

## *dextro*-Morphine attenuates the morphine-produced conditioned place preference via the $\sigma_1$ receptor activation in the rat

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### Abstract

An unbiased conditioned place preference paradigm was used to evaluate the effect of *dextro*-morphine on the morphine-produced reward in male CD rats. Morphine sulfate (1–10 mg/kg) given intraperitoneally dose-dependently produced the conditioned place preference. Pretreatment with *dextro*-morphine at a dose from 0.1 to 3  $\mu$ g/kg given subcutaneously dose-dependently attenuated the morphine-produced conditioned place preference. However, *dextro*-morphine at a higher dose 100  $\mu$ g/kg did not affect the morphine-produced conditioned place preference. Thus, *dextro*-morphine pretreatment induces a U-shaped dose-response curve for attenuating the morphine-produced conditioned place preference. The attenuation of the morphine-produced conditioned place preference was reversed by the pretreatment with the  $\sigma_1$  receptor antagonist BD1047 (*N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine dihydrobromide. *dextro*-Morphine or BD1047 given alone did not affect the baseline place conditioning. It is concluded that *dextro*-morphine attenuated the morphine-produced conditioned place preference via the  $\sigma_1$  receptor activation.

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### 1. Introduction

The naturally occurring morphine alkaloid, which is isolated from the juice of the opium poppy, *papaver somniferum*, is stereochemically identified as a *levorotatory* form. Morphine interacts with  $\mu$ -opioid receptors to produce potent analgesic, addictive and other pharmacological effects. The *dextrorotatory dextro*-morphine, which is synthesized from sinomenine (Iijima et al., 1978), does not have any affinity for  $\mu$ -opioid receptors and therefore does not produce any  $\mu$ -opioid receptor mediated pharmacological effects (Jacquet et al., 1977). However, we have previously demonstrated that *dextro*-morphine pretreatment attenuates the analgesia produced by morphine in mice (Wu et al., 2005). The interesting finding inspired us to determine if *dextro*-morphine can also exert the anti-addictive effect. The effect of *dextro*-morphine on the conditioned place preference produced by morphine was then studied. We now

report that *dextro*-morphine given systemically attenuates the systemic morphine-produced conditioned place preference.

The most likely receptor for *dextro*-morphine to act for producing the antianalgesic and anti-addictive effects is the  $\sigma_1$  receptor. Other *dextro*-opiates such as (+)-pentazocine and (+)-*N*-allyl-normetazocine interact with  $\sigma_1$  receptors, which are distinct from classical opioid receptors. We have found that the attenuation of the morphine-produced tail-flick inhibition induced by *dextro*-morphine is reversed by the  $\sigma_1$  receptor antagonist BD1047, indicating that the attenuation of the morphine analgesia is mediated by the  $\sigma_1$  receptor activation (Wu and Tseng, unpublished observation).  $\sigma_1$  receptors have been reported to play an important role in the modulation of analgesia produced by  $\mu$ -,  $\delta$ - or  $\kappa$ -opioid receptor agonists (Mei and Pasternak, 2002; Marrazzo et al., 2006; Chien and Pasternak, 1994) and the conditioned place preference produced by nicotine, cocaine, amphetamine or alcohol (Romieu et al., 2000, 2002; Matsumoto et al., 2001, 2002; Horan et al., 2001; Miyatake et al., 2004; Maurice et al., 2003; Liu et al., 2005; Nguyen et al., 2005). The experiment was then undertaken to determine if the attenuation of the morphine-produced conditioned place preference induced

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by *dextro*-morphine is mediated by the  $\sigma_1$  receptor activation. We now report that BD1047 pretreatment reverses the attenuation of the morphine-produced conditioned place preference induced by *dextro*-morphine pretreatment. The finding provides the evidence that activation of  $\sigma_1$  receptors is involved in the attenuation of the morphine-produced conditioned place preference induced by *dextro*-morphine.

## 2. Materials and methods

### 2.1. Animals

Male CD rats weighing 300–350 g (Charles River Breeding Laboratory, Wilmington, MA) were used. Animals were housed two per cage in a room maintained at  $22 \pm 0.5$  °C with an alternating 12-h light–dark cycle. Food and water were available *ad libitum*. Each animal was used only once. All experiments were approved by and conformed to the guidelines of the Animal Care Committee of the Medical College of Wisconsin.

### 2.2. Conditioned place preference

The place conditioning experiment consisted of pre-conditioning, conditioning and post-conditioning phases (Bals-Kubik et al., 1993; Terashvili et al., 2004). Injections of vehicle or drug were only done during the conditioning phase. A two-compartment box ( $60 \times 29.2 \times 29.2$  cm) with a transparent Plexiglas front separated by a gray cylinder platform (10.3 cm in diameter and 12 cm in height) was used. One compartment was white with a textured floor and the other was black with a smooth floor. For pre-conditioning, rats were initially placed on the neutral cylinder gray platform and allowed to step down off of the platform to either the white or black compartment. A sliding wall was then put down on the platform and the rat was free to access either compartment through two openings ( $9.5 \times 12$  cm) on each side of the platform. The amount of time spent in the black or white compartment was manually measured for 15 min. For pre-conditioning control, rat was tested once in the morning for their preference one day before conditioning sessions; only those rats that did not exhibit a significant preference between black and white compartments (350–550/900 s) were used for experiments. Rats, which spent less than 5 min 50 s in either the white or black compartment, were considered not to be neutral in preference for either side and were excluded from further study (less than 5% of rats).

The place conditioning session was carried out on days 2 to 4. The box was divided into two equal-sized compartments by putting down a sliding wall after removal of the gray cylinder platform. Conditioning session was conducted twice daily, morning and afternoon, and repeated for 3 days. Rats were placed in either the black or white compartment immediately following the injection and left in that compartment for 40 min. Forty min was in agreement with previous studies (Bals-Kubik et al., 1993; Shippenberg and Heidbreder, 1995). Rats were confined to either the black or white compartment after injection of drugs tested in the morning session of each day, and were

confined to the opposite compartment after the injection of vehicle for the afternoon session and vice versa. Animals receiving vehicle in both sessions served as controls. Drug treatment consisted of *dextro*-morphine or BD1047 (*N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine dihydrobromide) given intraperitoneally or morphine sulfate given subcutaneously. The morning session was carried out from 8–11 a.m. and the afternoon session was carried out from 2–5 p.m. of the day.

The post-conditioning session was carried out on day 5 and was exactly the same as the pre-conditioning. The scores for the drug-paired place were then calculated by subtracting the pre-conditioning score from post-conditioning score. A positive score represented conditioning place preference, while a negative score represented conditioning place aversion.

### 2.3. Drugs and drug-administration

Morphine sulfate and *dextro*-morphine base were obtained from the National Institute on Drug Abuse (Baltimore, MD). *N*-[2-(3,4-Dichlorophenyl)ethyl]-*N*-methyl-2-(dimethylamino)ethylamine dihydrobromide (BD1047) was purchased from Tocris (Ellisville, MO). Morphine and BD1047 were dissolved in 0.9% saline. The *dextro*-morphine was initially dissolved in 10 N hydrochloric acid and then titrated with 1 N sodium hydroxide to pH 7.0, which was then diluted to the intended concentrations in 0.9% saline for injection. Drugs were injected subcutaneously or intraperitoneally in an injection volume of 0.1 ml per 100 g body weight with a 26-gauge needle.

### 2.4. Statistical analysis

Conditioning scores were expressed as mean  $\pm$  S.E.M. The Student paired *t*-test was used to analyze the differences of the score between pre- and post-conditioning of each group of rats. One-way analysis of variance (ANOVA) followed by Dunnett's post-test was used to compare the difference between drug treated groups and the vehicle treated group. In all experiments,  $P < 0.05$  was considered a significant difference. The Prism statistical software was used to perform the statistics (version 4.1; GraphPad Software, Inc., San Diego, CA).

## 3. Results

### 3.1. Effect of morphine sulfate given subcutaneously on the production of the conditioned place preference

Groups of rats were injected subcutaneously with different doses of morphine sulfate (1, 5 or 10 mg/kg) or saline vehicle and placed in the conditioned place preference box immediately for place conditioning. Morphine sulfate at a dose, 1 and 5 mg/kg, dose-dependently increased the conditioned place preference. However, morphine sulfate at a higher dose, 10 mg/kg, produced no more increase of the conditioned place preference. Subcutaneous injection of the vehicle did not affect the baseline place conditioning response (Fig. 1). Five mg/kg of morphine sulfate was then chosen for the following experiments.

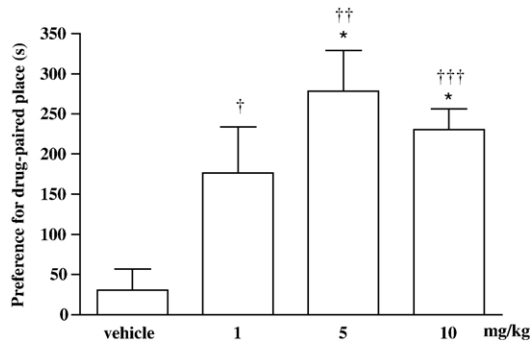


Fig. 1. Conditioned place preference produced by morphine sulfate given subcutaneously in rats. Groups of rats were injected subcutaneously with a various dose of morphine sulfate (1–10 mg/kg) alternatively with saline vehicle and placed in the conditioning box for place conditioning. Each column represents the mean and the vertical bar represents the S.E.M. with 8 rats in each group; †  $P < 0.05$ , ††  $P < 0.01$ , †††  $P < 0.001$  compared with the pre-conditioning score of the individual group; \*  $P < 0.01$  compared with the vehicle-injected group.

### 3.2. Effects of dextro-morphine given intraperitoneally on the conditioned place preference produced by morphine sulfate given subcutaneously

Groups of rats were pretreated intraperitoneally in the home cage with different doses (0.1–100  $\mu\text{g/kg}$ ) of dextro-morphine or saline vehicle for 1 h before subcutaneous injection of morphine sulfate (5 mg/kg) and were placed in the conditioned place preference box for place conditioning. Pretreatment with dextro-morphine at a dose from 0.1 to 3  $\mu\text{g/kg}$  dose-dependently attenuated the morphine-produced increase of the conditioned place preference. However, dextro-morphine at a

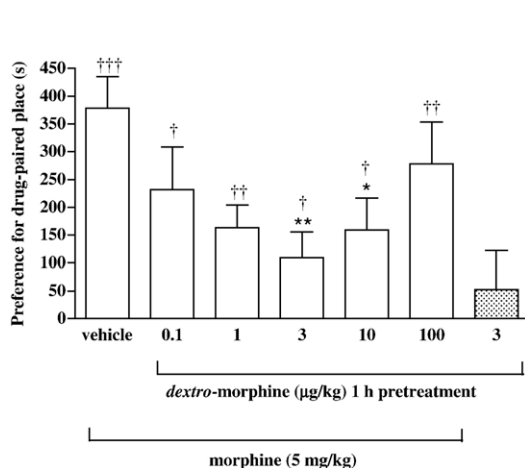


Fig. 2. Pretreatment with dextro-morphine attenuates the morphine-produced conditioned place preference in rats. Groups of rats were pretreated intraperitoneally with a various doses of dextro-morphine in the home cage for 1 h before subcutaneous injection of morphine sulfate (5 mg/kg) and were placed in the conditioning box for place conditioning. Each column represents the mean and the vertical bar represents the S.E.M. with 8–12 rats in each group; †  $P < 0.05$ , ††  $P < 0.01$ , †††  $P < 0.001$  compared with the pre-conditioning score of the individual group; \*  $P < 0.05$ , \*\*  $P < 0.01$  compared with the vehicle injected group. The dextro-morphine (3  $\mu\text{g/kg}$ ) given intraperitoneally alone (the first column from the right) produced neither conditioning place preference or conditioned place aversion.

higher dose 100  $\mu\text{g/kg}$  did not attenuate the increase of the conditioned place preference produced by morphine (Fig. 2). Thus, dextro-morphine at a dose range from 0.1 to 100  $\mu\text{g/kg}$  produced a U-shaped dose-response curve with a maximal inhibition at 3  $\mu\text{g/kg}$  for attenuating the morphine-produced conditioned place preference. However, dextro-morphine at 3  $\mu\text{g/kg}$ , which produced a maximal inhibition, still did not completely block the increase of the conditioned place preference produced by morphine. Pretreatment with dextro-morphine (3  $\mu\text{g/kg}$ ) given intraperitoneally alone did not affect the baseline place conditioning in rats treated subcutaneously with saline vehicle (Fig. 2).

### 3.3. Effects of sigma<sub>1</sub> receptor antagonist BD1047 given intraperitoneally on the attenuation of morphine-produced conditioned place preference induced by dextro-morphine

Since most (+)-opiates such as (+)-pentazocine and (+)-N-allyl-normetazocine interact stereospecifically with the sigma<sub>1</sub> receptors, the possibility that the sigma<sub>1</sub> receptors are involved in attenuating the increase of the morphine-produced conditioned place preference induced by dextro-morphine was then explored. The sigma<sub>1</sub> receptor antagonist BD1047 was used to determine if the effect of dextro-morphine is mediated by the sigma<sub>1</sub> receptor activation. Groups of rats were pretreated intraperitoneally in the home cage with a dose 1, 3 or 6 mg/kg of BD1047 and 3  $\mu\text{g/kg}$  of dextro-morphine for 1 h before subcutaneous injection of morphine sulfate (5 mg/kg) and were placed in the conditioned place preference box for place conditioning. Pretreatment with dextro-morphine given alone attenuated the increase of the

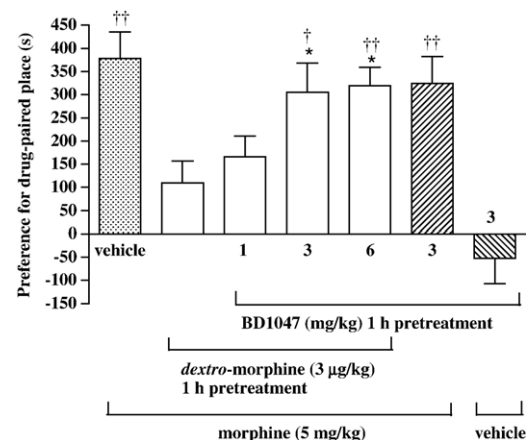


Fig. 3. Pretreatment with the sigma<sub>1</sub> receptor antagonist BD1047 reverses the attenuation of the morphine-produced conditioned place preference induced by dextro-morphine in rats. Groups of rats were pretreated intraperitoneally with a various dose of BD1047 (1, 3 or 6 mg/kg) and 3  $\mu\text{g/kg}$  of dextro-morphine in the home cage for 1 h before subcutaneous injection of morphine sulfate (5 mg/kg) and were placed in the conditioning box for place conditioning. Each column represents the mean and the vertical bar represents the S.E.M. with 8–12 rats in each group; †  $P < 0.05$ , ††  $P < 0.01$ , †††  $P < 0.001$  compared with the pre-conditioning score of the individual group; \*  $P < 0.05$ , compared with the vehicle injected group. The dextro-morphine (3  $\mu\text{g/kg}$ ) given intraperitoneally alone (the first column from the right) produced neither conditioning place preference or conditioned place aversion.

conditioned place preference produced by morphine. The attenuation of the morphine-produced conditioned place preference was reversed dose-dependently by the BD1047 pretreatment. Pretreatment with BD1047 (3 mg/kg) given alone did not affect the morphine-produced conditioned place preference, nor did it affect the baseline place preference in rats treated with saline vehicle (Fig. 3).

#### 4. Discussion

##### 4.1. Morphine, but not dextro-morphine, produces conditioned place preference given subcutaneously

The place conditioning, a technique that measures the secondary reinforcing effects of drugs, was used to assess the effect of *dextro*-morphine on the morphine-produced motivational effects. In this procedure, the association that develops between the presentation of a drug and a previously neutral stimulus, e.g. different colored compartment of a shuttle box is evaluated. The results obtained with this paradigm for rewarding drugs done by others are largely identical to those obtained with the self-administration paradigm technique (Spiraki, 1988; Carr et al., 1989).

Previous studies have demonstrated that  $\mu$ -opioid agonists such as morphine, D-Ala<sup>2</sup>-N-MePhe<sup>4</sup>-Gly<sup>5</sup>-ol-enkephalin or endomorphin-1 given systemically or intracerebroventricularly in mice or rats produce conditioned place preference (Neisewander et al., 1990; Piepponen et al., 1997; Suzuki et al., 1991; Terashvili et al., 2004; Wu et al., 2004). The results of our present studies are consistent with previous findings that morphine given subcutaneously dose-dependently produced conditioned place preference. The conditioned place preference produced by morphine is blocked by  $\mu$ -opioid receptor antagonist naltrexone or naloxonazine, indicating that the effect is mediated by the stimulation of  $\mu$ -opioid receptors (Olmstead and Burns, 2005; Piepponen et al., 1997).

Unlike optically *levorotatory* morphine alkaloid, which produces analgesia and other  $\mu$ -opioid receptor-mediated pharmacological effects, the *dextrorotatory dextro*-morphine does not have any affinity and efficacy for  $\mu$ -opioid receptors and therefore does not produce analgesia and other  $\mu$ -opioid receptor mediated effects (Jacquet et al., 1977). We found in the present studies that *dextro*-morphine at a dose 3  $\mu$ g/kg given systemically did not produce conditioned place preference or nor did it produce the conditioned place aversion. Mucha and Herz (1986) have previously reported that *dextro*-morphine even at a much higher dose 4 mg/kg given systemically does not produce any conditioned place preference or conditioned place aversion. Morphine at the same dose, on the other hand, produces conditioned place preference. These findings are consistent with the view that *dextro*-morphine does not interact with the  $\mu$ -opioid receptors and does not produce conditioned place preference or conditioned place aversion (Jacquet et al., 1977; Mucha and Herz, 1986). Thus, the conditioned place preference produced by morphine is stereospecific; it is only produced by the opioid receptor active isomers, such as *levorotatory* morphine, but not *dextrorotatory dextro*-morphine.

##### 4.2. *dextro*-Morphine at a dose range 0.1–100 $\mu$ g/kg given systemically produce a U-shaped dose-response curve in attenuating the morphine-produced conditioned place preference

We found in the present study that *dextro*-morphine at a dose range of 0.1–3  $\mu$ g/kg dose-dependently attenuated the morphine-produced conditioned place preference. Paradoxically, *dextro*-morphine at a higher dose 100  $\mu$ g/kg was ineffective in attenuating the morphine-produced conditioned place preference. Thus, *dextro*-morphine at a dose range from 0.1 to 100  $\mu$ g/kg induces a U-shaped dose-response curve with a maximal attenuation at a dose of 3  $\mu$ g/kg for attenuating the morphine-produced conditioned place preference. The therapeutic window of the dose of *dextro*-morphine for the anti-addiction therapy should be in the  $\mu$ g/kg dose range. Higher doses of *dextro*-morphine would not be effective in providing the therapeutic effect. *dextro*-Morphine can potentially be developed for the treatment of opiate addiction.

The U-shaped dose-response curve is also known as hormesis (Calabrese and Baldwin, 2003). A well-documented example of a U-shaped dose-response relationship concerns the actions of corticosteroid hormones in the CA1 area of the hippocampus (Diamond et al., 1992; Joëls and de Kloet, 1994; Joëls, 2006), a brain region that is important for learning and memory formation. The neurosteroids have been proposed to be the endogenous ligand for sigma<sub>1</sub> receptors in the central nervous system (Maurice, 2004; Maurice et al., 2001; Monnet and Maurice, 2006). In a modified passive-avoidance learning task in mice, pre-training or post-training administration of neurosteroids, pregnenolone sulfate or dehydroepiandrosterone sulfate enhances memory retention of passive-avoidance training. In both treatments, an inverted U-shaped dose-response curve is obtained covering 2- to 5-fold dose range in a manner typical for memory-enhancing substance. The neurosteroid-induced facilitation of memory retention may involve central sigma receptors, because the effect of neurosteroids is completely antagonized by sigma receptor antagonist haloperidol (Reddy and Kulkarni, 1998). It is postulated that *dextro*-morphine may mimic the effect of endogenous neurosteroids to stimulate the sigma<sub>1</sub> receptors for producing the anti-addictive effect (see details in the next section below). The U-shaped dose-response curve for *dextro*-morphine to attenuate the morphine conditioned place preference is consistent with this hypothesis.

##### 4.3. The attenuation of the morphine-produced conditioned place preference by *dextro*-morphine is mediated by sigma<sub>1</sub> receptor activation

Most of *dextrorotatory* opiates such as (+)-pentazocine and (+)-N-allyl-normetazocine ((+)-SKF10047) exhibit the sigma<sub>1</sub> receptor binding activity (Walker et al., 1992; Martin et al., 1984; De Costa et al., 1989). We therefore speculate that *dextro*-morphine acts on sigma<sub>1</sub> receptors to attenuate the increase of the conditioned place preference produced by morphine. BD1047, a selective sigma<sub>1</sub> receptor antagonist (McCracken et al., 1999) was then used to determine if the effect of *dextro*-



morphine is mediated by the  $\sigma_1$  receptor activation. We found in the present study that pretreatment with BD1047 dose-dependently reversed the attenuation of the morphine-produced conditioned place preference induced by *dextro*-morphine, indicating that  $\sigma_1$  receptors are involved in *dextro*-morphine-induced anti-addiction. The  $\sigma_1$  receptor stimulatory property of *dextro*-morphine can also be found in our other studies of the antianalgesic effect of *dextro*-morphine. Pretreatment with *dextro*-morphine attenuates the morphine-produced analgesia (Wu et al., 2005). The attenuation of the morphine-produced analgesia was also blocked by the pretreatment of the BD1047 (unpublished observation).

A role for  $\sigma_1$  receptors in antinociception has been demonstrated from the studies that show a relationship between  $\sigma_1$  receptor system and opioid analgesia (Chien and Pasternak, 1993, 1994, 1995; Guitart et al., 2004). Activation of  $\sigma_1$  receptors by the selective  $\sigma_1$  receptor agonist (+)-pentazocine given supraspinally or systemically attenuate the antinociception produced by morphine. (+)-Pentazocine given supraspinally also attenuates the antinociception produced by  $\delta$ - and  $\kappa$ -opioid agonists as well. On the other hand, the blockade of  $\sigma_1$  receptors with the  $\sigma_1$  antagonist haloperidol potentiates the morphine-produced analgesia (Chien and Pasternak, 1995; Mei and Pasternak, 2002). Pretreatment with antisense oligodeoxynucleotide to down regulate the  $\sigma_1$  receptors markedly enhances the antinociception produced by morphine (Mei and Pasternak, 2002). These observations indicate that  $\sigma_1$  receptors also play an important role in modulating the opioid analgesia.

The recent demonstration of Romieu et al. (2003) that neurosteroids, endogenous ligands for  $\sigma_1$  receptors, are able to modulate the acquisition of the cocaine-induced conditioned place preference suggests their influence on acquisition of drug addiction. Neurosteroids pregnenolone and dehydroxypregnenolone potentiates the acquisition of the cocaine-induced conditioned place preference, as do selective  $\sigma_1$  receptor agonists, like igmesine or PRE-084, and the effect is blocked by the  $\sigma_1$  receptor antagonist BD1047 (Romieu et al., 2002). Selective  $\sigma_1$  receptor antagonist, like BD1047 or NE100, or antisense oligodeoxynucleotide probe targeting the  $\sigma_1$  receptor also blocks acquisition or expression of the cocaine-induced conditioned place preference in mice (Romieu et al., 2000, 2002; Maurice et al., 2002). Similar observations could be presented for abuse of amphetamine and alcohol, which also involve  $\sigma$  receptor activation (Nguyen et al., 2005; Strefanski et al., 2004; Maurice et al., 2003). The activation of  $\sigma_1$  receptors by  $\sigma_1$  receptor agonist SA4503 (1-(3,4-dimethoxyphenethyl)-4-(phenylpropyl)piperazine) attenuates the acquisition of the conditioned place preference produced by nicotine (Horan et al., 2001). These observations clearly indicate that  $\sigma_1$  receptors are involved in the conditioned place preference produced by cocaine, amphetamine, alcohol and nicotine as well.

It is concluded that *dextro*-morphine at a  $\mu\text{g/kg}$  dose range given systemically attenuates the morphine-produced conditioned place preference. The attenuation of the morphine-produced conditioned place preference induced by *dextro*-

morphine was reversed by the pretreatment with the  $\sigma_1$  receptor antagonist BD1047, indicating that the effect of *dextro*-morphine is mediated by  $\sigma_1$  receptor activation. It is speculated that *dextro*-morphine can potentially be developed for the treatment of opiate addiction.

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