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Co-administration of dextromethorphan with morphine attenuates morphine rewarding effect and related dopamine releases at the nucleus accumbens.

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Abstract

Morphine is one of the most effective analgesics in clinic to treat postoperative pain or cancer pain. A major drawback of its continuous use is the development of tolerance and dependence. In our previous study we found that a widely used antitussive agent in clinics, dextromethorphan [(DM); also known as a non-competitive N-methyl-d-aspartate (NMDA) antagonist], could prevent the development of morphine tolerance. In the present study, we further investigated its effect on morphine addiction. Conditioned place preference (CPP) test and behavioral sensitization of locomotor activity were used to investigate the drug-seeking related behaviors, which were in correlation with psychological dependence. Our results showed that co-administered DM was able to abolish completely the CPP effect induced by morphine, but had no effect on morphine-induced behavioral sensitization. By employing the microdialysis technique in free-moving animals, we also determined the extracellular level of dopamine and serotonin metabolites in the shell region of the nucleus accumbens (NAc) in its response to morphine with/without DM. A significant increase in dopamine metabolites following morphine administration was demonstrated in the NAc. This increase by morphine could be attenuated by co-administered DM, whereas DM itself did not show any effect. Based on our results, it is speculated that DM may effectively attenuate morphine-induced psychological dependence. Neurochemical analysis revealed that the effect of DM could be through its action on the dopaminergic mesolimbic pathway, which could be activated by morphine and attributed to the cause of rewarding.

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