ELSEVIER

European Journal of Pharmacology 453 (2002) 197–202

www.elsevier.com/locate/ejphar

Dextromethorphan attenuates morphine withdrawal syndrome in neonatal rats passively exposed to morphine

Geng-Chang Yeh[a,b,*], Pao-Luh Tao[c], Julia Yi-Ru Chen[a], Ming-Cherng Lai[b], Fong-Shui Gao[b], Chum-Lin Hu[d]

[a] *Department of Pediatrics, Taipei Medical University Hospital, Taipei Medical University, Taipei, Taiwan, ROC*
[b] *Graduate Institute of Medical Science, Taipei Medical University, Taipei, Taiwan, ROC*
[c] *Department of Pharmacology, National Defense Medical Center, Taipei Medical University, Taipei, Taiwan, ROC*
[d] *Graduate Institute of Cell and Molecular Biology, Taipei Medical University, Taipei, Taiwan, ROC*

Received 2 May 2002; received in revised form 6 September 2002; accepted 12 September 2002

Abstract

We had previously found that co-injection of dextromethorphan, an antitussive drug and a non-competitive NMDA receptor antagonist, with morphine into dam rats throughout the pregnancy period could attenuate the naloxone-precipitated morphine withdrawal syndrome in their offspring. In the present study, we further tested whether postnatal injection of dextromethorphan into the neonatal rats or a 3-day co-injection of dextromethorphan with morphine into the dam rats before delivery is also effective. Female Sprague–Dawley rats were bi-daily injected with escalating doses of morphine from a week before mating till the first postnatal week. Withdrawal syndrome of morphine in the offspring, manifested mainly as abdominal stretching, was generated by injection of naloxone on postnatal day 5. Direct injection of dextromethorphan into the offspring effectively reduced the severity of naloxone-precipitated abdominal stretching in a dose-dependent manner. A 3-day co-treatment with dextromethorphan given to the dam rat before delivery also had a similar attenuating effect, but the efficacy was lower than that produced by postnatal injection. Thus, the results from the present study support that dextromethorphan is of potential in treating or preventing neonatal morphine withdrawal syndrome.

Keywords: NMDA receptor; Naloxone; Addiction; MK-801

1. Introduction

Infants passively exposed to morphine or heroin through their addicted mothers usually develop a characteristic morphine withdrawal syndrome after birth. The withdrawal symptoms include jitteriness, irritability, shrill crying, hyperactivity– hypertonicity, poor feeding, vomiting, diarrhea, sneezing, tachypnea, and seizure (Volpe, 1995). Most newborns presenting with apparent features of withdrawal syndrome require intensive care. In addition to supportive therapy to stabilize vital signs, drug therapy with paregoric, phenobarbital, chlorpromazine or diazepam is frequently used to minimize the symptoms of the central nervous and gastrointestinal systems. Although these medications can effectively attenuate most of the symptoms, their side effects in the central nervous system (CNS) require careful monitoring. Thus, to improve the treatment outcome for neonatal morphine withdrawal syndrome, development of new effective medication is necessary.

Activation of the NMDA receptor has been implicated in the expression of morphine withdrawal syndrome. Pretreatment with competitive antagonists, (±)-6-phosphonomethyl-decahydroisoquinoline-3-carboxylic acid (LY274614), (3*E*)-1-ethyl ester-2-amino-4-methyl-5-phosphono-3-pentenoic acid (CGP39551) (Tiseo et al., 1994; Tokuyama et al., 1996), or non-competitive antagonists of the NMDA receptor, dizocilpine maleate (MK-801), effectively attenuated the naloxone-precipitated withdrawal syndrome in adult rats (Gonzalez et al., 1997; Tanganelli et al., 1991;

* Corresponding author. Department of Pediatrics, Taipei Medical University Hospital, No. 252 Wu-Hsing Street, 110 Taipei, Taiwan, ROC. Tel.: +886-2-27361661-3225; fax: +886-2-23778620.
E-mail address: cmbyeh@tmu.edu.tw (G.-C. Yeh).

0014-2999/02/$ - see front matter © 2002 Elsevier Science B.V. All rights reserved.
PII: S0014-2999(02)02426-3

Tokuyama et al., 1996; Trujillo and Akil, 1991). However, these tested drugs are not yet proven to be safe for clinical use. For example, the use of MK-801 is limited by its narrow therapeutic window and profound side effects on motor functions (Ben-Eliyahu et al., 1992; Rasmussen et al., 1991).

Dextromethorphan, a morphine isomer without any action on the opioid receptor, is used as an antitussive drug. Human subjects can tolerate a wide range of dextromethorphan doses without apparent side effects (Bem and Peck, 1992). Previous reports showed that this compound can act as a non-competitive antagonist of the NMDA receptor by binding to a site inside the NMDA receptor channel, thereby blocking this channel (Church et al., 1994). Animal studies have shown that dextromethorphan can be effective in attenuating a variety of neuropathologies induced by overactivation of the NMDA receptor, including ischemia–hypoxia-induced neuronal injury and seizure (George et al., 1988; Kim et al., 1996; Laroia et al., 1997; Prince and Feeser, 1988; Tortella et al., 1994, 1995). In clinics, dextromethorphan has been used to treat several kinds of neurological diseases, including one severe type of intractable seizure in neonates, non-ketotic hyperglycinemia (Allen, 1993; Hamosh et al., 1992). Recent investigations have shown that dextromethorphan can effectively attenuate the tolerance and withdrawal syndrome of morphine in adult animals without apparent side effect (Farzin, 1999; Mao et al., 1996). Previously, we had found that the co-administration of dextromethorphan with morphine to dam rats throughout pregnancy significantly decreased naloxone-precipitated morphine withdrawal behavior in their offspring (Tao et al., 2001). However, such long-term use of dextromethorphan during pregnancy might expose the fetus to teratogenic toxicity of dextromethorphan and is less applicable if clinical use is considered (Andaloro et al., 1998; Einarson et al., 2001). Thus, in the present study, we determined whether a single injection of dextromethorphan given to the offspring postnatally or a 3-day prenatal injection of dextromethorphan given to the dam rats just before delivery could also effectively reduce the naloxone-precipitated morphine withdrawal syndrome in neonatal rats born to morphine-treated dam rats.

2. Methods and materials

2.1. Animals

Female Sprauge–Dawley rats (200–250 g, purchased from National Experimental Animal Center, Taipei, Taiwan) were housed individually in plexiglass cages under a 12-h light–dark cycle at the Animal Center of Taipei Medical University. The room temperature was maintained at 24 °C. Food and water were available ad libitum throughout the experiment. The animal study followed the guidelines of the Animal Center of Taipei Medical University.

2.2. Animal model of pre- and postnatal exposure to morphine

Adult female rats received bi-daily subcutaneous injections of morphine (2 mg/kg) for 7 days before mating. After conception, the dosage of morphine was increased by 1 mg/kg per week. After delivery of the newborn rats, the dosage of morphine was increased by 1 mg/kg till the offspring were used for experiments. Control dam rats received bi-daily injections of normal saline. Rats born to morphine-treated dam rats were denoted as the morphine group rats, and rats born to saline-treated dam rats were denoted as the control group rats.

2.3. Naloxone-induced behavioral changes in the neonatal rats

To precipitate the withdrawal syndrome in the neonatal rats, we subcutaneously injected 1 mg/kg of naloxone, a non-selective opioid receptor antagonist, into the morphine group rats on postnatal day 5. We quantified the frequency and latency of abdominal stretching during a 2-h observation period as an index of the severity of morphine withdrawal syndrome.

2.4. Postnatal treatment with dextromethorphan or MK-801 of the neonatal rats

For the postnatal treatment with dextromethorphan or MK-801, both the control and morphine group rats received a subcutaneous injection of dextromethorphan (2, 5, 10, or 20 mg/kg) or MK-801 (0.5 mg/kg) 30 min before injection of naloxone.

2.5. Prenatal treatment of dextromethorphan or MK-801

A group of morphine-treated dam rats received bi-daily subcutaneous co-injections of dextromethorphan (2, 5, or 10 mg/kg) or MK-801 (0.1 mg/kg) for three consecutive days before delivery. We denoted the offspring, according to the treatment schedule of their dam rats, as follows:

(1) Control group: neonatal rats born to saline-treated dam rats.
(2) Morphine group: neonatal rats born to morphine-treated dam rats.
(3) Morphine/dextromethorphan groups: neonatal rats born to morphine-treated dam rats which had received 2, 5 or 10 mg/kg dextromethorphan treatment, respectively, since 3 days before due date.
(4) Morphine/MK-801 group: neonatal rats born to morphine-treated dam rats which received 0.1 mg/kg MK-801 treatment since 3 days before due date.

2.6. Chemicals

Morphine hydrochloride was purchased from the Narcotic Bureau of the National Health Administration, Taipei, Taiwan, ROC. Naloxone, MK-801, and dextromethorphan were purchased from RBI (Natick, MA).

2.7. Statistic analysis

Ratios of mortality or ratios of rats presenting naloxone-precipitated abdominal stretching were analyzed using Chi-square test. For other data, unpaired *t* test or one-way analysis of variance (ANOVA) with post hoc Newman–Keuls test were used.

3. Results

3.1. Effects of morphine on the number of pups, birth body weight and postnatal mortality

There was no difference in the number of pups per litter between control group and morphine group rats. However, the mortality of morphine group rats was significantly higher and their birth body weight was significantly lower than those of control group rats (Table 1). All deaths among morphine group rats occurred during the first postnatal day. No gross malformation was observed in the morphine group rats, including the dead ones.

3.2. Effects of dextromethorphan or MK-801 on the expression of naloxone-precipitated abdominal stretching

All the morphine group rats on postnatal day 5 showed abdominal stretching after injection of naloxone (1 mg/kg s.c.) during a 2-h observation. Only a small proportion of control group rats showed similar behavior after naloxone injection, but their latency of abdominal stretching was significantly longer and the frequency was much lower than that of morphine group rats. Pre-injection of dextromethorphan into the morphine group rats on postnatal day 5 dose dependently reduced the percentage of morphine rats showing naloxone-precipitated abdominal stretching (Fig. 1A). It also significantly prolonged the latency and decreased the frequency of abdominal stretching in the morphine group rats (Fig. 1B,C). Dextromethorphan reduced the frequency of abdominal stretching to a level similar to that of control

Table 1
The effects of morphine treatment on birth weight and mortality of newborn rats

	Control	Morphine
Born rats per litter	11 ± 0.9 (six litters)	10 ± 1 (six litters)
Overall mortality ratio	3/66 (4.5%)	16/60 (26.7%)[a]
Birth weight (g)	7.6 ± 0.09 (n = 24)	6.6 ± 0.09 (n = 24)[b]

Data are means ± S.E. from six litters of each group.
[a] Means significantly different from that of control group rats (Chi-square test, $P < 0.05$).
[b] Means significantly different from that of control group rats (unpaired *t* test, $P < 0.05$).

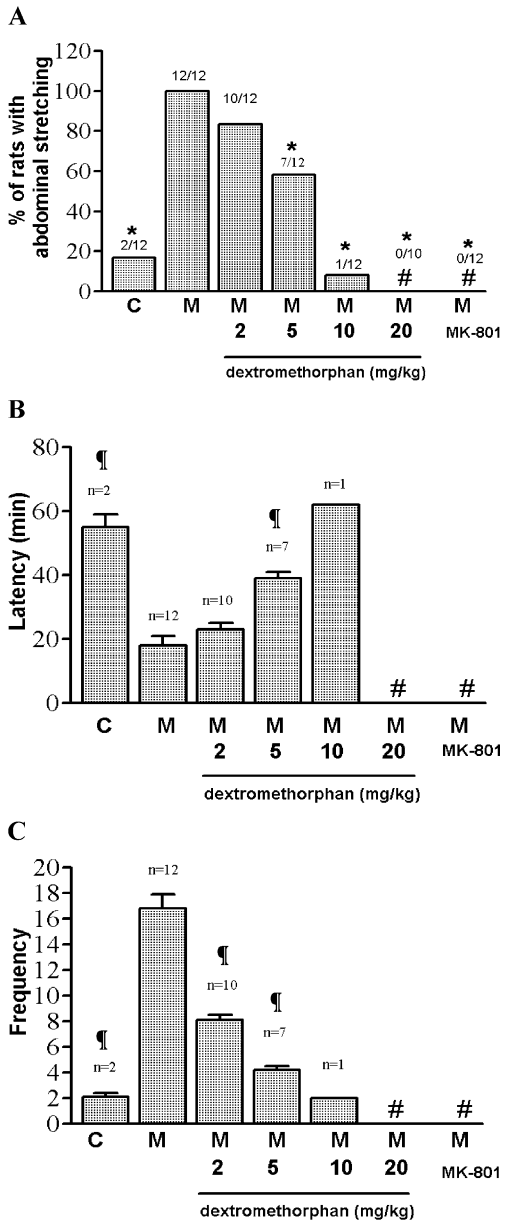

Fig. 1. The effect of postnatal injection of dextromethorphan or MK-801 on naloxone-precipitated abdominal stretching of control (C) and morphine (M) group rats. Data are means ± S.E. for 12 animals in each group. (A) Percentage of tested rats showing abdominal stretching in response to naloxone (1 mg/kg s.c.). The responding ratio of each group is listed in the top of each bar. (B) Latency to the first abdominal stretch. The numbers of rats showing abdominal stretching (n) are listed on the top of each bar. Since the number of rats showing abdominal stretching in the control or morphine group rats that received 10 or 20 mg/kg dextromethorphan, or 0.5 mg/kg MK-801, is 1 or none, these data were not included in the statistical analysis. A similar condition also applied when comparing the frequency of abdominal stretching in C. # means no animal showed abdominal stretching. * means significantly different from that of morphine group rats ($P < 0.05$, Chi-square test); ¶ means significantly different from that of morphine group rats ($P < 0.05$, one-way ANOVA with Newman–Keuls test).

Table 2
The effects of prenatal dextromethorphan or MK-801 treatment on the mortality and naloxone-precipitated abdominal stretching in newborn rats

	Mortality	Abdominal stretching		
		Ratio	Latency (min)	Frequency (time/2 h)
Control	1/29[a]	4/14[a]	69 ± 5.6[b]	2 ± 0.4[b]
Morphine	8/27	14/14	22 ± 3.2[c]	17 ± 1.1[c]
Morphine/D (2 mg/kg)	7/31	13/14	27 ± 2.3[c]	15 ± 0.8[c]
Morphine/D (5 mg/kg)	6/30	12/14	39 ± 3.7[b,c]	9 ± 0.6[b,c]
Morphine/D (10 mg/kg)	7/31	6/14[a]	46 ± 3.7[b,c]	4 ± 0.4[b,c]
Morphine/MK-801	8/28	4/14[a]	45 ± 3.4[b,c]	3 ± 0.5[b,c]

Mortality is the number of deaths among neonatal rats over the total number of born rats from three litters of each group. Ratios are the number of rats showing abdominal stretching over the total number of rats that received naloxone injection. The data for latency and frequency are means ± S.E. Rats that did not show abdominal stretching were not included in the calculation of these values of means. D: dextromethorphan.

[a] Means significantly different from that of morphine group ($P < 0.05$, Chi-square t test).

[b] Means significantly different from that of morphine group ($P < 0.05$, one-way ANOVA with post hoc Newman–Keuls test).

[c] Means significantly different from that of control group ($P < 0.05$, one-way ANOVA with post hoc Newman–Keuls test).

rats at a dose of 10 mg/kg, and 20 mg /kg of dextromethorphan completely abolished abdominal stretching. Injection of 0.5 mg/kg of MK-801 was sufficient to completely abolish the expression of abdominal stretching.

3.3. Effects of prenatal treatment with dextromethorphan or MK-801 on postnatal mortality and naloxone-precipitated abdominal stretching

Prenatal co-injection of dextromethorphan or MK-801 did not reduce the mortality of morphine group rats (Table 2). In contrast to a 100% responsiveness of the morphine group rats, very few control group rats responded to naloxone by showing abdominal stretching. Treatment with dextromethorphan dose dependently reduced the ratio of morphine group rats showing abdominal stretching, and prolonged the latency but reduced the frequency of abdominal stretching. Dextromethorphan significantly prolonged the latency at a dose of 5 mg/kg, but 10 mg/kg of dextromethorphan was required to significantly reduce the frequency of abdominal stretching. Co-administration of 0.1 mg/kg MK-801 significantly attenuated the severity of naloxone-precipitated abdominal stretching of morphine group rats to a level close to that produced by co-administration of 10 mg/kg of dextromethorphan.

4. Discussion

The present results demonstrated that dextromethorphan was effective, both when administered postnatally to newborn rats, and when administered to dam rats prenatally for three consecutive days before delivery, in attenuating naloxone-precipitated withdrawal syndrome in neonatal rats exposed to morphine prenatally.

Using the same morphine treatment protocol, in our previous report, we found that co-administration of dextromethorphan with morphine (dosage ratio is 1:1), starting before mating till the first postnatal month, significantly attenuated morphine-induced adverse effects on the offspring, including high postnatal mortality, loss of body weight gain, development of tolerance to the antinociceptive effect of morphine, decrease in NMDA receptor density in the hippocampus, and naloxone-precipitated behavioral changes related to morphine withdrawal (Tao et al., 2001). Particularly, the severity of naloxone-precipitated withdrawal changes was attenuated to a level similar to that observed in the rats born to saline-treated dam rats.

In this study, the ED_{50} of dextromethorphan in attenuating abdominal stretching after a single postnatal injection was roughly 5 mg/kg. This potency of dextromethorphan is generally close to that in suppressing morphine withdrawal syndrome in adult rats reported by others (Farzin, 1999; Mao et al., 1996). It is also within the potency range for attenuating other neuropathologies related to overactivation of the NMDA receptor in neonatal rats (Laroia et al., 1997; Prince and Feeser, 1988). In addition, the potency of MK-801 seems to be at least 40-fold higher than that of dextromethorphan, since postnatal injection of 0.5 mg/kg MK801 was as effective as that of 20 mg/kg of dextromethorphan, and prenatal co-injection of 0.1 mg/kg MK-801 was as effective as that of 10 mg/kg of dextromethorphan. This difference in potency between MK-801 and dextromethorphan is correlated with the difference in their potency in inhibiting NMDA receptor-mediated responses in vitro (Parsons et al., 1995). Taken together, it is likely that the effect of dextromethorphan on naloxone-precipitated withdrawal behavior is mediated by its antagonism of the NMDA receptor.

The effectiveness of dextromethorphan given by prenatal co-injection seemed to be lower than that of postnatal injections. When co-injected prenatally, at least 10 mg/kg of dextromethorphan was required to produce a similar attenuating effect that was produced by direct injection of 5 mg/kg into the pups. Given the fact that prenatal treatment with dextromethorphan was discontinued at birth, 5 days before naloxone injection, and dextromethorphan was not directly injected into the pups but rather received through the dam rats, this relatively lower effectiveness of dextromethorphan by prenatal co-injection might be attributed to lower body levels of dextromethorphan in these neonatal rats at the time of naloxone injection, as compared to the level in neonatal rats which received postnatal dextromethorphan injection. Nevertheless, the effectiveness of prenatal dextromethorphan co-treatment not only proves that the fetus can absorb dextromethorphan from the maternal circulation, but also suggests that a short-term prenatal dextromethorphan treatment just before birth is sufficient to suppress naloxone-precipitated behavior, to an extent

similar to that produced by long-term prenatal treatment as revealed in our previous report (Tao et al., 2001). Since the pups no longer received dextromethorphan after birth, it would be quite interesting to understand how the attenuating effect of dextromethorphan could be sustained until postnatal day 5 when naloxone was injected. One possibility is that dextromethorphan, which had prenatally accumulated in pups, could be kept within an effective concentration range for several days to suppress naloxone-precipitated withdrawal behavior postnatally. If so, then this must be related to the specific pharmacokinetic/pharmacodynamic property of dextromethorphan during this early life stage, which has not yet been determined. Alternatively, it is possible that prenatal treatment with dextromethorphan is sufficient to disrupt the maintenance of fetal abstinence intrauterinally. Therefore, the severity of withdrawal syndrome developed in neonatal rats after birth will become less apparent than that seen without disruption by dextromethorphan prenatally.

In contrast to our previous report, we did not find any significant effect of prenatal treatment with dextromethorphan or MK-801 in reducing the postnatal mortality of morphine group rats, suggesting that a long course of prenatal dextromethorphan is required to interfere with the pathological mechanisms responsible for the high postnatal mortality induced by prenatal exposure to morphine (Tao et al., 2001). Perhaps, the pathological mechanism has already taken place days before birth, and therefore, it cannot be reversed by treatment with dextromethorphan or MK-801.

Abdominal stretching has been reported as one of the naloxone-precipitated behaviors in both adult rats (Tokuyama et al., 1996) and neonatal rats (Jones and Barr, 1995; Tao et al., 2001; Thornton et al., 1997). However, in other previous reports, several kinds of behaviors elicited by naloxone were also documented, including wall climbing, ptosis and jumping (Jones and Barr, 1995; Thornton et al., 1997). The lack of these behavioral changes in this study and our previous report (Tao et al., 2001) can likely be attributed to the difference in morphine treatment and the age of observed animals since, in these two reports, morphine was directly infused into 14-day-old rats for 3 days, or was repeatedly injected into 7-day-old rats for 7 days before naloxone injection. In addition, the severity of naloxone-precipitated behavioral changes in the morphine group rats presented in this study was significantly lower than expected. In our previous report, the frequency of abdominal stretching of morphine group rats was about 60 times/2 h, and the wet-dog shaking behavior was apparent (Tao et al., 2001). In this study, the wet-dog shaking behavior was too subtle to be quantifiable, and the frequency of abdominal stretching was about 17 times/2 h. Interestingly, in the present study, control group rats were also less sensitive to naloxone stimulation, in that only a few rats showed abdominal stretching and the frequency of stretching was also significantly lower than that in our previous report. Therefore, we suspect that this disparity might be due to the difference in the batch of animals or experimental animal center. Nevertheless, in the present study, morphine group rats still clearly differed from control group rats by their higher postnatal mortality, lower birth body weight, and higher responsiveness to naloxone in inducing abdominal stretching. More importantly, the severity of abdominal stretching elicited by naloxone per se serves as a useful index for identifying the attenuating effect of dextromethorphan on the morphine withdrawal syndrome in neonatal rats.

In summary, the present animal study provides evidence to support the use of dextromethorphan in treating the acute neonatal morphine withdrawal syndrome either by directly treating the newborn postnatally, or by indirectly treating the fetus through the mother prenatally. All the dosages of dextromethorphan used in this study are within the dosage range that had been used in human neonates elsewhere (Allen, 1993; Hamosh et al., 1992). However, before being used in the clinic, more research is needed to define the therapeutic dosage of dextromethorphan and the pharmacokinetic/pharmacodynamic characteristics of dextromethorphan in the newborn, and to survey the potential toxicity of dextromethorphan on the fetus or newborn when prenatal treatment is considered.

Acknowledgements

This study is supported by the grant from National Health Research Institute, Taipei, Taiwan, Republic of China (NHRI-EX90-8909BP).

References

Allen, R.J., 1993. Dextromethorphan in nonketotic hyperglycinemia. Neurology 43, 2422–2423.

Andaloro, V.J., Monaghan, D.T., Rosenquist, T.H., 1998. Dextromethorphan and other *N*-methyl-D-aspartate receptor antagonists are teratogenic in the avian embryo model. Pediatr. Res. 43, 1–7.

Bem, J.L., Peck, R., 1992. Dextromethorphan. An overview of safety issues. Drug. Safety 7, 190–199.

Ben-Eliyahu, S., Marek, P., Vaccarino, A.L., Mogil, J.S., Sternberg, W.F., Liebeskind, J.C., 1992. The NMDA receptor antagonist MK-801 prevents long-lasting non-associative morphine tolerance in the rat. Brain Res. 575, 304–308.

Church, J., Sawyer, D., McLarnon, J.G., 1994. Interactions of dextromethorphan with the *N*-methyl-D-aspartate receptor-channel complex: single channel recordings. Brain Res. 666, 189–194.

Einarson, A., Lyszkiewicz, D., Koren, G., 2001. The safety of dextromethorphan in pregnancy: results of a controlled study. Chest 119, 466–469.

Farzin, D., 1999. Modification of naloxone-induced withdrawal signs by dextromethorphan in morphine-dependent mice. Eur. J. Pharmacol. 377, 35–42.

George, C.P., Goldberg, M.P., Choi, D.W., Steinberg, G.K., 1988. Dextromethorphan reduces neocortical ischemic neuronal damage in vivo. Brain Res. 440, 375–379.

Gonzalez, P., Cabello, P., Germany, A., Norris, B., Contreras, E., 1997. Decrease of tolerance to, and physical dependence on morphine by, glutamate receptor antagonists. Eur. J. Pharmacol. 332, 257–262.

Hamosh, A., McDonald, J.W., Valle, D., Francomano, C.A., Niedermeyer, E., Johnston, M.V., 1992. Dextromethorphan and high-dose benzoate therapy for nonketotic hyperglycinemia in an infant. J. Pediatr. 121, 131–135.

Jones, K.L., Barr, G.A., 1995. Ontogeny of morphine withdrawal in the rat. Behav. Neurosci. 109, 1189–1198.

Kim, H.C., Pennypacker, K.R., Bing, G., Bronstein, D., McMillian, M.K., Hong, J.S., 1996. The effects of dextromethorphan on kainic acid-induced seizures in the rat. Neurotoxicology 17, 375–385.

Laroia, N., McBride, L., Baggs, R., Guillet, R., 1997. Dextromethorphan ameliorates effects of neonatal hypoxia on brain morphology and seizure threshold in rats. Brain Res. Dev. Brain Res. 100, 29–34.

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.

Parsons, C.G., Quack, G., Bresink, I., Baran, L., Przegalinski, E., Kostowski, W., Krzascik, P., Hartmann, S., Danysz, W., 1995. Comparison of the potency, kinetics and voltage-dependency of a series of uncompetitive NMDA receptor antagonists in vitro with anticonvulsive and motor impairment activity in vivo. Neuropharmacology 34, 1239–1258.

Prince, D.A., Feeser, H.R., 1988. Dextromethorphan protects against cerebral infarction in a rat model of hypoxia–ischemia. Neurosci. Lett. 85, 291–296.

Rasmussen, K., Fuller, R.W., Stockton, M.E., Perry, K.W., Swinford, R.M., Ornstein, P.L., 1991. NMDA receptor antagonists suppress behaviors but not norepinephrine turnover or locus coeruleus unit activity induced by opiate withdrawal. Eur. J. Pharmacol. 197, 9–16.

Tanganelli, S., Antonelli, T., Morari, M., Bianchi, C., Beani, L., 1991. Glutamate antagonists prevent morphine withdrawal in mice and guinea pigs. Neurosci. Lett. 122, 270–272.

Tao, P.L., Yeh, G.C., Su, C.H., Wu, Y.H., 2001. Co-administration of dextromethorphan during pregnancy and throughout lactation significantly decreases the adverse effects associated with chronic morphine administration in rat offspring. Life Sci. 69, 2439–2450.

Thornton, S.R., Wang, A.F., Smith, F.L., 1997. Characterization of neonatal rat morphine tolerance and dependence. Eur. J. Pharmacol. 340, 161–167.

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.

Tokuyama, S., Wakabayashi, H., Ho, I.K., 1996. Direct evidence for a role of glutamate in the expression of the opioid withdrawal syndrome. Eur. J. Pharmacol. 295, 123–129.

Tortella, F.C., Robles, L., Witkin, J.M., Newman, A.H., 1994. Novel anticonvulsant analogs of dextromethorphan: improved efficacy, potency, duration and side-effect profile. J. Pharmacol. Exp. Ther. 268, 727–733.

Tortella, F.C., Klette, K.L., DeCoster, M.A., Davis, B.J., Newman, A.H., 1995. Dextromethorphan analogs are neuroprotective in vitro and block glutamate-induced excitotoxic calcium signals in neurons. Neurosci. Lett. 198, 79–82.

Trujillo, K.A., Akil, H., 1991. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science 251, 85–87.

Volpe, J.J., 1995. Teratogenic effects of drugs and passive addiction. In: Volpe, J.J. (Ed.), Neurology of the Newborn. W.B. Saunder, Philadelphia, PA, pp. 811–850.