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Effects of dextromethorphan on nocturnal behavior and brain c-Fos expression in adolescent rats

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Abstract

Dextromethorphan, an antitussive widely available over-the-counter, is abused, mostly by teenagers at high doses. In our previous report, a high dose of dextromethorphan activated the midbrain dopamine neurons of adolescent rats. In the present study, we performed c-Fos immunohistochemistry in the dopaminergic terminal regions of adolescent rat brain after the intraperitoneal administration of dextromethorphan at different doses (0, 10, 20, and 40 mg/kg), and also examined the effects on nocturnal behavior. The results showed that dextromethorphan increased c-Fos expression dose dependently in the anterior cingulate cortex, caudate putamen, nucleus accumbens, and central amygdala. Significant ataxia occurred and both locomotor and rearing activity decreased immediately after the dextromethorphan injection. We conclude that the neurons in the reward pathway of the adolescent rat brain appear to be activated by a single injection of dextromethorphan, and that activation of this pathway by dextromethorphan may correlate with the behavioral effects and abuse potential of the drug.

Keywords: Dextromethorphan; c-Fos; Drug abuse; Nocturnal behavior; Reward pathway

1. Introduction

Dextromethorphan, a non-competitive receptor antagonist of the *N*-methyl-D-aspartate (NMDA)-type of excitatory amino acid receptors, has long been used as a cough suppressant at low doses (30–60 mg/day, p.o.) (Bem and Peck, 1992). Recently, dextromethorphan has been clinically studied as potential treatment at relatively high doses for neurodegenerative diseases, chronic pain and epilepsy because of its neuroprotective and anticonvulsant properties (Tortella et al., 1989; Katz, 2000). However, it has been reported that teenage groups in some countries, such as the United States of America, Canada, and South Korea, abuse dextromethorphan, using high doses (300 mg/day or more) (Murray and Brewerton, 1993; Yoo et al., 1996).

The potential of dextromethorphan, not only as a neuroprotective drug (Verhagen Metman et al., 1998), but also as a drug of abuse, was supported by our previous study showing that a high dose of dextromethorphan activated midbrain dopamine neurons by increasing the gene expression of tyrosine hydroxylase, the rate-limiting enzyme of dopamine biosynthesis (Zhang et al., 2001). In the present study, we examined the neurons in the dopaminergic terminal regions of the brain to determine whether dextromethorphan activated the nigro-striatal and mesolimbic reward pathway. c-Fos immunohistochemistry, a conventional marker of neuronal activation, was performed in the rat brain regions involved in the reward pathway after dextromethorphan administration at different doses.

Although dextromethorphan, like some other NMDA receptor antagonists, activates midbrain dopamine neurons, its effects on rodent behavior have been found to vary among different investigations (Ginski and Witkin, 1994; Wu et al., 1995). We suggest that the effects of dextromethorphan on rodent behavior in the previous reports might have been masked by a 'ceiling' or 'floor' effect, because all the behavioral tests reported so far were carried out during the daytime, a period when the baseline locomotor activity of these nocturnal animals is low (Kelley, 1993). Furthermore, our previous study showed that the behavioral activity of rats increases significantly during nighttime, compared to daytime (Kim et al., 1999). Hence to avoid the possible 'floor' effect on daytime behavioral activity, we performed the present experiments during

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nighttime and used female rats since female rats are known to be more sensitive to NMDA receptor antagonists (Nabeshima et al., 1984; Ellison, 1995). Also, adolescent rats were used because dextromethorphan abuse occurs among teenagers (Murray and Brewerton, 1993; Yoo et al., 1996).

2. Materials and methods

2.1. Animals

Animals were supplied from the Division of Laboratory Animal Medicine, Yonsei University College of Medicine. All animal experiments were approved by the Committee for the Care and Use of Laboratory Animals at Yonsei University (Project license number #00204). Animals were cared for according to The Guide for Animal Experiments, 2000, edited by the Korean Academy of Medical Sciences, which is consistent with the NIH Guideline Guide for the Care and Use of Laboratory Animals, 1996 revised. In brief, Sprague-Dawley rats were housed and mated in a specific pathogen-free barrier area with a consistently controlled temperature (22 ± 1 °C) and humidity (55%) under a 12:12-h light/dark cycle (lights on 07:00 h). Pups were divided by sex, weighed and culled on postnatal day 2 to litters of five females each; the male pups were discarded.

Four pups in each of six different litters were used for the behavioral test at 4 to 5 weeks of age. One pup in each litter was assigned to the saline-injected (0 mg/kg of dextromethorphan) control group and the remaining three to the three different dextromethorphan doses (10, 20, and 40 mg/kg), and the fifth one was discarded. Therefore, the pups in each litter were evenly distributed over the saline and the dextromethorphan groups. The same rats were used for both the behavioral test and c-Fos immunohistochemistry.

2.2. Drug

Dextromethorphan HBr was purchased from Sigma (St. Louis, MO, USA). All other chemicals were of analytical reagent grade. Dextromethorphan was dissolved in physiological saline and injected intraperitoneally, in a volume of 2 ml/kg.

2.3. Behavioral assessment

Drug administration and the behavior test were performed under specific pathogen-free conditions. Dextromethorphan at each dose (0, 10, 20, and 40 mg/kg) was injected into the rats at 20:00 h, 1 h after the onset of the dark period, and the behavioral assessment was carried out immediately after the injection. For the measurement of locomotor activity, the rats were placed in an activity chamber (43.2 cm wide, 43.2 cm long, 30.5 cm high, MED Associates, VT, USA), one at a time, and their ambulatory and rearing activities were measured. The transparent acryl chamber was equipped with two horizontal planes (2.5 cm above the floor for the ambulation count and 12.7 cm for the rearing count) of 16 infrared photocell-detector pairs in each x, y dimension, spaced 2.5 cm apart. Animals were placed in the test room 6 h before the test. The light in the test chamber was adjusted to 2 lux of dimness 30 min prior to the test. This setting allowed just enough light for the tester to observe the movement of rats at a distance of 50 cm. Rats were acclimatized to the chamber for 30 min before drug injection and then, immediately after the injection, the ambulatory and rearing activities were recorded automatically for 150 min at 10-min intervals. The test chamber was cleaned with 70% ethanol after use to avoid any influence of the previously tested rat.

Ataxia was defined as impairment in the ability of the animal to execute coordinated motor responses, leading in the extreme to incapacitation. The ataxia was rated by the modified method of Sturgeon et al. (1979): 0, inactive or in-place activity, coordinated movement; 1, unusual, awkward or jerky movement, loss of balance during rearing, occasional falling sidewards; 2, awkward or jerky movements, moderate rate of falling sidewards while rearing or moving about; 3, frequent falling on backwards and/or sidewards while moving, partial impairment of antigravity reflexes. The ataxia rating was done for 1 min at the end of every 10-min period during the first 1 h after the injection. The total scores of the six different time-points were cumulated for the statistical analyses.

2.4. c-Fos immunohistochemistry

Thirty minutes after the end of the 150-min behavioral tests, and 3 h after dextromethorphan administration, the rats were deeply anesthetized with an overdose of sodium pentobarbital injected intraperitoneally and then transcardially perfused with heparinized isotonic saline (0.9% NaCl, 0.5% $NaNO_2$), followed by ice-cold fixative (4% paraformaldehyde, 0.1 M phosphate buffer, pH 7.2). The brains were immediately dissected out and post-fixed for 2 h in the same fixative and then cryoprotected with 30% sucrose solution for 24 h prior to sectioning. The brains were coronally sectioned at 40 μm thickness with a freezing, sliding microtome (MICROM Laborgeräte, Walldorf, Germany). Three consecutive sections each from two brain regions, at the closest levels to $+1.6$ or -2.56 mm from bregma (Paxinos and Watson, 1986), respectively, were prepared from each rat and processed for c-Fos immunohistochemistry.

Immunohistochemistry was carried by a conventional method using the Vector Elite ABC kit (Vector Laboratories, CA, USA) as described previously (Jahng et al., 1998). The rabbit anti-c-Fos polyclonal antibodies (Onco-

gene Research Product, Cambridge, HA, USA, Ab-5, 1:20,000) bound on the sections were visualized after a 5-min reaction with 0.05% of diaminobenzidine. The immunostained sections were mounted on gelatin-subbed slides in 0.05 M phosphate buffer, air dried, dehydrated through graded ethanol to xylene, and coverslipped. Results were analyzed by using a light microscope with the MCID imaging system (Imaging Research, Ontario, Canada). The number of c-Fos positive neurons within a unit area of 0.385 mm^2 in each section was counted.

2.5. Data analysis

Data are expressed as means ± S.E.M., and statistical analyses were completed with the aid of the StatView II program for Macintosh computers (Abacus Concepts, CA, USA). All data were analyzed by one-way analysis of variance (ANOVA) and preplanned comparisons with the control were performed by Dunnett's *t*-statistic.

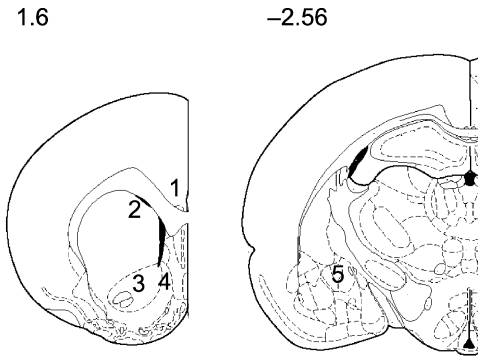

Fig. 2. Representative schematic diagram of each region analyzed. Numbers at the top left of each section represent the distance in millimeters from bregma. Numbers in the sections represent the regions analyzed as follows: 1, cingulate cortex; 2, caudate putamen; 3, nucleus accumbens core; 4, nucleus accumbens shell; 5, central amygdala. Drawings were adapted from the atlas by Paxinos and Watson (1986).

3. Results

3.1. Effects on nocturnal behavior

Decreases in locomotor activity were detected during the 150-min period after injection of dextromethorphan at high doses (20, 40 mg/kg). The locomotor activity of the 40 mg/kg-treated group was significantly impaired for the whole test period, but in the 20 mg/kg-treated group, a significant impairment was noticed only in the period between 30 and 90 min after the injection (Fig. 1A,B,C). Ataxia occurred immediately after the dextromethorphan injections at all doses and the severity of ataxia increased in a dose-dependent way (Fig. 1D). The rats treated with

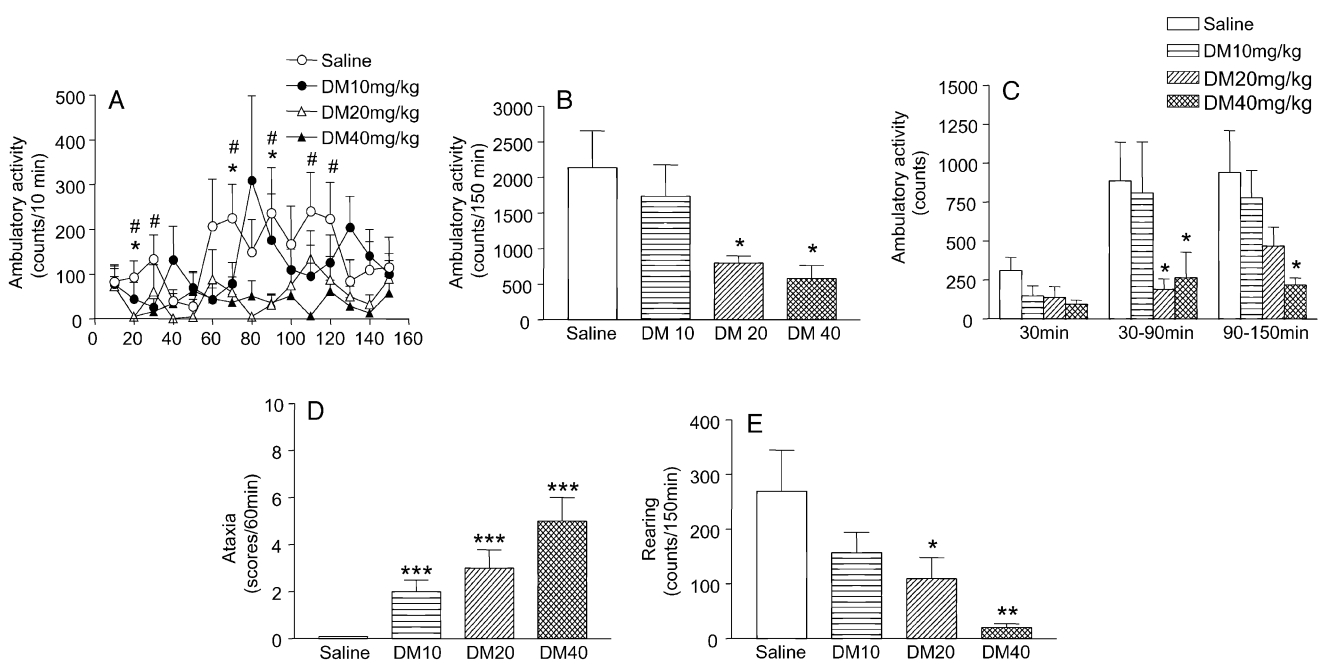

Fig. 1. Effects of acute dextromethorphan at different doses on the nocturnal behavior of adolescent female rats. Dextromethorphan was intraperitoneally injected into the rats 1 h after the onset of the dark period at doses of 0, 10, 20, and 40 mg/kg, and the behavioral assessment was performed immediately after the injection. Ambulatory activity and rearing were measured for 150 min, and ataxia was evaluated as cumulative scores of the behavioral rating measured for 1 min at the end of every 10 min over a 60-min period. (A) ambulatory activity, (B) cumulative ambulatory activity, (C) ambulatory counts summed in 30 or 60 min bins, (D) ataxia, (E) rearing. The saline group and each dextromethorphan group all comprised six rats ($n = 6$). All values are means ± S.E.M. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, degree of significance for each dextromethorphan group compared with the saline group; $\#P < 0.05$, degree of significance for the 40 mg/kg-treated dextromethorphan group compared with the saline group in (A). DM, dextromethorphan.

dextromethorphan frequently showed jerky movements and a loss of balance during rearing. Rearing also decreased dose dependently with the loss of balance (Fig. 1E).

3.2. c-Fos immunoreactivity in the brain

The number of c-Fos-immunopositive cells 3 h after the dextromethorphan injection was counted in each brain region, using the MCID image analysis system (Fig. 2). Representative microscopic pictures of the brain regions of the adolescent female rats showed a strong induction of c-Fos expression by high doses of dextromethorphan (Fig. 3).

Dextromethorphan dose dependently increased the number of c-Fos-immunopositive cells in the cingulate cortex, the dorsal caudate putamen, the nucleus accumbens core and shell, and the central amygdala (Fig. 4). The most significant dose-dependent effect on c-Fos induction by dextromethorphan was found in the central amygdala.

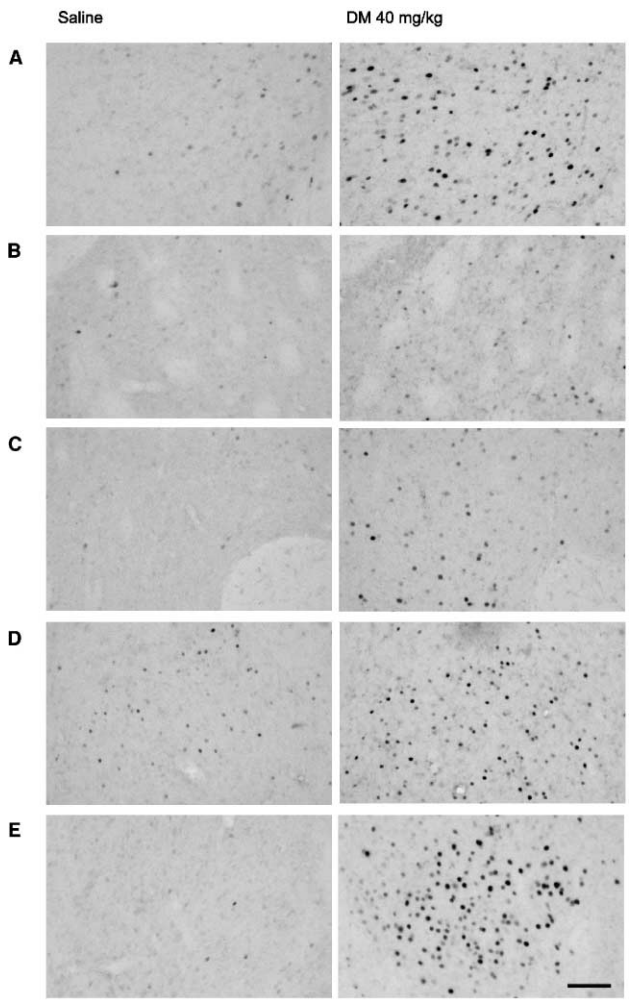

Fig. 3. Representative microscopic pictures of c-Fos immunohistochemistry. Pronounced increases in c-Fos immunoreactivity were detected in all brain regions examined 3 h after the dextromethorphan injections. A, anterior cingulate cortex; B, caudate putamen; C, nucleus accumbens core; D, nucleus accumbens shell; E, central amygdala. Scale bar: 100 μm.

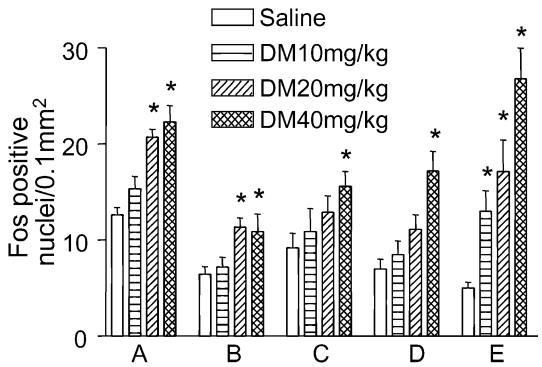

Fig. 4. Number of c-Fos-positive cells in each brain region. Rats were killed for c-Fos immunohistochemistry 3 h after the injection of dextromethorphan at different doses (0, 10, 20, and 40 mg/kg). Number of c-Fos-positive neurons in the examined areas was significantly increased by dextromethorphan in a dose-dependent manner, with the greatest dose effect occurring in the central amygdala. $^{*}P < 0.05$, degree of significance compared with the saline group. A, anterior cingulate cortex; B, caudate putamen; C, nucleus accumbens core; D, nucleus accumbens shell; E, central amygdala.

4. Discussion

The results showed that acute dextromethorphan at high doses decreases the nocturnal locomotor activity of rats in a dose-dependent manner. A number of previously published reports examining daytime behavior have shown inconsistent results for the effect of dextromethorphan on locomotor activity. Whereas Ginski and Witkin (1994) reported that dextromethorphan had no effect on daytime locomotor activity at all, Wu et al. (1995) reported that acute dextromethorphan at a high dose (60 mg/kg) increased locomotor activity 60 min after intraperitoneal injection, but not after subcutaneous injection. They suggested that the increased locomotor activity following intraperitoneal, but not subcutaneous, dextromethorphan implies that the major metabolite of dextromethorphan, dextrophan, which produces phencyclidine-like behavioral effects, may be responsible for the effects on locomotor activity. It also has been reported that dextrophan affects locomotor activity (Szekely et al., 1991). However, the behavioral effects of dextromethorphan in our present study occurred too quickly to expect an action of its metabolite, that is, the behavioral changes including locomotor activity were detected immediately after dextromethorphan injection.

In our preliminary experiment, daytime locomotor activity was not changed by dextromethorphan. We also noticed that the rats showed minimal baseline activity during daytime, no doubt because they are nocturnal animals. Being suspicious of the daytime results reported by others because rats show very low baseline activity during

the daytime, we decided to examine their locomotor activity at nighttime, when they are in their active phase. We found that a high dose of dextromethorphan immediately decreased nocturnal locomotor activity. Consistent with the decreased ambulation, rearing was also decreased by dextromethorphan administration in a dose-dependent manner. Acute dextromethorphan at doses of 5–80 mg/kg has been reported to cause modest muscle relaxation in mice (Kaur and Starr, 1995), which might explain the effects of this drug in decreasing both locomotor activity and rearing.

All previous reports about the effects of dextromethorphan on locomotor activity were daytime studies using both male and female adult rats. In this study, we performed the behavioral tests during the nighttime and used only adolescent female rats. We believe that these different experimental conditions might have yielded different results, because we previously found that not only the nocturnal ambulatory activity of rats was far higher than their daytime activity, but also that female rats exhibited significantly greater behavioral activity than male rats during adolescence (Kim et al., 1999).

Our study demonstrated that significant induction of c-Fos expression by dextromethorphan occurred in the nucleus accumbens, both core and shell, and in the caudate putamen. The striatum is considered to be the main brain region involved in the alteration of stereotyped behavior induced by dopaminergic agonists (Perez et al., 1998), and, actually, a high dose of dextromethorphan acutely increased the gene expression of tyrosine hydroxylase, the rate-limiting enzyme of dopamine biosynthesis, in the midbrain dopaminergic neurons (Zhang et al., 2001). In the present report, the dextromethorphan-induced c-Fos expression in the striatum may partly be a secondary effect of the dextromethorphan-induced activation of the midbrain dopamine neurons innervating the striatum. Taken together, dextromethorphan at high doses appeared to activate the nigro-striatal dopaminergic pathway and this may partly contribute to an increase in stereotyped behavior. However, dextromethorphan did not significantly change the stereotyped behavior of female rats during the nighttime in the present study (data not shown). We speculate that the effect of dextromethorphan in increasing stereotyped behavior, if it did, might be hidden by the increased baseline activity during nighttime.

We also found that dextromethorphan dose dependently induced c-Fos expression in the cingulate cortex and central amygdala. c-Fos induction by dextromethorphan in the cingulate cortex may reflect a cytotoxic effect of dextromethorphan as a NMDA receptor antagonist, because it has been reported that the cingulate cortex is a predominant site of the cytotoxic effect of various NMDA receptor antagonists, such as phencyclidine, MK-801, and even dextrophan, the major metabolite of dextromethorphan (Nakki et al., 1995; Lan et al., 1997). The nucleus of the central amygdala appears to be implicated in the reward pathway. There is a bi-directional innervation between the ventral tegmental area and the central amygdala. Dopaminergic neurons in the ventral tegmental area project to the central amygdala and the efferent fibers from the central amygdala project to the ventral tegmental area. Together, these projections constitute part of the mesolimbic reward circuit (Rodriguez de Fonseca and Navarro, 1998). The dose-dependent induction of c-Fos expression by dextromethorphan in the central amygdala suggests that this area might be targeted by high doses of dextromethorphan for the emotional seeking behavior associated with the drug of abuse.

The mechanism of c-Fos induction by dextromethorphan is not clear. We speculate that the c-Fos induction by dextromethorphan may be mediated, at least partly, by phencyclidine sites, because it has been reported that phencyclidine induces c-Fos expression in brain regions directly or indirectly by various kinds of receptors including sigma (σ) sites, NMDA-ion channel receptor complex and D-1 dopamine receptor (Dahmen et al., 1996; Sharp, 1997; Griffiths et al., 1999; Vaisanen et al., 1999), and dextromethorphan as well as its major metabolite, dextrophan, bind to the phencyclidine sites (Murray and Leid, 1984; DeHaven-Hudkins et al., 1993).

The pattern of c-Fos induction by acute dextromethorphan might have not been directly related to its behavioral effects in this study. However, it should be noticed that the reward pathway appeared to be activated by a single injection of dextromethorphan, that the behavioral alterations occurred concomitantly, and that, therefore, repeated injections of dextromethorphan, as commonly occurring with abuse drugs, may generate more provocative effects on brain function and behavior. In this regard, we found that behavioral sensitization had occurred in adolescent female rats 10 days after a daily intraperitoneal injection with dextromethorphan at a dose of 40 mg/kg/day between postnatal days 28 and 37, as well as after a challenge with the same dose at postnatal day 45 (Zhang et al., 1999).

In conclusion, this study is relevant because it is the first behavioral report of the effect of dextromethorphan on nocturnal animals, rodents, studied during the nighttime, when they are in the active phase. Also, the use of adolescent rats provides a better chance of understanding the abuse potential of this drug, which is abused mostly by teenagers. Our results showed that dextromethorphan increased c-Fos expression dose dependently in the brain regions implicated in the reward pathway, including the anterior cingulate cortex, caudate putamen, nucleus accumbens, and central amygdala. The behavioral alterations included ataxia and decreases in rearing and locomotor activity, and were detected immediately after the dextromethorphan injection. Taken together with our previous reports on the behavioral sensitization and the activation of midbrain dopamine neurons by dextromethorphan (Zhang et al., 1999, 2001), we suggest that the neurons in the reward pathway of adolescent rat brain appear to be acti-

vated by a single injection of dextromethorphan, and that the activation of this pathway by dextromethorphan may correlate with the behavioral effects and abuse potential of the drug. However, the mechanism of c-Fos induction in the brain regions by dextromethorphan needs to be studied further.

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