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Minocycline Attenuates Hyperlocomotion and Prepulse Inhibition Deficits in Mice after Administration of the NMDA Receptor Antagonist Dizocilpine

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The present study was undertaken to examine whether the second generation antibiotic drug minocycline attenuates behavioral changes (eg, acute hyperlocomotion and prepulse inhibition (PPI) deficits) in mice after the administration of the *N*-methyl-D-aspartate (NMDA) receptor antagonist (+)-MK-801 (dizocilpine). Dizocilpine (0.1 mg/kg)-induced hyperlocomotion was significantly attenuated by pretreatment with minocycline (40 mg/kg). Furthermore, the PPI deficits after a single administration of dizocilpine (0.1 mg/kg) were attenuated by pretreatment with minocycline (10, 20, or 40 mg/kg), in a dose-dependent manner. Moreover, *in vivo* microdialysis study in the free-moving mice revealed that pretreatment with minocycline (40 mg/kg, i.p.) significantly attenuated the increase of extracellular dopamine (DA) levels in the frontal cortex and striatum after administration of dizocilpine (0.1 mg/kg), suggesting that the inhibition of dizocilpine-induced DA release by minocycline may, at least in part, be implicated in the mechanism of action of minocycline with respect to dizocilpine-induced behavioral changes in mice. These findings suggest that minocycline could attenuate behavioral changes in mice after the administration of the NMDA receptor antagonist dizocilpine. Therefore, it is possible that minocycline would be a potential therapeutic drug for schizophrenia.
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INTRODUCTION

Multiple lines of evidence suggest that a dysfunction in the glutamatergic neurotransmission via the *N*-methyl-D-aspartate (NMDA) receptors might be involved in the pathophysiology of schizophrenia (Javitt and Zukin, 1991; Olney and Farber, 1995; Coyle, 1996; Krystal *et al*, 1999; Tamminga, 1998; Hashimoto *et al*, 2003, 2004, 2005). Therefore, the NMDA receptor antagonists such as (+)-MK-801 (dizocilpine) have been used widely in animal models for schizophrenia (Al-Amin and Schwarzkopf, 1996; Hashimoto *et al*, 1997; Bakshi and Geyer, 1998; Varty *et al*, 1999; Morimoto *et al*, 2002; Okamura *et al*, 2004).

Prepulse inhibition (PPI) of the acoustic startle response is a form of sensorimotor gating, defined as an inhibition of the startle response when a low-intensity stimulus, the prepulse, precedes the startling stimulus (Braff and Geyer, 1990; Braff and Freedman, 2002; Geyer *et al*, 2001). Deficits in PPI have been reported in several psychiatric disorders including schizophrenia, suggesting that deficient PPI *per se* or abnormalities in neural circuits regulating PPI may cause some symptoms (eg, cognitive deficits) of schizophrenia (Braff and Geyer, 1990; Perry *et al*, 1999; Swerdlow and Geyer, 1998; Braff and Freedman, 2002). In experimental animals, PPI deficits can be induced by the administration of the NMDA receptor antagonist dizocilpine (Al-Amin and Schwarzkopf, 1996; Bakshi and Geyer, 1998; Varty *et al*, 1999; Yee *et al*, 2004; Long *et al*, 2006). Therefore, pharmacological models of PPI deficits by NMDA receptor antagonism are excellent predictors of antipsychotic activity (Swerdlow and Geyer, 1998; Geyer *et al*, 2001; Levin *et al*, 2005).

Accumulating evidence suggest that the second-generation tetracycline minocycline produces neuroprotective effects in several animal models of neurological diseases, including Parkinson's disease (Du *et al*, 2001; Wu *et al*, 2002), amyotrophic lateral sclerosis (Zhu *et al*, 2002), Huntington's disease (Chen *et al*, 2000; Wang *et al*, 2003), and ischemia (Yrjanheikki *et al*, 1998, 1999). The neuroprotective effects of minocycline can occur indirectly by microglial activation and proliferation (Yrjanheikki *et al*, 1998; Tikka *et al*, 2001; Wu *et al*, 2002; Domercq and Matute, 2004; Yong *et al*, 2004; Blum *et al*, 2004; Thomas

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and Le, 2004; Stirling *et al*, 2005). Recently, we reported that minocycline could ameliorate the behavioral changes (eg, acute hyperlocomotion and the development of behavioral sensitization) and neurotoxicity in mice or monkey by the administration of methamphetamine or 3,4-methylenedioxymethamphetamine (Zhang *et al*, 2006a, b; Hashimoto *et al*, 2007), suggesting that minocycline may be a potential therapeutic drug for neuropsychiatric disorders including schizophrenia.

In this study, we investigated the effects of minocycline on behavioral changes (acute hyperlocomotion and PPI deficits) in mice induced by the administration of dizocilpine. Furthermore, using *in vivo* microdialysis technique, we examined the effects of minocycline on the dopamine (DA) release in prefrontal cortex and striatum after the administration of dizocilpine as DA in these brain regions has been implicated in the behavioral changes by the NMDA receptor antagonism.

METHODS

Animals

Male Std:ddy mice (8 weeks old, 32–39 g body weight at the beginning of the experiment) were housed under a 12-h light/12-h dark cycle (lights on from 0700 to 1900 h; room temperature, $22 \pm 2^{\circ}$C; humidity, $55 \pm 5\%$) with free access to food and water. All experiments were performed in accordance with the Guide for Animal Experimentation, Chiba University Graduate School of Medicine.

Drugs Administration

(+)-MK-801 hydrogen maleate (dizocilpine) (0.1 mg/kg. as a hydrogen maleate salt; Sigma-Aldrich Corporation, St Louis, MO), dissolved in physiological saline, was injected subcutaneously (s.c.) in a volume of 10 ml/kg. The dose (0.1 mg/kg) of dizocilpine was selected because this dose caused PPI deficits in mice. Minocycline hydrochloride (10, 20, or 40 mg/kg as a hydrochloride salt; Wako Pure Chemical Industries, Ltd, Osaka, Japan), dissolved in physiological saline, was injected intraperitoneally (i.p.) in a volume of 10 ml/kg. The other chemicals used were purchased from commercial sources.

Effects of Minocycline on Hyperlocomotion after a Single Administration of Dizocilpine

Thirty minutes after a single i.p. injection of minocycline (10, 20, or 40 mg/kg, $n=6$) or vehicle (10 ml/kg, $n=6$), dizocilpine (0.1 mg/kg, $n=6$) or vehicle (10 ml/kg, $n=6$) was administered s.c. into the mice. Locomotor activity was measured using an animal movement analysis system (SCANET SV-10, Melquest, Toyama, Japan), as reported previously (Zhang *et al*, 2006a). The system consisted of a rectangular enclosure (480×300 mm). The side walls (height, 60 mm) of the enclosure were equipped with 144 pairs of photosensors located at 5-mm intervals at a height of 30 mm from the bottom edge. An animal was placed in the observation cage 60 min from injection of vehicle or dizocilpine. A pair of photosensors was scanned every 0.1 s to detect the animal's movements. The intersection of paired photosensors (10 mm apart) in the enclosure was counted as one unit of locomotor activity. Data collected for 180 min were used in this study.

Measurement of Acoustic Startle Reactivity and Prepulse Inhibition of Startle

The mice were tested for their acoustic startle reactivity (ASR) in a startle chamber (SR-LAB, San Diego Instruments, CA) using standard methods described by Swerdlow and Geyer (1998). After an initial 10-min acclimation period in the chamber, the test sessions began. They consisted of six trial types: (1) pulse alone, 40 ms broadband burst; pulse preceded 100 ms by a 20 ms prepulse that was (2) 4 dB, (3) 8 dB, (4) 12 dB, or (5) 16 dB over background (65 dB); and (6) background only (no stimulus). The amount of PPI is expressed as the percentage decrease in the amplitude of the startle reactivity caused by presentation of the prepulse (% PPI).

For the effect of minocycline on PPI, minocycline (10, 20, or 40 mg/kg) or vehicle (10 ml/kg) were administered 40 min (including 10-min acclimation period) before the machine records, and dizocilpine (0.1 mg/kg) or vehicle (10 ml/kg) was administered s.c. 10 min (including 10-min acclimation period) before. The PPI test lasted 20 min in total.

In Vivo Microdialysis

Mice were anesthetized with sodium pentobarbital before the stereotaxic implantation of a probe into the left frontal cortex (+2.1 mm anteroposterior, +1.0 mm mediolateral from the bregma, and −1.2 mm dorsoventral with respect to dura) or striatum (+0.0 mm anteroposterior, +2.5 mm mediolateral from the bregma, and −4.4 mm dorsoventral with respect to dura). Probes were secured onto the skull using stainless-steel screws and dental acrylic. Twenty-four hours after surgery, *in vivo* microdialysis was performed on conscious mice. Probes were perfused continuously with artificial CSF (147 mM NaCl, 4 mM KCl, and 2.3 mM $CaCl_2$) at a rate of 2 μl/min. The dialysate was collected in 30-min fractions. Levels of DA were measured by high-performance liquid chromatography (HPLC) using a reversed phase column (Eicompak CA-5ODS 2.1 mm × 150 mm; Eicom, Kyoto, Japan), as reported previously (Zhang *et al*, 2006a). Four samples were obtained in order to establish the baseline levels of extracellular DA before the administration of dizocilpine.

Statistical Analysis

The data are presented as the mean ± standard error of the mean (SEM). The computation was carried out using the SPSS 12.0J software (SPSS 12.0J, Tokyo, Japan). The results of the acute behavioral study and *in vivo* microdialysis were analyzed by two-way analysis of variance (ANOVA) for repeated measures, with treatment as the between-subjects factor and time as the within-subjects factor. When appropriate, group means at individual time points were compared by one-way ANOVA, followed by Bonferroni/Dunn *a posteriori* analysis.

PPI was calculated as the percent inhibition of the startle amplitude evoked by the pulse alone: % PPI = 100 × (magnitude on pulse alone trial−magnitude on prepulse + pulse trial/magnitude on pulse alone trial). The PPI data were analyzed using a with treatment drug as a between-subjects factor and prepulse intensity as a within-subjects factor. There were significant effects of prepulse intensity (which were always significant), which will not be discussed, and drug treatment data were collapsed across prepulse intensity for presentation purposes. The PPI data were analyzed by multivariate analysis of variance (MANOVA). When appropriate, group means at individual dB levels were compared by one-way ANOVA, followed by Bonferroni/Dunn *a posteriori* analysis. The dose-dependent relationship was evaluated by MANOVA, followed by one-way ANOVA with contrast (polynomial). Significance for the results was set at $p < 0.05$.

RESULTS

Effects of Minocycline on Hyperlocomotion after a Single Administration of Dizocilpine

A single administration of dizocilpine (0.1 mg/kg, s.c.) markedly increased locomotion in mice. Two-way ANOVA analysis revealed significant differences among the five groups studied ($F(44, 275) = 2.599$, $p < 0.0001$). Pretreatment with minocycline (40 mg/kg, i.p., 30 min before the administration of dizocilpine) significantly attenuated dizocilpine-induced hyperlocomotion in mice (Figure 1). In contrast, administration of minocycline (40 mg/kg) alone did not alter locomotion in mice.

Effects of Minocycline on PPI Deficits after a Single Administration of Dizocilpine

Figure 2 shows the effects of minocycline (10, 20, or 40 mg/kg) on dizocilpine (0.1 mg/kg)-induced PPI deficits in mice. The MANOVA analysis of all PPI data revealed that there was a significant effect (Wilks lambda = 0.395, $p < 0.001$). Subsequent ANOVA analysis revealed significant differences at all dB groups (4, 8, 12, and 16 dB). A *posteriori* analysis indicated a significant ($p < 0.01$) difference between vehicle + vehicle group and vehicle + dizocilpine (0.1 mg/kg) group (Figure 2). Furthermore, *a posteriori* analysis demonstrated that minocycline (40 mg/kg) significantly ($p < 0.05$) attenuated PPI deficits in mice induced by dizocilpine (0.1 mg/kg) (Figure 2). Next, we analyzed whether the effects of minocycline on dizocilpine-induced PPI deficits were dose-dependent. The MANOVA analysis of four groups (0, 10, 20, and 40 mg/kg of minocycline) revealed a significance (Wilks lambda = 0.621, $p = 0.029$). Moreover, the subsequent analysis using contrast (polynomial) showed that minocycline significantly attenuated dizocilpine-induced PPI deficits at 8 dB ($p = 0.003$), 12 dB ($p < 0.001$), and 16 dB ($p < 0.001$), in a dose-dependent manner (Figure 2). In contrast, minocycline (40 mg/kg) alone did not alter PPI in mice (Figure 2).

Effects of Minocycline on Dizocilpine-Induced DA Release in the Frontal Cortex and Striatum

In order to explore the mechanisms by which minocycline inhibits the psychopharmacological effects of dizocilpine, we used an *in vivo* microdialysis technique to examine the *in vivo* effects of minocycline on the dizocilpine-induced increase in extracellular DA levels in the frontal cortex and striatum of conscious mice. A single administration of dizocilpine (0.1 mg/kg, s.c.) caused a marked increase in extracellular DA levels in the frontal cortex and striatum. Peak levels of extracellular DA were increased to approximately five-fold the baseline level. Two-way ANOVA analysis revealed significant differences among the three

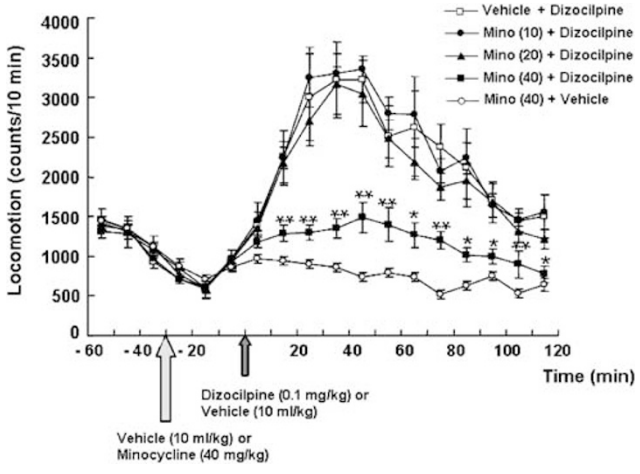

Figure 1 Effects of minocycline on dizocilpine-induced hyperlocomotion in mice. Thirty minutes after a single i.p. injection of minocycline (10, 20, or 40 mg/kg) or vehicle (10 ml/kg), dizocilpine (0.1 mg/kg) or vehicle (10 ml/kg) was administered s.c. into the mice. Behavior (locomotion) in the mice was evaluated. Each value (counts per 10 min) is the mean ± SEM ($n = 6$ per group). $^{*}p < 0.05$, $^{**}p < 0.01$ as compared with the vehicle + dizocilpine group.

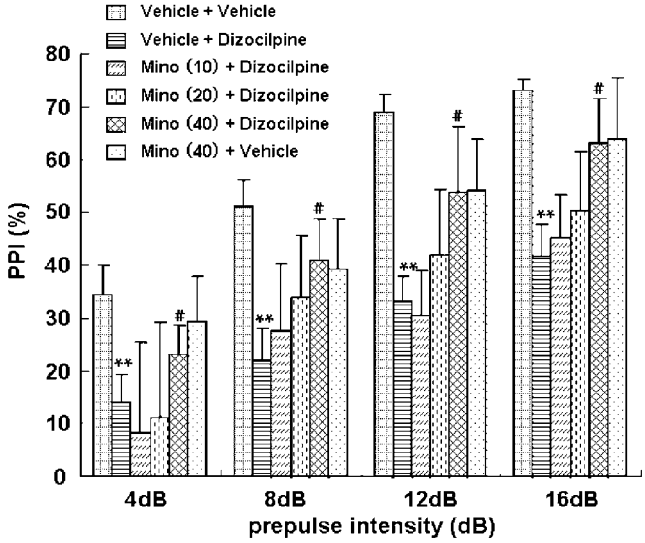

Figure 2 The effect of minocycline on dizocilpine-induced PPI deficits in mice. Thirty minutes after i.p. injection of vehicle (10 ml/kg) or minocycline (10, 20, or 40 mg/kg), dizocilpine (0.1 mg/kg) or vehicle (10 ml/kg) was administered s.c. to the mice. Each value is the mean ± SEM ($n = 12$–14 per group). $^{**}p < 0.01$ as compared with vehicle + vehicle group, $^{\#}p < 0.05$ as compared with vehicle + dizocilpine group.

groups studied (frontal cortex: $F(10, 110) = 58.47$, $p < 0.001$; striatum: $F(10, 100) = 60.07$, $p < 0.001$). Subsequent analysis revealed that pretreatment with minocycline (40 mg/kg, i.p., 30 min before dizocilpine treatment) significantly attenuated dizocilpine-induced increases in extracellular DA levels in the frontal cortex (Figure 3a) and in the striatum (Figure 3b). Effects of minocycline on dizocilpine-induced DA release in the frontal cortex were greater than those of minocycline in the striatum. In contrast, we found that minocycline alone did not alter the extracellular

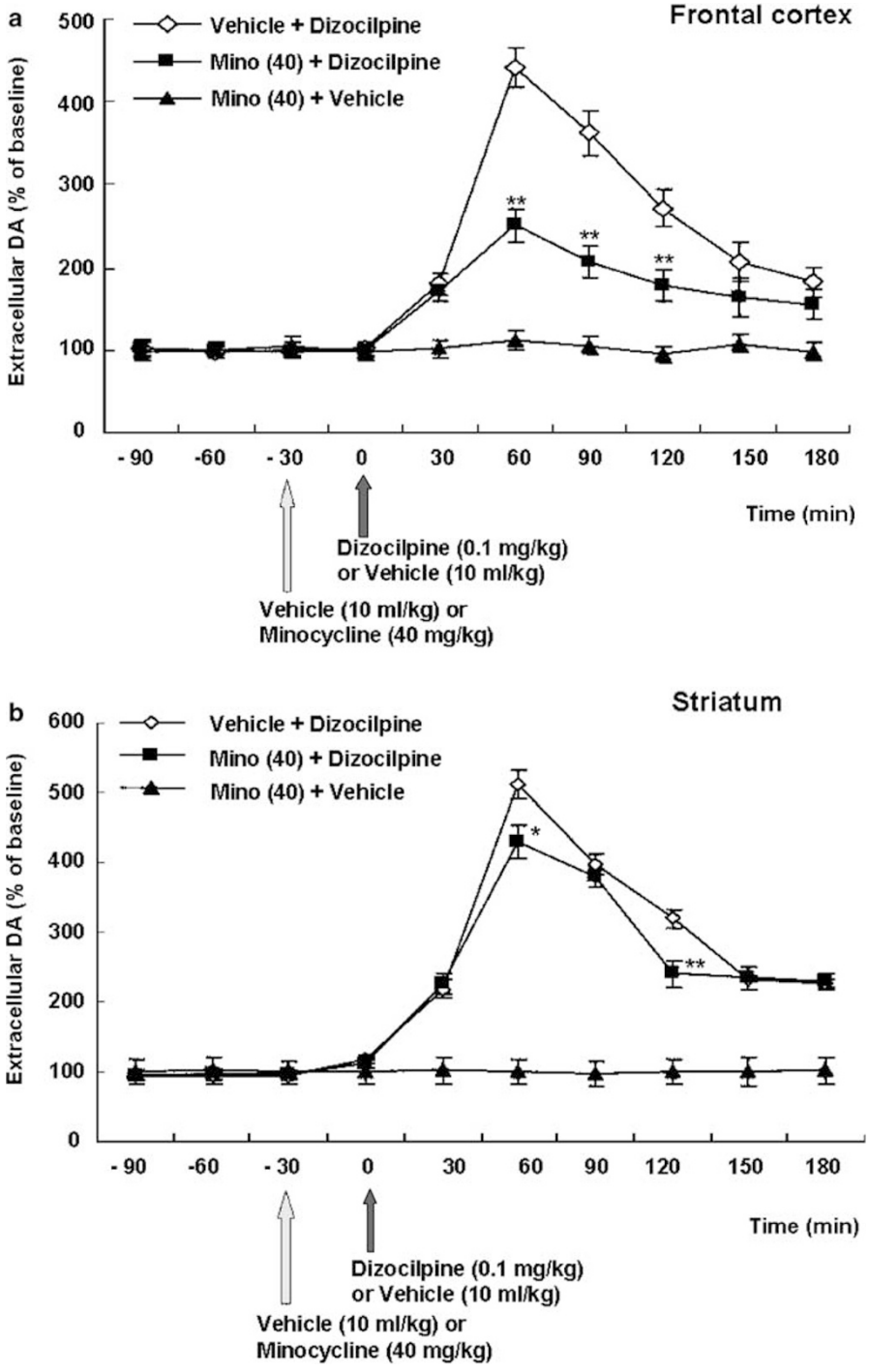

Figure 3 Effects of minocycline on extracellular DA levels in the frontal cortex and striatum after the administration of dizocilpine. Thirty minutes after i.p. injection of minocycline (40 mg/kg) or vehicle (10 ml/kg), MK-801 (0.1 mg/kg, s.c.) or vehicle (10 ml/kg, s.c.) was administered to mice. Extracellular levels of DA in the mouse frontal cortex (a) and striatum (b) were measured by *in vivo* microdialysis in conscious mice. The basal extracellular DA levels were 0.424 ± 0.019 pg/20 μl in the frontal cortex (mean ± SEM of 8–9 mice) and 2.697 ± 0.269 pg/20 μl in the striatum (mean ± SEM of 8–9 mice). $^{*}p < 0.05$, $^{**}p < 0.01$ compared with dizocilpine-treated group.

DA levels in the frontal cortex (Figure 3a) and striatum (Figure 3b).

DISCUSSION

The major findings of the present study are that minocycline significantly attenuated behavioral changes (hyperlocomotion and PPI deficits) in mice after the administration of dizocilpine, and that minocycline significantly attenuated increase of extracellular DA levels in the frontal cortex and striatum after the administration of dizocilpine. To our knowledge, this is the first report demonstrating that minocycline can restore behavioral changes (eg, hyperlocomotion and sensorimotor gating deficits) induced by the NMDA receptor antagonist dizocilpine. Several studies demonstrated that atypical antipsychotic drugs including clozapine can ameliorate hyperlocomotion and PPI deficits in mice after the administration of dizocilpine (Leriche *et al*, 2003; Levin *et al*, 2005; Lipina *et al*, 2005; Long *et al*, 2006). Therefore, our findings indicate that minocycline has a potential antipsychotic activity in animal models of schizophrenia.

Schizophrenia is associated with a dysregulation of DA function in both the prefrontal cortex and striatum (reviewed by Goldman-Rakic, 1999; Goldman-Rakic *et al*, 2004; Weinberger *et al*, 2001; Abi-Dargham and Moore, 2003), and the role of prefrontal cortex in working memory had received a great deal of attention because most patients with schizophrenia exhibit deficits in working memory-related tasks (reviewed by Goldman-Rakic, 1999; Goldman-Rakic *et al*, 2004). It has been reported that the NMDA receptor antagonists such as dizocilpine and ketamine dose-dependently impaired the spatial delayed alteration performance, and that these drugs preferentially increased the release of DA in the prefrontal cortex compared with the striatum of rats (Verma and Moghaddam, 1996). Interestingly, it has been reported that repeated administration of dizocilpine significantly increased the density of DA D1 receptors in the prefrontal cortex and decreased working memory performance in monkeys (Tsukada *et al*, 2005), indicating the dizocilpine-induced impairment of DA neuronal system in prefrontal cortex. A recent report showed that DA D1 receptor agonists rather than D2 receptor agonists disrupt PPI in mice, suggesting that DA D1 receptors may play a more prominent role in the modulation of PPI in mice (Ralph-Williams *et al*, 2003). Taken together, it is likely that the inhibition of dizocilpine-induced DA release by minocycline in the prefrontal cortex may be implicated in the mechanism of action of minocycline with respect to dizocilpine-induced PPI deficits in mice although the mechanism(s) underlying the modulation of dizocilpine-induced DA release by minocycline are currently unclear. Therefore, it is likely that minocycline may have potential therapeutic activity for schizophrenia.

Some studies demonstrated that the medial prefrontal cortex (mPFC) might be involved in the PPI deficits after the administration of dizocilpine (Bakshi and Geyer, 1998; Schwabe and Koch, 2004). First, it has been reported that dizocilpine significantly decreased PPI after infusion into the amygdala or dorsal hippocampus, but not nucleus accumbens, ventral hippocampus, or dorsomedial thalamus, and that a trend toward PPI deficits was also observed with administration into mPFC (Bakshi and Geyer, 1998). These findings suggest that multiple limbic forebrain regions including mPFC might mediate dizocilpine-induced PPI deficits in rats (Bakshi and Geyer, 1998). Second, Schwabe and Koch (2004) reported that dizocilpine failed to disrupt PPI in rats with ibotenic acid lesions of the mPFC, suggesting that mPFC is an important brain region within the neuronal circuit responsible for dizocilpine-induced PPI deficits. In this study, we found that the increase in extracellular DA levels in prefrontal cortex after the administration of dizocilpine was significantly attenuated by pretreatment with minocycline (40 mg/kg). Based on the key role of DA in the behavioral changes by the NMDA receptor antagonists, it is also likely that the inhibition of dizocilpine-induced DA release by minocycline in the prefrontal cortex may, in part, be implicated in the mechanism of action of minocycline with respect to dizocilpine-induced behavioral changes in mice.

Minocycline can readily cross the blood–brain barrier, regardless of the dose and route of administration (Barza *et al*, 1975; Aronson, 1980; Zhang *et al*, 2006a). Recent clinical trials have been aimed primarily at assessing the safety and tolerability of minocycline in several neurodegenerative diseases (reviewed by Blum *et al*, 2004; Domercq and Matute, 2004; Thomas and Le, 2004; Yong *et al*, 2004; Stirling *et al*, 2005; Smith and Leyden, 2005). In these clinical trials, minocycline was well tolerated at 200 mg/day over 6 months, and no side effects or negative interactions with other simultaneously administered drugs were observed (Domercq and Matute, 2004). Taken together, it might be of great interest to study the effects of minocycline on several symptoms in schizophrenic patients.

In conclusion, the present findings suggest that minocycline ameliorated behavioral changes (hyperlocomotion and PPI deficits) in mice after the administration of the NMDA receptor antagonist dizocilpine, and minocycline significantly attenuated the release of DA in the frontal cortex after the administration of dizocilpine. Therefore, minocycline would be a potential therapeutic drug for schizophrenia.

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