1}, s.c.) and U-50,488H (20 mg kg^{-1}, s.c.) were studied using the tail-flick test in male Sprague–Dawley rats. Coadministration of DM (20 mg kg^{-1}, i.p.) with these opioids was also performed and investigated.

3 The pharmacokinetic effects of DM on morphine and codeine were examined, and the free concentration of morphine or codeine in serum was determined by HPLC.

4 It was found that DM potentiated the antinociceptive effects of some μ-opioid agonists but not codeine or κ-opioid agonists in rats. DM potentiated morphine's antinociceptive effect, and acutely increased the serum concentration of morphine. In contrast, DM attenuated the antinociceptive effect of codeine and decreased the serum concentration of its active metabolite (morphine).

5 The pharmacokinetic interactions between DM and opioids may partially explain the differential effects of DM on the antinociception caused by opioids.
British Journal of Pharmacology (2005) **144,** 400–404. doi:10.1038/sj.bjp.0706086
Published online 10 January 2005

Keywords: Opioid drugs; dextromethorphan; antinociception

Abbreviations: AUC, area under the time–response curve; DM, dextromethorphan; HPLC, high-performance liquid chromatography; NMDA, *N*-methyl-D-aspartate

Introduction

The opioid drugs such as morphine, meperidine, etc. are still the most effective analgesic drugs used in the treatment of severe and chronic pain. There are three major types of opioid receptors, mu (μ), delta (δ) and kappa (κ), which are expressed in the brain and spinal cord. The opioid drugs act on the corresponding opioid receptors and produce their antinociceptive effects. However, side effects such as vomiting, pruritus, respiratory depression, tolerance and dependence have restricted their clinical use. Dextromethorphan (DM) is the dextrorotatory isomer of levomethorphan, but lacks opioid-like activity and is best known for its antitussive effects (Wang *et al*., 1977). DM has been demonstrated to have anticonvulsant (Ferkany *et al*., 1988) and neuroprotective properties through antagonizing the glycine and Mg^{2+} sites, as well as the phencyclidine-binding site on the *N*-methyl-D-aspartate (NMDA) receptor complex. DM has been shown to prevent the development of tolerance to the antinociceptive effects of morphine in rodents (Elliott *et al*., 1994a; Mao *et al*., 1996; Manning *et al*., 1996). DM also attenuated signs of naloxone-precipitated withdrawal in morphine-dependent rats (Mao *et al*., 1996; Manning *et al*., 1996). DM is a particularly attractive candidate for clinical use since it has been dispensed as a nonprescription drug for over 40 years and is known to have a wide margin of safety. It has been reported that coadministration of DM with morphine or methadone could potentiate their antinociceptive effects (Grass *et al*., 1996; Hoffmann & Wiesenfeld-Hallin, 1996; Bulka *et al*., 2002); however, the mechanism is not clear.

There are two major aims in the present study. One is to investigate the effects of DM on the antinociceptive effects of different opioids; the second is to investigate the possible pharmacokinetic mechanism involved.

Methods

Animals

Male Sprague–Dawley rats, weighing 350–400 g, were purchased from the National Experimental Animal Centre, Taipei, Taiwan. All rats were kept in an animal room with a 12 h light/dark cycle, at a temperature of 25±2°C and

*Author for correspondence; E-mail: pltao@ndmctsgh.edu.tw
Published online 10 January 2005

humidity of 55%. Standard diet and water were provided *ad libitum*. The animals were acclimated for at least 3 days before the experiments. The care of animals was carried out in accordance with institutional and international standards (Principles of Laboratory Animal Care, NIH) and the protocol has got approval from the Institutional Animal Care and Use Committee of National Defense Medical Center, Taiwan, R.O.C.

Determination of the antinociceptive effect of drugs

Selected doses of opioids with submaximal antinociceptive effect (morphine 5 mg kg^{-1}, meperidine 25 mg kg^{-1}, codeine 25 mg kg^{-1}, nalbuphine 8 mg kg^{-1} or U-50,488H 20 mg kg^{-1}) were administered to different groups of rats subcutaneously (s.c.). DM (20 mg kg^{-1}; i.p.) was coadministered with the opioid in other comparative groups. Saline (1 ml kg^{-1}; i.p.) was administered in control group. There were at least six rats in each group and different rats were used in each experiment. Drug-induced antinociception was evaluated using the tail-flick test (Amour & Smith, 1941). Using a tail-flick apparatus (Model: DS-20, Ugo Basile, Italy), tail-flick latency was recorded at 30, 60, 90, 120, 150, 180 min after drug administration. The intensity of the heat source was set to make the basal tail-flick latency to be controlled between 2.5 and 3.5 s for all animals (cutoff: 10 s). The area under the time–response curve (AUC) was calculated using the Trapezoidal and Simpson's rules. The AUC value was regarded as an index of the antinociceptive effect of the drug(s).

In vivo *pharmacokinetic study*

Individual rats were placed in a restrainer, and blood (0.5–1 ml) was collected from the tail vein at the 30, 60, 90, and 150 min after drug administration. The blood was collected from the same animal at different time points, and the animals were not used in the tail-flick test. The whole blood sample was centrifuged at $3000 \times g$ for 10 min at 4°C. The serum was collected and filtered through Millipore Amicon Microcon YM-3 centrifugal filters (MW cut-off 3000) at $17{,}800 \times g$ for 40 min at 4°C. The recovery rate of the filtration is 100%. The filtered sample was then injected into the high-performance liquid chromatography (HPLC) system for the measurement of free drug concentration. The free form of morphine was determined as described below in HPLC analysis.

High-performance liquid chromatography (HPLC analysis)

We used a HPLC method for the quantification of the morphine concentration in serum. Quantification was performed by HPLC-coupled electrochemical detection. Using linear regression, calibration curves (standard curves) were constructed and covered a wide range of concentrations (10–1000 nM). The samples were compared with the standard curves to determine their contents of drugs. The electrochemical chromatographic system consisted of a pump (LC-10AD, Shimadzu, Japan), a TSKgel ODS-80T$_M$ C18 column (Tosoh, Japan), and an electrochemical detector (ESA Coulochem II, Chelmsford, MA, U.S.A.) containing a 5020 guard cell and 5010 analytical cells. For the determination of the free form of morphine in serum, 20 μl samples were injected into the HPLC system. The voltages of the guard cell and analytical cells were set at 650 and 550 mV (detecting potential), respectively. The mobile phase (ESA MDTM mobile phase) consisted of 75 mM sodium dehydrogenate phosphate (monohydrate), 1.7 mM 1-octanesulfonic acid (sodium salt), 100 μl l^{-1} triethylamine, 25 μM EDTA, 10% acetonitrile, pH 3.00, which was delivered at a flow rate of 1.0 ml min^{-1}.

Statistical analysis

The data were expressed as means ± s.e.m. One-way ANOVA and Newman–Keuls test were used to analyze the data. A difference was considered to be significant at $P<0.05$ or $P<0.01$.

Chemicals

Morphine hydrochloride, meperidine, and codeine were purchased from the National Bureau of Controlled Drugs, National Health Administration, Taipei, Taiwan, R.O.C. Nalbuphine was purchased from Mallinckrodt Inc. (St Louis, Missouri, U.S.A.). U-50,488H was a gift from Dr Chen-Yu Cheng, who prepared it as described in our previous paper (Su *et al*., 1998). All other chemicals were supplied by Sigma (St Louis, MO, U.S.A.). The chemicals were all of analytical grade and the solvents were of HPLC grade.

Results

DM potentiated the antinociceptive effects of morphine and meperidine but not codeine or kappa-opioid agonists in rats

As shown in Figure 1, coadministration of DM (20 mg kg^{-1}) acutely and significantly increased the antinociceptive effect of morphine (5 mg kg^{-1}) ($P<0.01$). Similarly, coadministration of DM (20 mg kg^{-1}) also significantly potentiated the antinociceptive effect of meperidine (mg kg^{-1}). However, DM did not potentiate the antinociceptive effect of another μ-opioid agonist – codeine (25 mg kg^{-1}) – and, in addition, it decreased

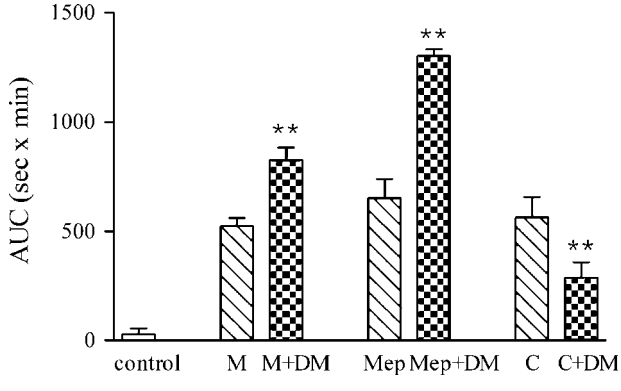

Figure 1 The effect of DM (20 mg kg^{-1}, i.p.) on the antinociceptive effect of mu opioid agonists: morphine (M; 5 mg kg^{-1}, s.c.); meperidine (Mep; 25 mg kg^{-1}, s.c.) and codeine (C; 25 mg kg^{-1}, s.c.). Values are means ± s.e.m. ANOVA and Newman–Keuls test were used to analyze the data. $^{**}P<0.01$ represents a significant difference between the opioid and opioid + DM groups.

codeine's effect. Conversely, DM did not affect the antinociceptive effect of the κ-opioid agonists: U-50,488H (20 mg kg^{-1}) or nalbuphine (8 mg kg^{-1}) (Figure 2). These results indicate that DM had differential effects on the antinociceptive effect of different opioid agonists in rats. Most interestingly, DM showed opposite effects on opioid agonists acting on the same μ-opioid receptors, such as morphine and codeine. In order to investigate whether pharmacokinetic mechanisms are involved, we carried out the following study in pharmacokinetics.

The effect of DM on the serum concentration of the free form of morphine

When DM was coadministered with morphine, the serum concentration of morphine (free form) was higher than in the morphine group after drug administration, as shown in Figure 3a and b. In contrast, when DM was coadministered with codeine, the serum concentration of morphine (the active metabolite of codeine) was lower than in the codeine group (Figure 4). These data indicate that DM increased the serum concentration of morphine and potentiated the antinociceptive effect of morphine (Figures 1 and 3). Conversely, DM decreased the serum concentration of morphine and therefore attenuated the antinociceptive effect of codeine (Figures 1 and 4).

Discussion

A number of studies indicate that NMDA receptor antagonists such as MK-801, LY274614 and ketamine can attenuate the development of morphine tolerance and dependence (Kest *et al*., 1993; Gutstein & Trujillo, 1993; Elliott *et al*., 1994b; Tiseo *et al*., 1994; Trujillo & Akil, 1994; Herman *et al*., 1995; Manning *et al*., 1996; Mao *et al*., 1996). However, MK-801 has been shown to have great toxicity to animals and cannot be used in clinical treatment. Owing to its NMDA antagonist action and lower toxic properties, DM has been used with morphine to test if DM could prevent the development of morphine tolerance and dependence. Studies have shown that DM can attenuate and reverse analgesic tolerance to morphine (Elliott *et al*., 1994a; Mao *et al*., 1996). On the other hand, recent animal studies have reported the potentiation of opioid antinociception by coadministration of NMDA receptor antagonists such as MK-801, ketamine and DM (Grass *et al*., 1996; Hoffmann & Wiesenfeld-Hallin, 1996; Zhu *et al*., 2003).

In the present study, we found that DM significantly potentiated the antinociceptive effects of certain μ-opioid agonists such as morphine or meperidine, but not the κ-opioid

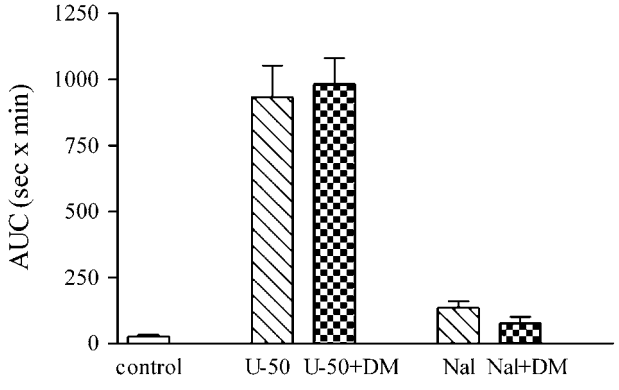

Figure 2 The effect of DM (20 mg kg^{-1}, i.p.) on the antinociceptive effect of kappa opioid agonists: U-50,488 (U-50; 20 mg kg^{-1}, s.c.) and nalbuphine (Nal; 8 mg kg^{-1}, s.c.). Values are means ± s.e.m. ANOVA and Newman–Keuls test were used to analyze the data.

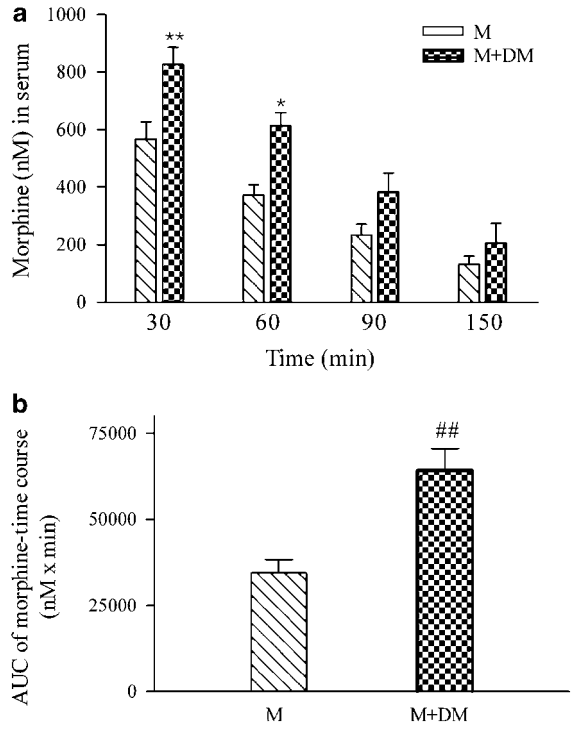

Figure 3 The pharmacokinetic effect of dextromethorphan (DM; 20 mg kg^{-1}, i.p.) on the morphine (M; 5 mg kg^{-1}, s.c.). (a) Time course of the serum concentration of morphine (nM) after drug administration. (b) Area under curve (AUC) value of upper plot in (a). ANOVA and Newman–Keuls test were used to analyze the data. Values are means ± s.e.m. $^{*}P<0.05$, $^{**}P<0.01$ represents a significant difference between the M and M + DM groups at the same time. $^{\#\#}P<0.01$ represents a significant difference of AUC value between the M and M + DM groups.

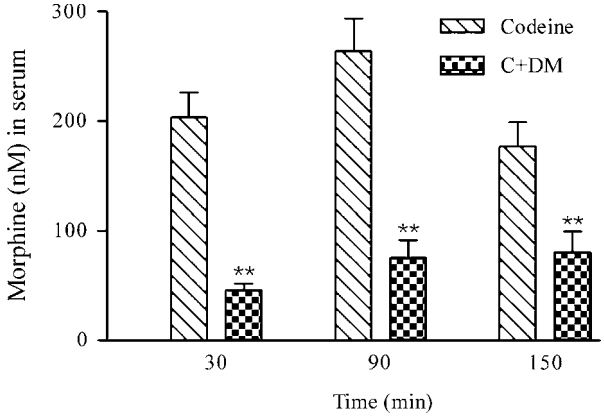

Figure 4 The pharmacokinetic effect of dextromethorphan (DM; 20 mg kg^{-1}, i.p.) on the codeine (C; 25 mg kg^{-1}, s.c.). ANOVA and Newman-Keuls test were used to analyze the data. Values are means ± s.e.m. $^{**}P<0.01$ represents a significant difference between the C and C + DM groups at the same time.

agonists U-50,488H or nalbuphine in rats. These results are consistent with the previous report that DM potentiates the antinociceptive effects of μ- but not κ-opioid agonists in a mouse model of acute pain (Allen *et al*., 2002; Baker *et al*., 2002). Morphine is a natural opiate that is metabolized mainly through glucuronidation by uridine diphosphate glucuronosyl transferase (UGT) 2B enzymes in the liver (Pritchard *et al*., 1994; Coffman *et al*., 1997; King *et al*., 2000). DM undergoes O-demethylation to dextrorphan and N-demethylation to 3-methoxymorphinan. The N-demethylation of DM to 3-methoxymorphinan is catalyzed primarily by cytochrome *P*450 3A (CYP3A) enzymes in the liver. The O-demethylation pathway to dextrorphan is catalyzed primarily by cytochrome *P*450 2D6 (CYP2D6) enzymes in the human liver (Dayer *et al*., 1988; Ladona *et al*., 1991; Jacqz-Aigrain & Cresteil, 1992; Jacqz-Aigrain *et al*., 1993).

As mentioned above, morphine and DM are metabolized in different metabolic pathways. How could DM increase the serum concentration of morphine? The exact mechanism is unknown. However, liver microsomal studies have shown inhibition of morphine-3-glucuronide (M3G) formation by DM (Wahlstrom *et al*., 1988) and this may play a role in the mechanism of DM to potentiate morphine antiniciceptive effect. On the other hand, in our other studies, we found that intrathecal DM also potentiated the antinociceptive effect of morphine at the spinal level, in addition to the potentiation by DM injected systemically (Chow *et al*., 2004). Therefore, apart from the pharmacokinetic factor, there must be some other mechanism(s) involved in the effects of DM in potentiating morphine antinociception.

Codeine is widely used for analgesia and cough suppression. Its analgesic effect is through its active metabolite morphine and therefore, codeine is classified as a μ-opioid agonist. In the present study, DM potentiated the antinociceptive effect of two μ-opioid agonists: morphine and meperidine, but not codeine. Why? Is the pharmacokinetic factor involved again in this case? We know that codeine is metabolized by CYP2D6 to the more potent drug morphine in human liver (Dayer *et al*., 1988; Ladona *et al*., 1991) but metabolized by CYP2D1 in rats (Cleary *et al*., 1994). DM is also a potent CYP2D1 substrate (Kerry *et al*., 1993; Tyndale *et al*., 1999) and has been shown to be an inhibitor of morphine formation from codeine (Mikus *et al*., 1991). Our results have shown that coadministration of DM with codeine decreases the serum morphine concentration, metabolized from codeine. This indicates that CYP2D1 inhibition by DM may result in a decrease in the analgesic effects of codeine in rats.

In summary, DM can differentially potentiate the antinociceptive effect of μ-opioid agonists in rats, and pharmacokinetic factor(s) may be one of the important mechanisms involved.

This study was supported by the grant from National Health Research Institutes, Taiwan, R.O.C. (NHRI-EX-92-8909BP) and was supported in part by the C.Y. Chai Foundation for Advancement of Education, Science and Medicine, Taiwan, R.O.C.

References

ALLEN, R.M., GRANGER, A.L. & DYKSTRA, L.A. (2002). Dextromethorphan potentiates the antinociceptive effects of morphine and the delta-opioid agonist SNC80 in squirrel monkeys. *J. Pharmacol. Exp. Ther.,* **300,** 435–441.

AMOUR, E.E. & SMITH, D.L. (1941). A method for determining loss of pain sensation. *J. Pharmacol. Exp. Ther.,* **72,** 74–79.

BAKER, A.K., HOFFMANN, V.L. & MEERT, T.F. (2002). Dextromethorphan and ketamine potentiate the antinociceptive effects of mu- but not delta- or kappa-opioid agonists in a mouse model of acute pain. *Pharmacol. Biochem. Behav.,* **74,** 73–86.

BULKA, A., WIESENFELD-HALLIN, Z. & XU, X.J. (2002). Differential antinociception by morphine and methadone in two sub-strains of Sprague–Dawley rats and its potentiation by dextromethorphan. *Brain Res.,* **942,** 95–100.

CHOW, L.-H., HUNG EAGLE, Y.-K., HO, S.-T., LEE, T.-Y. & TAO, P.-L. (2004). Dextromethorphan potentiates morphine antinociception at the spinal level in rats. *Can. J. Anesth.,* **51,** 905–910.

CLEARY, J., MIKUS, G., SOMOGYI, A. & BOCHNER, F. (1994). The influence of pharmacogenetics on opioid analgesia: studies with codeine and oxycodone in the Sprague–Dawley/Dark Agouti rat model. *J. Pharmacol. Exp. Ther.,* **271,** 1528–1534.

COFFMAN, B.L., RIOS, G.R., KING, C.D. & TEPHLY, T.R. (1997). Human UGT2B7 catalyzes morphine glucuronidation. *Drug Metab. Dispos.,* **25,** 1–4.

DAYER, P., DESMEULES, J., LEEMANN, T. & STRIBERNI, R. (1988). Bioactivation of the narcotic drug codeine in human liver is mediated by the polymorphic monooxygenase catalyzing debrisoquine 4-hydroxylation (cytochrome *P*-450 dbl/bufI). *Biochem. Biophys. Res. Commun.,* **152,** 411–416.

ELLIOTT, K., HYNANSKY, A. & INTURRISI, C.E. (1994a). Dextromethorphan attenuates and reverses analgesic tolerance to morphine. *Pain,* **59,** 361–368.

ELLIOTT, K., MINAMI, N., KOLESNIKOV, Y.A., PASTERNAK, G.W. & INTURRISI, C.E. (1994b). The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, *NG*-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids. *Pain,* **56,** 69–75.

FERKANY, J.W., BOROSKY, S.A., CLISSOLD, D.B. & PONTECORVO, M.J. (1988). Dextromethorphan inhibits NMDA-induced convulsions. *Eur. J. Pharmacol.,* **151,** 151–154.

GRASS, S., HOFFMANN, O., XU, X.J. & WIESENFELD-HALLIN, Z. (1996). *N*-methyl-D-aspartate receptor antagonists potentiate morphine's antinociceptive effect in the rat. *Acta Physiol. Scand,* **158,** 269–273.

GUTSTEIN, H.B. & TRUJILLO, K.A. (1993). MK-801 inhibits the development of morphine tolerance at spinal sites. *Brain Res.,* **626,** 332–334.

HERMAN, B.H., VOCCI, F. & BRIDGE, P. (1995). The effects of NMDA receptor antagonists and nitric oxide synthase inhibitors on opioid tolerance and withdrawal. Medication development issues for opiate addiction. *Neuropsychopharmacology,* **13,** 269–293.

HOFFMANN, O. & WIESENFELD-HALLIN, Z. (1996). Dextromethorphan potentiates morphine antinociception, but does not reverse tolerance in rats. *Neuroreport,* **7,** 838–840.

JACQZ-AIGRAIN, E. & CRESTEIL, T. (1992). Cytochrome *P*450-dependent metabolism of dextromethorphan: fetal and adult studies. *Dev. Pharmacol. Ther.,* **18,** 161–168.

JACQZ-AIGRAIN, E., FUNCK-BRENTANO, C. & CRESTEIL, T. (1993). CYP2D6- and CYP3A-dependent metabolism of dextromethorphan in humans. *Pharmacogenetics,* **3,** 197–204.

KERRY, N.L., SOMOGYI, A.A., MIKUS, G. & BOCHNER, F. (1993). Primary and secondary oxidative metabolism of dextromethorphan. *In vitro* studies with female Sprague–Dawley and Dark Agouti rat liver microsomes. *Biochem. Pharmacol.,* **45,** 833–839.

KEST, B., MOGIL, J.S., SHAMGAR, B.E., KAO, B., LIEBESKIND, J.C. & MAREK, P. (1993). The NMDA receptor antagonist MK-801 protects against the development of morphine tolerance after intrathecal administration. *Proc. West Pharmacol. Soc.,* **36,** 307–310.

KING, C., FINLEY, B. & FRANKLIN, R. (2000). The glucuronidation of morphine by dog liver microsomes: identification of morphine-6-*O*-glucuronide. *Drug Metab. Dispos.,* **28,** 661–663.

LADONA, M.G., LINDSTROM, B., THYR, C., DUN-REN, P. & RANE, A. (1991). Differential foetal development of the O- and N-demethylation of codeine and dextromethorphan in man. *Br. J. Clin. Pharmacol.,* **32,** 295–302.

MANNING, B.H., MAO, J., FRENK, H., PRICE, D.D. & MAYER, D.J. (1996). Continuous co-administration of dextromethorphan or MK-801 with morphine: attenuation of morphine dependence and naloxone-reversible attenuation of morphine tolerance. *Pain,* **67,** 79–88.

MAO, J., PRICE, D.D., CARUSO, F.S. & MAYER, D.J. (1996). Oral administration of dextromethorphan prevents the development of morphine tolerance and dependence in rats. *Pain,* **67,** 361–368.

MIKUS, G., SOMOGYI, A.A., BOCHNER, F. & EICHELBAUM, M. (1991). Codeine O-demethylation: rat strain differences and the effects of inhibitors. *Biochem. Pharmacol.,* **41,** 757–762.

PRITCHARD, M., FOURNEL-GIGLEUX, S., SIEST, G., MACKENZIE, P. & MAGDALOU, J. (1994). A recombinant phenobarbital-inducible rat liver UDP-glucuronosyltransferase (UDP-glucuronosyltransferase 2B1) stably expressed in V79 cells catalyzes the glucuronidation of morphine, phenols, and carboxylic acids. *Mol. Pharmacol.,* **45,** 42–50.

SU, M.-T., LIN, W.-B., LUE, W.-M., CHENG, C.-Y. & TAO, P.-L. (1998). Blockade of the development of morphine tolerance by U-50, 488, an AVP antagonist or MK-801 in the rat hippocampal slice. *Br. J. Pharmacol.,* **123,** 625–630.

TISEO, P.J., CHENG, J., PASTERNAK, G.W. & INTURRISI, C.E. (1994). Modulation of morphine tolerance by the competitive *N*-methyl-D-aspartate receptor antagonist LY274614: assessment of opioid receptor changes. *J. Pharmacol. Exp. Ther.,* **268,** 195–201.

TRUJILLO, K.A. & AKIL, H. (1994). Inhibition of opiate tolerance by non-competitive *N*-methyl-D-aspartate receptor antagonists. *Brain Res.,* **633,** 178–188.

TYNDALE, R.F., LI, Y., LI, N.Y., MESSINA, E., MIKSYS, S. & SELLERS, E.M. (1999). Characterization of cytochrome *P*-450 2D1 activity in rat brain: high-affinity kinetics for dextromethorphan. *Drug Metab. Dispos.,* **27,** 924–930.

WAHLSTROM, A., PACIFICI, G.M., LINDSTROM, B., HAMMAR, L. & RANE, A. (1988). Human liver morphine UDP-glucuronyl transferase enantioselectivity and inhibition by opioid congeners and oxazepam. *Br. J. Pharmacol.,* **94,** 864–870.

WANG, S.C., CHOU, D.T. & WALLENSTEIN, M.C. (1977). Studies on the potency of various antitussive agents. *Agents Actions,* **7,** 337–340.

ZHU, H., JENAB, S., JONES, K.L. & INTURRISI, C.E. (2003). The clinically available NMDA receptor antagonist dextromethorphan attenuates acute morphine withdrawal in the neonatal rat. *Brain Res. Dev. Brain Res.,* **142,** 209–213.

(Received July 19, 2004
Revised October 19, 2004
Accepted November 4, 2004)