Dextromethorphan potentiates morphine antinociception at the spinal level in rats

[Le dextrométhorphane potentialise l'antinociception de la morphine au niveau rachidien chez les rats]

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Purpose: Morphine is an effective analgesic, but adverse effects limit its clinical use in higher doses. The non-opioid antitussive, dextromethorphan (DM), can potentiate the analgesic effect of morphine and decrease the dose of morphine in acute postoperative pain, but the underlying mechanism remains unclear. We previously observed that DM increases the serum concentration of morphine in rats. Therefore, we investigated the effects of drugs administered at the spinal level to exclude possible pharmacokinetic interactions. As DM has widespread binding sites in the central nervous system [such as N-methyl-D-aspartate (NMDA) receptors, sigma receptors and $\alpha_3\beta_4$ nicotinic receptors], we investigated whether the potentiation of morphine antinociception by DM at the spinal level is related to NMDA receptors.

Methods: We used MK-801 as a tool to block the NMDA channel first, and then studied the interaction between intrathecal (i.t.) morphine and DM. The tail-flick test was used to examine the antinociceptive effects of different combinations of morphine and other drugs in rats.

Results: DM (2–20 μg) or MK-801 (5–15 μg) showed no significant antinociceptive effect by themselves. The antinociceptive effect of morphine (0.5 μg, i.t.) was significantly enhanced by DM and reached the maximal potentiation (43.7%–50.4%) at doses of 2 to 10 μg. Pretreatment with MK-801 (5 or 10 μg, i.t.) significantly potentiated morphine antinociception by 49.9% or 38.7%, respectively. When rats were pretreated with MK-801, DM could not further enhance morphine antinociception (45.7% *vs* 50.5% and 43.3%).

Conclusion: Our results suggest that spinal NMDA receptors play an important role in the effect of DM to potentiate morphine antinociception.

Objectif : *Analgésique efficace, la morphine a cependant des effets indésirables qui en limite l'usage clinique à fortes doses. L'antitussif, dextrométhorphane (DM), peut augmenter l'effet analgésique de la morphine et permettre d'en utiliser une dose postopératoire plus faible, mais le mécanisme responsable de cette action est encore inconnu. Nous savons que le DM augmente la concentration sérique de la morphine chez les rats. Nous avons donc voulu explorer les effets de médicaments administrés au niveau rachidien afin d'exclure des interactions pharmacocinétiques possibles. Les sites de fixation du DM étant nombreux dans le système nerveux central [comme les récepteurs N-méthyl-D-aspartate (NMDA), les récepteurs sigma et les récepteurs nicotiniques $\alpha_3\beta_4$], nous avons vérifié si la potentialisation de l'antinociception de la morphine par le DM au niveau rachidien est reliée aux récepteurs NMDA.*

Méthode : *Nous avons utilisé le MK-801 pour bloquer d'abord le canal NMDA et étudier ensuite l'interaction entre la morphine intrathécale (i.t.) et le DM. Le test de latence de rétraction de la queue a été utilisé pour vérifier les effets antinociceptifs de différentes combinaisons de morphine et d'autres médicaments chez les rats.*

Résultats : *Le DM (2–20 μg) ou le MK-801 (5–15 μg) n'ont montré aucun effet antinociceptif significatif par eux-mêmes. L'effet antinociceptif de la morphine (0,5 μg, i.t.) a été significativement accru par le DM et a atteint sa potentialisation maximale (43,7 % –50,4 %) aux doses de 2 à 10 μg. Un prétraitement avec MK-801 (5 ou 10 μg, i.t.) a significativement augmenté l'effet antinociceptif de la morphine de 49,9 % ou de 38,7 %, respectivement. Chez les rats prétraités avec MK-801, le DM ne pouvait augmenter davantage l'antinociception de la morphine (45,7 % vs 50,5 % et 43,3 %).*

Conclusion : *Nos résultats indiquent que les récepteurs NMDA jouent un rôle important dans l'effet de potentialisation de l'antinociception de la morphine par le DM.*

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MORPHINE is an effective analgesic used in the treatment of severe and chronic pain. Some adverse effects of morphine such as nausea, vomiting, and respiratory depression limit its clinical use in higher doses. The development of tolerance and dependence are also major disadvantages associated with the long-term use of morphine.[1–3] In recent animal studies, N-methyl-D-aspartate (NMDA) receptor antagonists such as MK-801 and ketamine have been shown to enhance the antinociceptive effects of morphine without increasing side effects and also prevented the development of morphine tolerance.[4–7] However, since MK-801 and ketamine either have a narrow therapeutic window or produce certain side effects (including hallucination and neurotoxicity), these drugs may not be the most appropriate adjuvants in acute pain management.[3,8,9]

Dextromethorphan (DM), a non-opioid antitussive, has widespread binding sites in the central nervous system (including NMDA receptors, sigma receptors and $\alpha_3ß_4$ nicotinic receptors) and produces both anticonvulsant and neuroprotective effects.[10–12] It is particularly attractive for clinical use as an NMDA antagonist since it has been dispensed as a non-prescription drug for 40 years and is known to have a wide margin of safety.[13]

Preoperative administration of DM attenuates postoperative pain and morphine consumption in humans.[14–17] The co-administration of morphine and DM potentiates the antinociceptive effect of morphine[18–20] and also attenuates the dependence and tolerance to morphine in rats.[2,6,8] It has been speculated that DM potentiates morphine antinociception by antagonizing NMDA receptors, but the evidence is not available.[10,18,21] In our preliminary study, we observed that DM increases the serum concentration of morphine (free form) in rats (data not shown). Therefore, the purpose of this study was to investigate, in rats, the effects of drugs administered at the spinal level to exclude possible pharmacokinetic interactions.

Methods

Animals

The experimental protocol was approved by the Animal Care and Use Committee of the National Defense Medical Center. The experimental animals were ten-week-old male Sprague-Dawley rats weighing between 300 and 350 g (purchased from the National Experimental Animal Center, Taipei, Taiwan). All animals were bred in the Animal Facility of the National Defense Medical Center. The animal rooms were maintained at 23 ± 2°C with a 12-hr light/dark cycle. Food and water were available *ad libitum* throughout the experiment. Animals were taken to the testing room in the morning of the experiment; the experiments were carried out during the light cycle.

Surgical preparations

All surgical procedures were performed under sodium pentobarbital anesthesia (50 $mg \cdot kg^{-1}$, *ip*) and a PE10 i.t. catheter was implanted for drug administration, as in our previous study.[22] Before testing, each i.t. catheter was injected with 20 µL of 2% lidocaine. Correct position of the catheter was evidenced by prompt motor block of the lower limbs, developing in one to five minutes and lasting for ten to 20 min. Any rat showing no motor blockade of lower limbs was excluded. Location of the distal end of the catheter was verified at the end of experiment. The location was confirmed by the injection of 10 µL of methylene blue and post-mortem examination of the spinal cord. Animals were housed individually after surgery with free access to food and water and were allowed to recover at least four days before experiments. Drugs were administered in 1 to 3 µL of solution, and the drug administration was followed by flushing with 10 µL of saline.

Determination of the antinociceptive effects of drugs

Morphine- or drug-induced antinociception was evaluated by the tail-flick test.[1,23] Basal latency (tail-flick latency before drug administration) was determined and found to range from 2.5 to 3.5 sec. The cut-off time was set at ten seconds to prevent injury to the tail.

For each rat, basal latency was determined at least three times, and the drug to be tested was injected intrathecally. Tail-flick latency was recorded at 30, 60, 90, 120, 150, 180, 210, and 240 min after drug administration. Analgesia was evaluated by calculating the area under the time-response curve (AUC) obtained by plotting tail-flick latency (sec) on the ordinate and time after drug administration (from 30 to 240 min at 30-min intervals) on the abscissa. The AUC was calculated using the Trapezoidal rule and regarded as an index of the antinociceptive effect of drug(s). An example is presented in Figure 1. In order to ensure that the doses of DM or MK-801 used had no antinociceptive effect, the tail-flick test was also performed for DM (2, 5, 10, or 20 µg, i.t.) or MK-801 alone (5, 10, 15, or 30 µg, i.t.).

Determination of the doses of DM or MK-801 that maximally enhance the antinociceptive effect of morphine

Rats were randomly assigned to six groups. Randomization of animals was carried out by animal

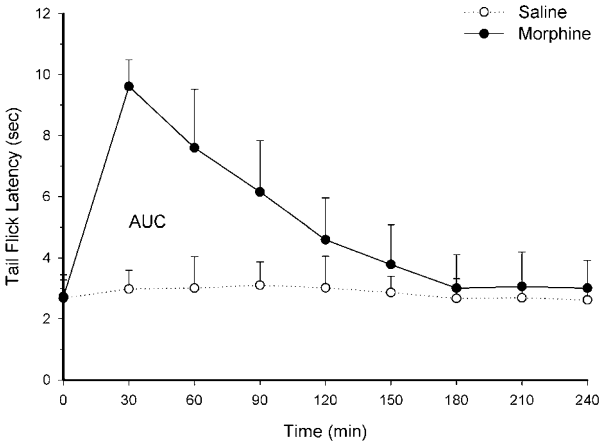

FIGURE 1 The antinociceptive effect of morphine (0.5 μg, i.t.) and normal saline (1 μL, i.t.) in rats. Values are presented as means ± S.D. Each group contains at least six rats. The AUC is considered an index of antinociceptive effect. i.t. = intrathecal; AUC = area under the time-response curve.

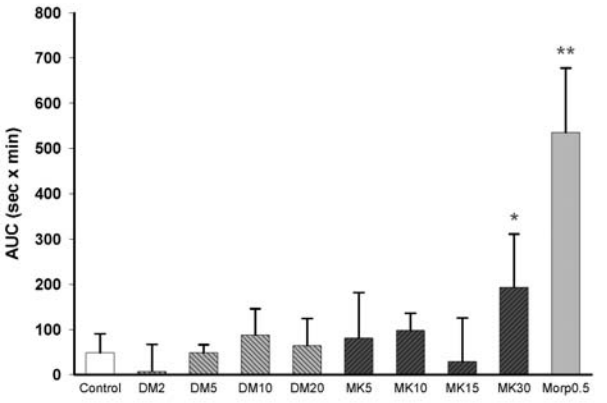

FIGURE 2 The antinociceptive effects of DM (2, 5, 10, 20 μg, i.t.), MK-801 (5, 10, 15, 30 μg, i.t.), and morphine (0.5 μg, i.t.). Values are presented as means ± S.D. Each group contains at least three rats. $*P < 0.05$, $**P < 0.01$ ***vs*** control group. i.t. = intrathecal; AUC = area under the time-response curve; DM = dextromethorphan; MK = MK-801; Morp = morphine.

house staff who were blinded to the experiment. Each group received morphine (0.5 μg) with either saline or DM at different doses (0.5, 1, 2, 5, or 10 μg) intrathecally. The doses of DM that enhanced the effect of morphine maximally were found to be at or above 2 μg i.t. Therefore, 2 μg of DM i.t. was chosen for the subsequent experiments. In another set of experiments, rats were randomly divided into three groups and pre-treated separately with either saline or MK-801 at a dose of 5 or 10 μg i.t. 20 min before the injection of morphine (0.5 μg, i.t.), in order to determine whether these doses ensure maximal potentiation of morphine antinociception.

Determination of the effect of DM on potentiating morphine antinociception after pretreatment with a maximal dose of MK-801

To evaluate the influence of MK-801 on the antinociceptive effect of the DM-morphine combination, rats were randomly divided into four groups. Both M and DM+M groups were pretreated with saline 20 min before drug injection intrathecally. Then the M group was given 0.5 μg morphine i.t. The DM+M group received an i.t. injection of 2 μg DM and 0.5 μg morphine i.t. The MK5+DM+M group was pretreated with 5 μg MK-801 i.t. 20 min before injection of 2 μg DM and 0.5 μg morphine i.t.. The MK10+DM+M group was pretreated with 10 μg MK-801 i.t. 20 min before injection of 2 μg DM i.t. and 0.5 μg morphine i.t.

Statistical analyses

Based on our preliminary results, the mean difference in AUC among different groups was approximately 240 sec × min and the standard deviation 120 sec × min. With 80% power and a statistically significance set at 0.05, we calculated that the required sample size was six per group.

Experimental data were analyzed by analysis of variance (ANOVA), followed by Newman-Keuls post hoc test for multiple comparisons. All data are expressed as mean ± S.D.; $P < 0.05$ was considered to be statistically significant.

Results

Determination of the doses of DM or MK-801 which have no antinociceptive effect

DM at doses of 2, 5, 10 or 20 μg i.t. or MK-801 at doses of 5, 10 or 15 μg i.t. had no significant antinociceptive effect or overt behavioural evidence of neurotoxicity. A significant antinociceptive effect was observed with 30 μg of MK-801 i.t. as shown in Figure 2. An i.t. injection of 40 μg MK-801 produced significant signs of neurotoxicity, including single-side rotation, rolling, or jumping and the tail-flick test was difficult to administer at this dose. Therefore, we used DM and MK-801 at doses lower than 10 μg in subsequent experiments.

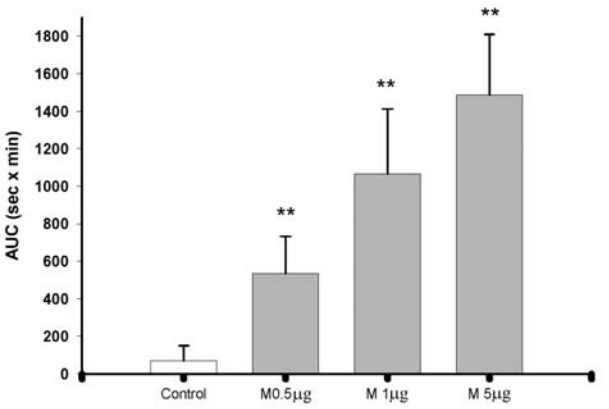

FIGURE 3 Dose-dependent antinociceptive effects of morphine (0.5, 1, or 5 μg, i.t.). Values are presented as means ± S.D. Each group contains at least eight rats. $**P < 0.01$ *vs* control group. i.t. = intrathecal; AUC = area under the time-response curve; M = morphine.

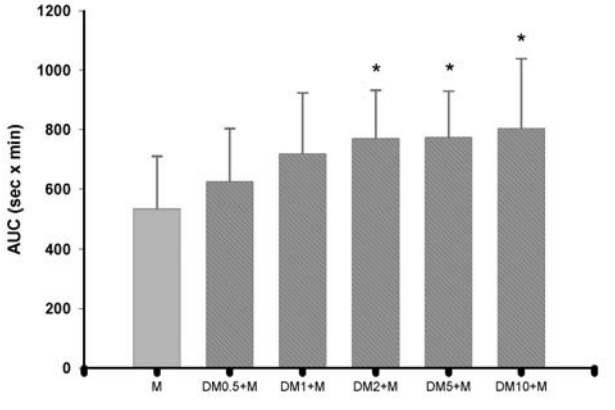

FIGURE 4 The potentiating effects of DM (0.5, 1, 2, 5, or 10 μg, i.t.) on the antinociceptive effect of morphine (0.5 μg, i.t.). Each group contains at least six rats. $*P < 0.05$ *vs* morphine group. i.t. = intrathecal; AUC = area under the time-response curve; DM = dextromethorphan; M = morphine).

Dose-response of the antinociceptive effect of morphine

An i.t. injection of morphine (0.5, 1, or 5 μg) showed dose-dependent antinociceptive effects (548.0 ± 198.3, 1066.4 ± 346.5, and 1485.6 ± 323.3 respectively, $P < 0.01$; Figure 3). In order to maintain some capacity for enhancement of the antinociceptive effect of morphine, morphine 0.5 μg was chosen for subsequent experiments.

Effect of DM on potentiation of morphine antinociception

As shown in Figure 4, the antinociceptive effects (AUC) of DM0.5+M, DM1+M, DM2+M, DM5+M, or DM10+M (625.2 ± 179.1, 719.1 ± 205.2, 768.9 ± 163.0, 774.3 ± 155.1, and 805.2 ± 233.4, respectively) indicated that DM dose-dependently potentiated morphine antinociception (535.2 ± 175.1) and reached the maximal effect at the dose of 2 μg, (143.7% of morphine group, $P < 0.05$). When the doses of DM were increased to 5 or 10 μg, the potentiation of morphine antinociception was not increased further (144.9% and 150.4% respectively).

Effect of MK-801 on the potentiation of morphine antinociception

The AUC for MK5+M group (879.3 ± 119.4) or MK10+M group (814.2 ± 90.5) was significantly higher than the AUC for morphine (586.5 ± 179.6, $P < 0.01$; Figure 5). Both doses of MK-801 showed a similar degree of potentiation (149.9% and 138.7%) on morphine's antinociceptive effect.

Effect of DM on morphine antinociception after pretreatment with MK-801

When rats were pretreated with either saline or MK-801 (5 μg or 10 μg, i.t.) 20 min before DM (2 μg, i.t.) and morphine (0.5 μg, i.t.) administration, the AUC reached 145.7% (DM+M), 150.5% (MK5+DM+M) and 143.3% (MK10+DM+M) ($P < 0.05$) of morphine (Figure 6).

Discussion

DM is a dextro- form isomer of levorphanol. Unlike opioids, DM has an established safety record. The therapeutic cough suppressant dose (1 $mg \cdot kg^{-1} \cdot day^{-1}$) produces no major opioid-like respiratory or hemodynamic side effects and does not induce complications related to histamine release.[13,24] DM has been reported to potentiate the analgesic effects of morphine in both animal and human studies.[5,8,13,15–20,25] Grass and colleagues[20] showed that DM at the dose of 30 $mg \cdot kg^{-1}$ *ip* produced stronger and more prolonged potentiation on morphine-induced antinociception than that of MK-801 at 0.1 $mg \cdot kg^{-1}$ *ip* or CGS19755 at 5 $mg \cdot kg^{-1}$ *ip* in Sprague-Dawley rats. Hoffmann and Wiesenfeld-Hallin[18] reported that DM potentiated morphine antinociception, but did not reverse tolerance in rats. In a clinical trial, Kawamata and colleagues[15] examined the role of DM as an adjuvant in postoperative pain management and found that premedication with oral DM (45 mg) reduced postoperative pain after tonsillectomy. Wong and colleagues[14]

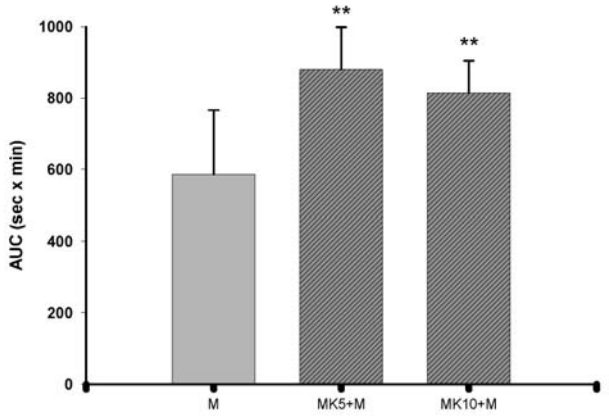

FIGURE 5 The potentiating effects of MK-801 (5 or 10 μg, i.t.) on the antinociceptive effect of morphine (0.5 μg, i.t.). Each group contains at least eight rats. $^{**}P < 0.01$ *vs* morphine group. i.t. = intrathecal; AUC = area under the time-response curve; MK = MK-801; M = morphine.

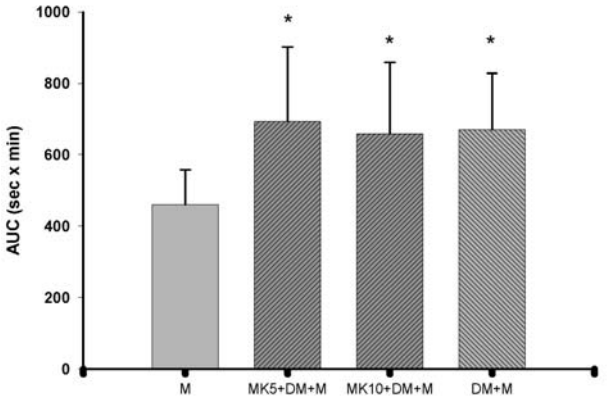

FIGURE 6 Effect of MK-801 (5 or 10 μg, i.t.) pretreatment on the antinociceptive effect of DM+M. Each group contains at least six rats. $^{*}P < 0.05$ *vs* morphine group. No significant difference was found when MK5+DM+M or MK10+DM+M group was compared with DM+M ($P = 0.50$ to 0.76). i.t. = intrathecal; AUC = area under the time-response curve; DM = dextromethorphan; MK = MK-801; M = morphine).

also pointed out that DM can effectively attenuate the postoperative pain and morphine requirement after modified radical mastectomy. Oral DM (30–90 mg) attenuated acute pain and reduced the amount of analgesic required in the majority of postoperative DM-treated patients in a study by Weinbroum and co-workers.[17] In our previous clinical trial,[16] we also found that preoperative *iv* administration of DM reduced postoperative morphine consumption. However, there was also a recent report showing that oral DM could not enhance i.t. morphine analgesia in patients after a Cesarean section.[26] Although the reason of this conflicting result is still unknown, patients receiving DM had a lower incidence of nausea and vomiting, which may also reveal certain beneficial potentials of DM in clinical pain management.

DM was given systemically in most of the above studies. Few studies have addressed the mechanism by which DM potentiates morphine analgesia. Caruso has reported that there is no pharmacokinetic interaction between DM and morphine in a human study.[27] However, our preliminary experiment has shown that DM increases the serum concentration of morphine (free form) in rats (data not shown). Therefore we designed the present study on the i.t. administration of drugs to exclude pharmacokinetic factor interactions.

In the present study, we found that DM potentiates the antinociceptive effect of morphine administered i.t. (Figure 4). It means that there must be a mechanism(s), other than pharmacokinetic, involved in the effect of DM on morphine antinociception at the spinal level. Second, we found that pre-treatment with MK-801 (5 or 10 μg i.t.) also maximally potentiates morphine antinociception (Figure 5). Since MK-801 is a selective NMDA receptor antagonist, we assume that most spinal NMDA receptors involved in the potentiation of morphine antinociception were blocked by MK-801. When we pretreated animals with these doses of MK-801 (5–10 μg i.t.), DM could not further enhance the antinociceptive effect of morphine (49.9% *vs* 50.5% and 38.7% ***vs*** 43.3%, Figures 5 and 6). This indicates that NMDA receptors indeed play an important role in the mechanism of DM to potentiate morphine antinociception. However, it should be also noted that the tail-flick test is only one of several types of animal analgesic behavioural tests and there is no absolute correlation with pain in humans.

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