

Original Article

Antipsychotic-like effect of minocycline in a rat model

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Abstract: Objectives: Tetracycline antibiotic drug minocycline has strongly neuroprotective and anti-inflammatory effects. Minocycline has also remarkable brain tissue penetration, is clinically entirely tolerated and properly absorbed when taken orally. In our study, we class with the effects of minocycline and chlorpromazine, a conventional antipsychotic drug, by evaluating the novelty-induced rearing, apomorphine-induced stereotypic behavior, and brain MDA levels in rats. Materials and Methods: Four groups of rat (n = 7) were applied with minocycline (50 and 100 mg/kg, i.p.), chlorpromazine (1 mg/kg, i.p.), or isotonic saline (1 mL/kg, i.p.). One hour later, apomorphine (2 mg/kg, s.c.) was applied to each rat. Result: Our results showed that both doses of minocycline significantly decreased the rearing behavior in rats, whereas the decrease with chlorpromazine was higher. Minocycline also decreased the stereotypy scores in a dose-dependent manner. Conclusion: We concluded that minocycline has beneficial effects on rearing behavior and stereotypy, which are accepted to be indicators of antipsychotic effect. Taken together, minocycline, as an anti-oxidant and cytoprotective agent, can be useful in neuroprotection especially on early stages of psychosis or prepsychotic patients with insignificant symptoms. Minocycline is worthy of being investigated for its anti-psychotic effects as a primary or an adjunctive drug.

Keywords: Minocycline, schizophrenia, psychosis, novelty-induced rearing, stereotypic behavior

Introduction

Schizophrenia is one of the most mysterious and costliest mental disorders in terms of human suffering and societal expenditures [1]. In spite of comprehensive research and significant advances in the neurobiological, neurochemical and genetic point of view this disabling mental illness, the underlying etiological approaches remain a challenge for basic researchers and clinicians alike [2].

Schizophrenia is representing itself with characteristic set of symptoms which involve positive, negative and cognitive derangements. It is thought to have close relationship with hyperdopaminergic activity [3]. Based upon pharmacological, all in one clinical, evidence, hyperdopaminergic activity in the mesolimbic pathway is believed to be responsible for the positive symptoms, whereas hypodopaminergic activity in the mesocortical pathway triggers cognitive impairment and affective symptoms [4, 5].

Drugs applied in the treatment of the disease have the potential to cause extrapyramidal side effects by blocking D2 dopamine receptors generally located in the striatum [6, 7].

Majority of the studies reported a significant imbalance between oxidative stress levels and antioxidative enzyme activities in schizophrenia. For example, Pazvantoglu [8] demonstrated that the severity of the symptoms was negatively correlated with the total antioxidant potentials, whereas Padurariu [9] found conflicting results demonstrating the increased superoxide dismutase (SOD) activity and decreased glutathione peroxidase (GPx) activity in patients with schizophrenia compared to controls. However, the studies on the lipid peroxidation markers, such as malonyl dialdehyde (MDA) and 4-hydroxynonenal (4-HNE), showed more consistent results [9-11]. Wang showed increased levels of 4-HNE in schizophrenic patients compared to normal controls [11]. Also, MDA levels have been found elevated in peripheral tissues of schizophrenic patients [9, 10].

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The second-generation tetracycline antibiotic drug minocycline has strongly neuroprotective and anti-inflammatory effects [12, 13]. Minocycline has also remarkable brain tissue penetration, clinically rather tolerated and entirely absorbed when taken orally [14, 15]. Minocycline is supposedly efficacious in patients with schizophrenia [16-18] as good as in animal models of schizophrenia [19] and drug abuse [20, 21]. Minocycline was reported to attenuate behavioral impairment as good as neurotoxicity after application of methamphetamine [22, 23], 3,4-methylenedioxymethamphetamine (MDMA) [20] N-methyl-D-aspartate (NMDA) receptor antagonist dizocilpine [24], and viral mimetic polyriboinosinic-polyribocytidilic acid (PolyI: C) [25]. Minocycline has been utilized successfully in some clinical trials since as an adjunctive therapy to antipsychotics for schizophrenia [26]. Moreover, in patients with schizophrenia showed that minocycline could improve their negative symptoms and/or cognitive functions. Treatment with minocycline for one year was deemed safe [17, 27]. In animal models of schizophrenia, minocycline has neuroprotective effects [28]. In order to determine its efficacy in psychosis, we class with the effects of minocycline and chlorpromazine, a conventional antipsychotic drug, by evaluating the novelty-induced rearing, apomorphine-induced stereotypic behavior, and brain MDA levels in rats.

Materials and methods

Animals

The experimental protocol applied in the study was confirmed by the Institutional Animal Care and Ethics Committee of the Mustafa Kemal University (2014-05/3). 28 adult male Wistar rats (220-240 g) were taken in the study. All animals were regiment standard 12 h light/dark cycle in a temperature controlled ($22 \pm 2^\circ\text{C}$) environment with *ad libitum* access to rat chow. All experimental procedures were applied during the light cycle.

Chemicals

All drugs were freshly prepared. Apomorphine hydrochloride (Sigma Chemical Co., St. Louis, MO) was dissolved in saline containing 0.1% ascorbic acid before experiments. Minocycline was dissolved in saline. Saline (0.9% NaCl) was utilized as control solution. All solutions were applied intraperitoneally (i.p.).

Assessment of novelty-induced rearing behavior

Novelty-induced rearing behavior is employ to appraise the central excitatory locomotor behavior in rats [29]. Four groups of rat ($n = 7$ for each group) were applied minocycline (50 and 100 mg/kg, i.p.), chlorpromazine (1 mg/kg; i.p.), or isotonic saline (1 mL/kg, i.p.). One hour later, novelty-induced rearing behavior was inspected by placing the animal pass-through from home cages to a transparent Plexiglas cage (45 cm \times 25 cm \times 25 cm). The rearing frequency (number of times the animal stood on its hind limbs or with its fore limbs against the walls of the observation box or free in the air) was recorded for 10 min. All rats were monitored individually by two observers who were blinded to the study groups. The arena was cleaned with 5% alcohol to eliminate olfactory bias before beginning a fresh animal.

Apomorphine-induced stereotypic behavior test

Nigrostriatal and mesolimbic dopaminergic pathways play important roles in the mediation of locomotor activity and stereotyped behavior. Apomorphine-induced stereotypy is owing to the stimulation of dopamine receptors and has been applied as an appropriate method for *in vivo* screening of dopamine agonists or antagonists and assessment of dopaminergic activity [25, 26]. Concisely, four groups of rat ($n = 7$) were applied minocycline (50 and 100 mg/kg, i.p.), chlorpromazine (1 mg/kg, i.p.), and isotonic saline (1 mL/kg, i.p.). One hour later, apomorphine (2 mg/kg, s.c.) was applied to each rat. First, rats were put into the cylindrical metal cages (18 \times 19 cm) containing vertical (1 cm apart) and horizontal (4.5 cm apart) metal bars (2 mm) with upper lid for 10 minutes for orientation period. After apomorphine application, the rats were directly placed back into the metal cages and viewed for stereotypic behavior. Signs of stereotypy, which contain generally sniffing and gnawing, were inspected and scored as follows: absence of stereotypy (0), rarely sniffing (1), rarely sniffing with rarely gnawing (2), frequent gnawing (3), intense continuous gnawing (4), and intense gnawing and staying on the same spot (5). The stereotypic behavior was rated after every minute, and mean of 15 min period was calculated and recorded [30-32].

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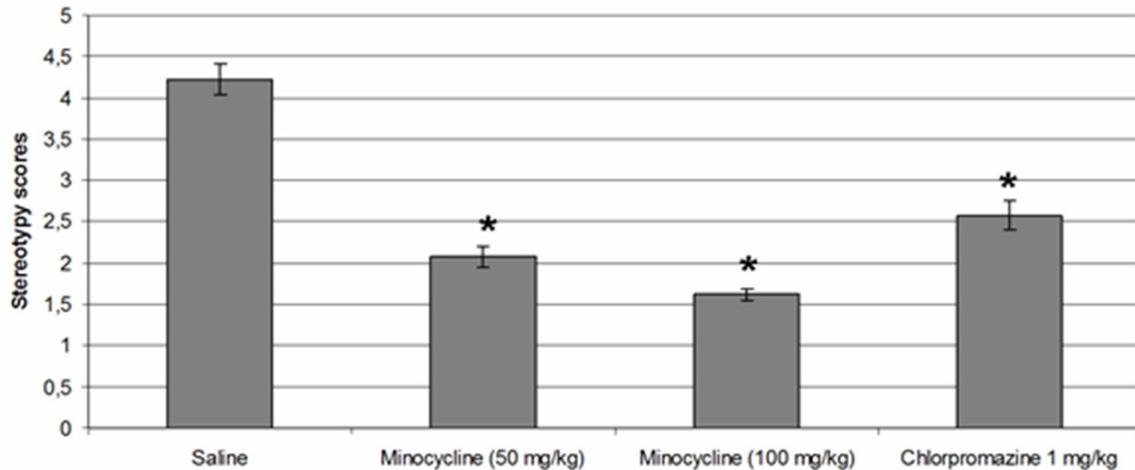


Figure 1. Apomorphine-induced stereotypy scores (After one hour later minocycline and saline applications apomorphine (2 mg/kg, s.c.) was applied to each rat). Data are expressed as mean \pm SEM. Statistical analysis was performed by one way analysis of variance (ANOVA) and Bonferroni's post hoc test. * $p < 0.000$ (different from saline).

Evaluations of brain lipid peroxidation

Lipid peroxide formation was assayed by evaluating the thiobarbituric acid reacting substances (TBARS) in the homogenates. The samples were concisely mixed with 50 mM potassium phosphate monobasic buffer pH 7.4, 63 μ L of the homogenate was mixed with 100 μ L of 35% perchloric acid, then the samples were centrifuged (5000 rpm/10 min) and 150 μ L of the supernatant was take back and mixed with 50 μ L of thiobarbituric acid 1.2% then heated in a boiling water bath for 30 min. After cooling, the lipid peroxidation was assessed by the absorbance at 535 nm and was stated as μ mol of malondialdehyde (MDA)/mg of protein [33].

Statistical analysis

Statistical evaluation was performed by one-way analysis of variance (ANOVA). Post hoc Bonferroni test was applied to determine differences between the experimental groups. MDA levels were evaluated between and within the groups by the Kruskal-Wallis variance analysis and the Mann-Whitney *U*-test where appropriate results are presented as mean \pm SEM. A value of $P < 0.05$ was considered to be significant.

Results

The effect of minocycline on apomorphine-induced stereotypic behavior test

Figure 1 depicts the effects of minocycline and chlorpromazine treatment on stereotypy sco-

res. ANOVA results demonstrated significant differences between the groups ($P < 0.000$). Post-hoc Bonferonni test showed a significant decrease in stereotypy scores in both doses of minocycline and chlorpromazine compared to saline group ($P = 0.000$, $P = 0.000$, $P = 0.000$, resp.). The decrease was significantly larger with 100 mg/kg of minocycline compared to 50 mg/kg.

The effect of minocycline on novelty-induced rearing behavior

Figure 2 represents the effects of minocycline and chlorpromazine treatment on rearing behavior. ANOVA results revealed significant differences between the groups ($P < 0.01$). Post-hoc Bonferroni test demonstrated a highly significant reduction in rearing behavior in minocycline (50 and 100 mg/kg) and chlorpromazine (1 mg/kg) applied rats compared to saline group ($P = 0.01$, $P = 0.001$, $P = 0.000$, resp.). The inhibitory effect of minocycline on rearing behavior was dose dependent, being more evident at a higher dose (100 mg/kg).

The effect of minocycline on brain lipid peroxidation

Figure 3 represents the effects of minocycline and chlorpromazine treatment on brain MDA levels. Kruskal-Wallis variance analysis and the Mann-Whitney *U*-test results showed significant differences between the groups ($P < 0.001$). The test demonstrated a highly signi-

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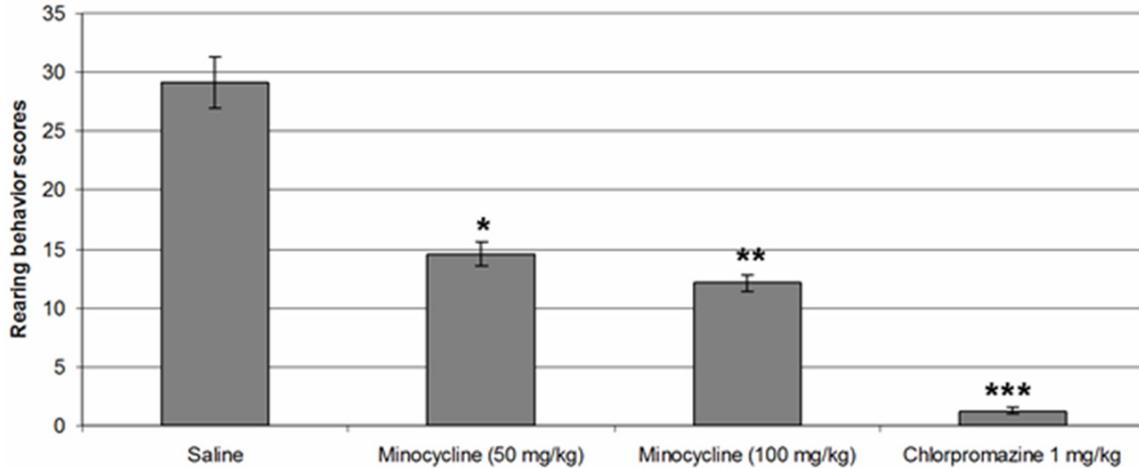


Figure 2. Rearing behavior scores. Data are expressed as mean \pm SEM. Statistical analysis was performed by one-way analysis of variance (ANOVA) and Bonferroni's post hoc test. * $p < 0.01$, ** $p < 0.001$, *** $p < 0.000$ (different from saline).

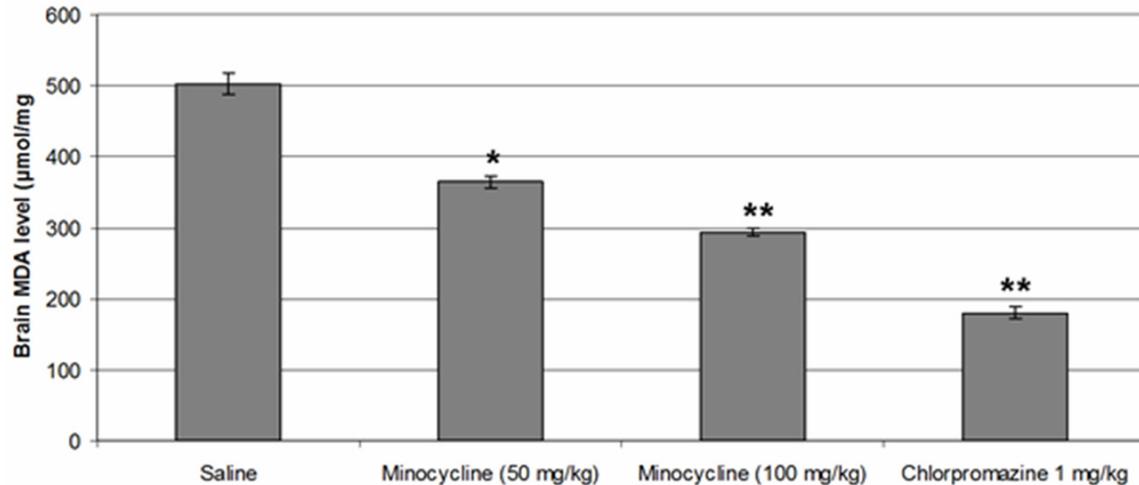


Figure 3. Brain MDA levels. Data are expressed as mean \pm SEM. Statistical analyses were performed by the Kruskal-Wallis variance analysis and the Mann-Whitney *U*-test. * $p < 0.001$, ** $p < 0.000$ (different from saline).

ficant decrease in MDA levels in both doses of minocycline and chlorpromazine compared to saline group ($P = 0.001$, $P = 0.000$, resp.).

Discussion

The results of this study showed that the beneficial effects of minocycline on rearing behavior stereotypy which are accepted to be indicators of anti-psychotic effect. Theoretically, antipsychotic effect is mediated by means of antidopaminergic activity in certain regions of central nervous system. But adverse drug effects have brought a big burden for the patients. Therefore, clinical and nonclinical investigations focused on new drugs, which cause fewer side effects.

There were some experiments about minocycline adjunct to schizophrenia. A case report [34] suggested that adjunctive treatment with minocycline could improve schizophrenic positive symptoms. Tsuyoshi Miyaoka [35] reported that minocycline in combination with antidepressants is effective and well tolerated in the treatment of unipolar psychotic depression.

Miyaoka et al. [36] reported that they applied minocycline (150 mg per day) adjunct to antipsychotic medication to 22 patients with schizophrenia for four weeks. Kristian Liaury et al. [37] showed that minocycline improves recognition memory and attenuates the activation of microglial cells in the hippocampal den-

tate gyrus of Gunn rat, a possible hyperbilirubinemia-induced animal model of schizophrenia.

Exposure of rats to a new environment causes novelty-induced behavior syndrome composed of rearing, grooming, and wet-dog shakes. The novelty-induced rearing behavior reaction is regulated by various neurotransmitter systems including GABAA, opioid, and dopamine D2 receptors [38]. In a previous study, Tejashree examined the anti-psychotic-like effects of liraglutide, a GLP-1 agonist, and sitagliptin, which is a dipeptidyl peptidase (4DPP-4) inhibitor [39]. Liraglutide treatment significantly attenuated apomorphine-induced cage climbing behavior, which is thought to be first preclinical evidence for anti-psychotic-like effect [39]. In Tejashree's study, liraglutide showed equal effect with haloperidol in reversing apomorphine-induced cage climbing behavior. In our study, minocycline decreased rearing behavior in rats in a dose-related manner, which is also reduced by chlorpromazine more efficiently. Chlorpromazine, a very effective antagonist of D2 dopamine receptors, exerts additional anti-adrenergic, anticholinergic, and antihistaminergic effects [40]. Hence, the efficacy of chlorpromazine on rearing behavior may be associated with its sedative effect, which is principally maintained by anticholinergic and antihistaminergic properties of that drug.

Sotoing Taiwe et al. [38] examined the effect of aqueous extract and alkaloid fraction of *Crassocephalum bauchiense* in rats. Both aqueous extract and the alkaloid fraction caused dose-dependent inhibition in the rearing behavior, which is mediated through GABA-A, opioid, and D2 dopamine receptors [38]. Stereotypical behavior is a common feature manifested in schizophrenia and is increased by apomorphine probably through D2 receptors. Besides rearing behavior, Sotoing Taiwe et al. showed that aqueous extract and alkaloid fraction of *Crassocephalum bauchiense* decreased the apomorphine-induced stereotypy scores [38]. In our study, minocycline also significantly lessened the stereotypy scores. Application of minocycline may be D2 dopamine receptors and lead to extrapyramidal type adverse reaction.

It is well known that anti-psychotic drugs are the first choices for the treatment of schizoph-

renia. Majority of the studies indicated the increased levels of oxidative stress parameters after the treatment with classical antipsychotics. For example, Sagara et al. [41] showed that haloperidol induced a sixfold increase in levels of reactive oxygen species (ROS) and treatment of antioxidants, such as vitamin E, lowered the levels of ROS, and protected the cells. Similarly, Reinke et al. [42] revealed that haloperidol and clozapine were related with oxidative stress in the rat brain, but haloperidol-receiving group showed a higher increase compared to clozapine. More recently, Kropp et al. [43] measured the MDA levels in schizophrenic patients during treatment with first- and second-generation antipsychotics. According to their results, MDA levels in patients receiving clozapine, quetiapine, and risperidone were lower than the first-generation antipsychotic receiving group. They found that atypical anti-psychotics attenuated the oxidative stress and decreased oxidative damage markers. On the other hand, it has been claimed that increased oxidative stress seen in some clozapine treated patients could be related to the illness severity since clozapine is generally applied in refractory patients [44].

All these studies point out that there is a growing body of evidence proving the importance of oxidative stress in schizophrenia both in pathogenesis and treatment modalities.

So, it is suggested that antioxidants might be useful in the treatment of schizophrenia. For instance, Dakhale et al. [45] indicated that vitamin C and oral anti-psychotic combination reduced concise psychiatric rating scale scores and MDA levels. As the majority of the studies show the improving effects of anti-oxidants as an adjunct therapy, we propose that minocycline might be beneficial with its obvious antioxidant effects in schizophrenia.

Conclusion

In view of the effects of minocycline on rearing behavior and stereotypical behavior in rats, we propose that minocycline may have anti-psychotic-like potential because of its antidopaminergic effects. On the other hand, minocycline, as an anti-oxidant and cytoprotective agent, can be useful in neuroprotection especially on early stages of psychosis or prepsychotic patients with insignificant symptoms. In addition,

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as glutamatergic excitotoxicity is responsible for the neurodegeneration and neuron loss, which is possibly related with negative symptoms and cognitive dysfunction, minocycline might be having a potential as a regulator on glutamatergic system. However, as we have little data about trimetazidine's anti-dopaminergic effects and glutamatergic modulating roles compared to its well-known anti-oxidant effects in psychotic patients, this study needs to be supported by further experimental and clinical research.

Disclosure of conflict of interest

None.

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