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# Antidepressant-like effect of minocycline in mice forced swimming test: Minor involvement of the noradrenergic system

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## ABSTRACT

**Introduction:** Minocycline is a tetracycline antibiotic drug that is receiving attention as an alternative for the treatment of depression. Several mechanisms have been proposed for this effect. The current study evaluated the involvement of the noradrenergic system in the antidepressant-like effect of minocycline. **Materials and Methods:** The total immobility time was evaluated as an index of depression in mice forced swimming test (FST). Minocycline (40 mg/kg) was injected for 3 days. Imipramine (5 mg/kg, a tricyclic antidepressant), prazosin (1 mg/kg, an α1-adrenoceptor antagonist), yohimbine (1 mg/kg, an α2-adrenoceptor antagonist), and propranolol (2 mg/kg, a β-adrenoceptor antagonist) were injected 30 min before the last dose of minocycline, α-methyl-p-tyrosine (100 mg/kg, an inhibitor of tyrosine hydroxylase) was administered 4 h before minocycline final dose. **Results:** Minocycline decreased the immobility time during FST. The injection of prazosin prevented the anti-depressant like effect of minocycline, while imipramine, yohimbine or propranolol potentiates the anti-depressant like effect of minocycline during the FST. Besides that, the pretreatment of mice with α-methyl-p-tyrosine did not change the minocycline antidepressant-like effect in the FST. **Conclusion:** The present study suggests that the noradrenergic system has a trivial role in the antidepressant-like effect of minocycline; the impact on neuroinflammation and cytokines might be more important.

**Keywords:** Adrenoceptor, depression, forced swimming test, minocycline, noradrenergic system

## INTRODUCTION

Antidepressant drug therapy is widely in use recently and ample drugs are available on the market to improve depression. Unfortunately, the clinical response to most of the available antidepressants is with a significant delay, and many patients undergoing antidepressant therapy experienced adverse drug effects.[1] Therefore, improving the activity of these conventional antidepressant drugs, new strategies, and alternative medicine would be applicable for treating depression.

Minocycline a semisynthetic tetracycline antibiotic drug has shown great anti-inflammatory and neuroprotective effects.[2,3] Minocycline reduces transcription of the downstream proteins related to inflammation, nitric oxide (NO) synthase and cyclooxygenase-2, and subsequently the release of NO, interleukin (IL) 1-β, and prostaglandin-E2. Its neuroprotective abilities are also related to its ability to reduce NO levels; it also reduces glutamate neurotransmission.[4] Therefore, minocycline might be useful for treatment of diseases related with high brain glutamate levels, such as human depression.[5] Therefore, minocycline is promising as a potential agent for the treatment of major depression disorder (MDD).[6,7] While some animal studies support the antidepressant effects of minocycline, but a study that used C57BL/6 was against it.[8] Minocycline in male Wistar rats reduced immobility and enhanced the antidepressant-like effect of subthreshold doses of desipramine in the forced swimming test (FST).[9] During learned helplessness (LH) test in rats (an animal model

of depression) dopamine levels was reduced, and following minocycline treatment the levels of dopamine and its metabolites were significantly increased in the amygdala in comparison with untreated rats.[10] It was also evaluated that serotonin (5-HT) turnover to 5-hydroxyindoleacetic acid (5-HIAA) was increased in the orbitofrontal cortex of LH rats, but the increases in 5-HIAA/5-HT ratio remained unchanged after treatment with minocycline.[11] While researchers in this study did not find significant changes for norepinephrine (NE) concentration; other researchers concluded that minocycline exerts an antidepressant-like effect through the NE system since it had caused an increase in the climbing behavior during the FST.[9] Complementary studies were suggested to interpret the involvement of NE systems.

Adrenergic receptors (AR) are found on nerve fibers that initiate from the locus coeruleus and proceed to many parts of the forebrain.[12] Noradrenergic heteroreceptors are also located on glutamate, gamma-aminobutyric acid (GABA), DA, 5-HT, and histamine neurons. The NE signaling is auto-regulated by presynaptic α2- ARs, and β2-ARs,[13] adrenergic system is also regulated by other neurotransmitters, such as excitatory glutamate and inhibitory GABA system.[12] Taken together, this suggests that ARs through these pathways play a role in various brain functions such as depression, stress response, memory consolidation, and sleep/wakefulness.[14]

Because the involvement of the noradrenergic system in the antidepressant-like effect of minocycline is vague, this study was designed. By conducting the mice FST the aim was: First, to observe minocycline antidepressant effect; second, to observe the changes in depressive behavior following the administration of imipramine (a tricyclic antidepressant, [TCA]), α1-AR antagonist (prazosin), α2-AR antagonist (yohimbine), and β-AR antagonist (propranolol), and finally to observe the change in the animal behavior after administrating α-methyl-p-tyrosine (AMPT) a selective inhibitor of the enzyme tyrosine hydroxylase (TH).

## MATERIALS AND METHODS

### Animals

Male albino mice weighing 28 ± 2 g were maintained at 21 ± 2°C with free access to tap water and standard mice chow, while the lights were on from 6 a.m. to 6 p.m. Each experimental group included six animals that were housed per cage and they were placed in the experimental room 24 h before the test for acclimatization. All the experiments were performed between 8 a.m. and 1 p.m. in the pharmacology laboratory. All animal procedures were performed in accordance with guidelines for the Care and Use of Laboratory Animals Issued by The National Ethical Committee (Ethical No: IR.MUI.REC.1397.367). All the efforts in the experiments were made to minimize animal suffering and to reduce the number of animals used in the experiments.

### Locomotor Test

The motor activity of mice was assessed before the FST in an open arena (Borj Sanat, Iran) divided into 15 zones by red beams. Mice were allowed to explore the field for 3 min, by passing through the beams the number of zone entries was counted automatically while rears on hind-legs were recorded manually. Finally, total activity for each animal was calculated which was the sum of zone entries (horizontal exploration) and rears (vertical exploration).

### Splash Test

This test was conducted with minor modifications from Isingrini *et al*., 2010.[15] A 10% sucrose solution was sprayed on the dorsal coat of each mice that were placed in a clear plexiglas box. Animals normally initiate grooming behavior after feeling their sticky fur because of the sucrose solution viscosity. The total time spent on grooming was manually recorded for a period of 5 min. The plexiglas box was cleaned with a 10% ethanol solution between tests.

### FST

This test was performed as an animal model of despair behavior. Mice were forced to swim in 25°C water in a glass beaker (diameter 12.5 cm and depth 12 cm) for 6 min.[16] The behaviors that were measured during the past 4 min of the trial were: Climbing behavior, defined as the time animal intends to climb the glass beaker; swimming behavior, defined as horizontal movement throughout the beaker which involved at least two limbs; and immobility, measured when no additional activity was observed other than that required to keep the mice head above the water.[17] The whole experiment was recorded by a camera and analyzed later. After 6 min, the mice were dried carefully and returned to their home cage.

### Sucrose Preference Test

Following 2 days of habituating the animals to sucrose solution (1% w/v), mice had access to two bottles containing 100 ml of sucrose solution and 100 ml of tap water. After 24 h, the amount of sucrose solution and water consumptions was recorded and sucrose preference was calculated.[16]

### Drugs Administration

Minocycline hydrochloride 40 mg/kg (Sigma, Germany) was injected intraperitoneally (i.p.) for 3 consecutive days, according to pilot studies and literature.[9] The tests (first locomotor test, then the splash test and finally the FST) for each animal were performed on the past day an hour after the last dose of minocycline. Yohimbine (Sigma, Germany) 1 mg/kg; prazosin (gift from Amin Industry, Iran) 1 mg/kg; imipramine (Sigma, Germany) 5 mg/kg; and propranolol (1 mg/ml ampule POLFA S A, Poland) 2 mg/kg were all administered i.p. after diluted in normal saline and the doses were in accordance with previous studies.[18,19] They were injected either alone 30 min before the tests or on the 3rd day 30 min before minocycline final dose. AMPT (Sigma, Germany) 100 mg/kg i.p., was freshly prepared in dimethyl sulfoxide (DMSO) solution and it was administered either alone 4 h before the tests or 4 h before the final dose of minocycline.[20] Control animals received the relevant vehicle since the results for the control DMSO solution were not different from the normal saline group it is not reported separately. All the injections were adjusted for 10 ml/kg mice body weight.

### Data Processing and Statistical Analysis

The results are presented as group mean ± standard error of the mean (SEM) and they were analyzed by one-way

analysis of variance (ANOVA), followed by Tukey's multiple comparison tests. $P < 0.05$ was considered significant. The software programs used for data analyzing and making graphs were Excel 2010 and the GraphPad Prizm 6.

## RESULTS

### The Effect of the Noradrenergic Modulating Drugs Alone on Depressive Behavior

Animals total locomotor activity was similar in various treatment groups [Table 1] that is in the applied doses animal normal movement was not influenced. As shown in Figure 1a, the immobility time that measures the index of depressive-like behavior during the FST was only decreased by imipramine (88 ± 5 s, $P < 0.05$ vs. control group 118 ± 4 s), while other treatments did not cause any noticeable change. The changes observed during the splash test were parallel with the FST [Figure 1b], imipramine treated mice spent more time for grooming (98 ± 8.5 s, $P < 0.001$ vs. control 51.6 ± 6 s). As suggested by the modified FST protocol, the mobile phase was also recorded; the results are shown in Table 1. Prazosin significantly increased the climbing time compared to the control group (61 ± 4 s, $P < 0.01$), while it caused a lower swimming time in animals (65 ± 5 s, $P < 0.05$ vs. control 98 ± 7 s).

In the locomotor test, total activity count = (horizontal + vertical) exploration. All the drugs were IP injected; control animals received normal saline. Number of animals in each group was six. Results are expressed as group mean ± SEM and analyzed by ANOVA followed by Tukey's comparison test.

### The Effect of the Noradrenergic Modulating Drugs following Minocycline Administration on Depressive Behavior

Minocycline did not cause a noticeable change in animal activity during the locomotor test compared with the control group (93 ± 10) [Table 2]. When propranolol was added to the treatment animal activity reduced to a considerable amount of 44 ± 11; the two drugs together have curtailed the animal mobility. Figure 2a shows that minocycline has significantly reduced the immobility time during the FST (78 ± 8 s, $P < 0.05$ vs. control group 117 ± 4 s). Minocycline also severely augmented the grooming time [Figure 2b] (119 ± 6 s, $P < 0.01$ vs. control 46 ± 8 s). The antidepressant effect of minocycline was further supported by the increase in the sucrose preference test to 73 ± 2% compared with the control group 62 ± 1%. By coadministration of imipramine, yohimbine, propranolol, and AMPT with minocycline the immobility time during the FST reduced although no significant change was observed from the vehicle group. However, prazosin coadministration with minocycline increased the

**Table 1:** Effects of the noradrenergic modulating drugs alone on animal behavior during the locomotor test and the forced swimming test

| Groups | Locomotor test | Forced swimming test | |
|---|---|---|---|
| | Total activity (count) | Swimming time (s) | Climbing time (s) |
| Control | 138±10 | 98±7 | 24±7 |
| Imipramine (5 mg/kg) | 146±22 | 114±13 | 47±11 |
| Prazosin (1 mg/kg) | 87±23 | 65±5* | 61±4** |
| Yohimbine (1 mg/kg) | 109±10 | 97±4 | 31±6 |
| Propranolol (2 mg/kg) | 85±6 | 94±8 | 27±9 |
| α-methyl-p-tyrosine (100 mg/kg) | 126±12 | 106±4 | 4±2 |

*$P$<0.05 and **$P$<0.01 compared with the control group

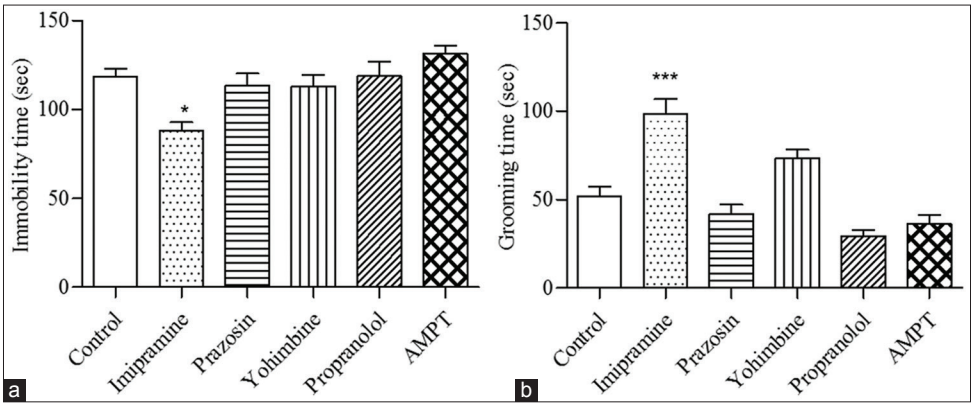


**Figure 1:** Effect of drugs alone on depressive behavior. (a) The immobility time during the last 4 min of the forced swimming test. (b) The grooming time during 5 min splash test. Imipramine (5 mg/kg, a tricyclic antidepressant), propranolol (β-adrenergic receptor [AR] antagonist, 2 mg/kg), prazosin (α1-AR antagonist, 1 mg/kg), yohimbine (α2-AR antagonist, 1 mg/kg), and α-methyl-p-tyrosine (α-methyl-p-tyrosine a selective inhibitor of tyrosine hydroxylase, 100 mg/kg) were all administered intraperitoneally before testing. Number of animals in each group was six; control animals received saline. Results are expressed as group mean ± standard error of the mean and analyzed by analysis of variance followed by Tukey's comparison tests. *$P < 0.05$ and ***$P < 0.001$ compared with the control group

immobility time to 106 ± 6 s; probably it was able to revert the antidepressant-like effects of minocycline. As shown in Table 2, while almost all therapies applied with minocycline increased the swimming time prazosin significantly reduced it. On the other hand, climbing time increased during the FST with the administration of prazosin and yohimbine. The grooming time [Figure 2b] showed the parallel results since prazosin significantly reduced the grooming time (47 ± 11 s, $P < 0.05$ vs. vehicle group).

In the locomotor test, total activity count = (horizontal + vertical) exploration. Minocycline (mino) 40 mg/kg was injected for 3 consecutive days. All the drugs were injected i.p.; control animals received normal saline the vehicle was also normal saline. The selected doses were imipramine (5 mg/kg), prazosin and yohimbine (1 mg/kg), propranolol (2 mg/kg), and AMPT (100 mg/kg) that were injected on the 3rd day. Number of animals in each group was six. Results are expressed as group mean ± SEM and analyzed by ANOVA followed by Tukey's comparison test.

**Table 2:** Effects of the adrenergic modulating drugs following minocycline administration on animal behavior during the locomotor test and the forced swimming test

| Groups | Locomotor test Total activity (count) | Forced swimming test | |
|---|---|---|---|
| | | Swimming time (s) | Climbing time (s) |
| Control | 93±10 | 107±5 | 14±5 |
| Mino+Vehicle | 112±18 | 150±7** | 12±8 |
| Mino+Imipramine | 119±7 | 161±9** | 10±3 |
| Mino+Prazosin | 98±16 | 75±10## | 59±9*## |
| Mino+Yohimbine | 151±4 | 123±9 | 62±17*## |
| Mino+Propranolol | 44±11# | 163±9** | 17±5 |
| Mino+AMPT | 66±19 | 158±9** | 5.6±5 |

*$P$<0.05 and **$P$<0.01 compared with the control group; #$P$<0.05 and ##$P$<0.01 compared with the vehicle group

## DISCUSSION

In agreement with previous literature in our study, minocycline caused antidepressant-like behavior in mice.[9,10] Among the noradrenergic modulatory drugs, we applied only prazosin was able to revert the antidepressant-like effects of minocycline. Minocycline also increased the sucrose preference, this test was performed to measure another index of depression in animal, anhedonia, and a decrease in sucrose preference measured to a level below 65% was taken as a criterion for anhedonia.[21] Minocycline also increased the grooming time, grooming in rodents is an index of self-care and motivating behavior. Grooming time could be measured to model some symptoms of depression such as passive behavior.[15] Reference antidepressants reduce immobility time during the FST, while evaluating the mobile behavior may help to interpret different neurotransmitters' involvement.[17] That is, improvement of NE neurotransmission may mediate climbing, while the improvement of 5-HT neurotransmission may mediate swimming behavior during the FST.[17,22] Imipramine is a non-selective NE and 5-HT reuptake inhibitor TCA. Therefore, in agreement with previous literature imipramine single dose increased swimming and climbing time, it is feasible to propose that during the FST the behavioral effects of imipramine treatment are related to both neurotransmitters NE and 5-HT. Prazosin injection alone did not cause change in the immobility time, but it induced lower swimming time and higher climbing time in the FST. The α1-AR stimulation in the dorsal raphe nucleus (DRN) increases 5-HT release.[23] On the other hand, it was shown that prazosin antagonizes the reduction of 5-HT release that was caused by phenylephrine in DRN.[24] Although on the downside of the research, we did not measure the 5-HT or NE levels our results during FST attested the possible effect of prazosin on inhibiting the release of 5-HT.

Minocycline antidepressant-like effect was augmented when imipramine, yohimbine, and propranolol were administered on the 3rd day. This was in line with researches

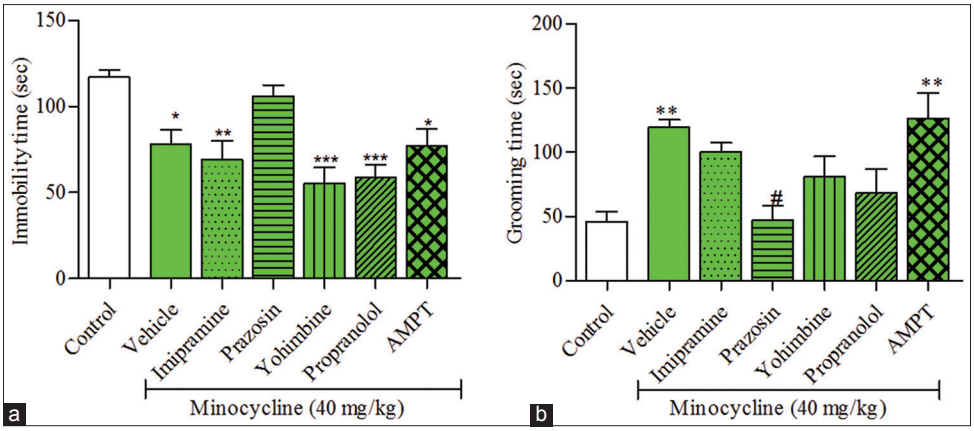


**Figure 2:** Effect of the drugs on minocycline induced antidepressant-like effects. (a) The immobility time during the last 4 min of the forced swimming test. (b) The grooming time during 5 min splash test. Minocycline 40 mg/kg was injected intraperitoneally for 3 consecutive days. The tests were performed on the past day an hour after the last dose of minocycline. Imipramine (5 mg/kg, a tricyclic antidepressant), propranolol (β-adrenergic receptor [AR] antagonist, 2 mg/kg), prazosin (α1-AR antagonist, 1 mg/kg), Yohimbine (α2-AR antagonist, 1 mg/kg), and α-methyl-p-tyrosine (AMPT a selective inhibitor of TH, 100 mg/kg) were all administered i.p. before minocycline final dose on the last day. Number of animals in each group was six; control animals received saline. Results are expressed as group mean ± standard error of the mean and analyzed by analysis of variance followed by Tukey's comparison tests. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ compared with the control group; #$P < 0.05$ compared with the vehicle group

suggesting that minocycline may be useful for noradrenergic antidepressant drugs potentiation.[7,9] Imipramine is a TCA that acts by inhibiting the plasma membrane transporters for serotonin and noradrenaline.[25] Researchers are in favor of the beneficial effect of α2-AR antagonists on depression behavior following the administration of antidepressants.[26] In addition, mirtazapine is an antidepressant drug that blocks α2-ARs and 5-HT2 receptors.[12] By collecting brain tissue from patients who committed suicide and using radioligand experiments, it was found that α2-AR densities are higher in the prefrontal cortex of patients with MDD, and following antidepressant treatment the α2-AR density remained high.[27] Therefore, perhaps following applying minocycline, the α2-AR density has upregulated, thus after yohimbine injection the antidepressant effects have increased.

The locomotor activity should be tested before many behavioral tasks since variations in locomotor activity nonspecifically affect performance in many behavioral tests. In our experiment, although propranolol alone only slightly reduced the activity in the open field its administration following minocycline injection greatly reduced activity during the locomotor test. On the other hand, propranolol injected following minocycline administration further reduced the immobility time during the FST that means it augmented minocycline antidepressant effect, with an increase in the swimming time. Minocycline 40 mg/kg was cautiously applied according to previous studies[8] it has been shown that 45 mg/kg minocycline could cause harmful effects in a mice model of Parkinson's such as impaired coordination, locomotion, and balance in the open field and rotarod tests.[28] Previously propranolol 2 mg/kg, despite the higher doses, reduced locomotor activity in the open-field test that is in accordance with earlier research reported the anxiogenic-like effect of propranolol in mice.[29,30] On the basis of this evidence, propranolol is responsible for the decline in the locomotor activity following minocycline injection in the lower unexpected doses. On the other hand, β-AR blockade prevents cerebral hypoperfusion by inhibiting the effect of NE on the β-AR, by micro PET imaging it was shown that applying propranolol after brain injury in mice increases cerebral perfusion and reduces the cerebral hypoxia.[31] Therefore, increase in cerebral perfusion could be the reason for increased antidepressant-like effects of minocycline following propranolol coadministration.

Analogs of tyrosine, such as AMPT, are competitive inhibitors of TH (the rate-limiting step in catecholamine synthesis) and they can induce depression in some individuals. Depletion of the catecholamine system was specifically observed after treatment with AMPT.[32] Preceding researches have shown that treatment of mice with AMPT (100 mg/kg) was able to reverse the antidepressant effect of lamotrigine in the FST.[20] In our study, AMPT did not reverse minocycline antidepressant-like effect. Indicating that minocycline antidepressant effect is caused by various mechanisms and the NE system may play a minor role in it.

Minocycline antidepressant-like effects in our study were followed by an increase in the swimming time. This indicates that the serotonergic system may play a much important role in minocycline antidepressant effects, according to Cryan *et al*., 2002.[17] This was against a former study that minocycline administration reduced immobility in the FST by increasing the climbing time.[9] These differences could be due to differences in the method followed by Molina-Hernández *et al*., (2008)[9] and the present study. First, we used a cylinder of water as suggested by the standard method designed for FST,[33] they used a rectangular glass aquarium filled to a depth of 40.0 cm. Second, we injected minocycline (40 mg/kg) for 3 days and tested on the past day, while they administered minocycline 23, 5, and 1 h before the behavioral tests. Finally, we used adult male albino mice (26–30 g); conversely they used adult male Wistar rats (250–300 g).

## CONCLUSION

While various mechanism are suggested for minocycline antidepressant effects such as: In LH mice minocycline changed the DA level in the amygdala, and prevented 5-HT turnover,[10] it decreased markers of neuroinflammation (IL-1β, toll-like receptor 2, and indoleamine 2,3-dioxygenase),[34] and it attenuated the lipopolysaccharide-induced expression of cytokines and development of depressive-like behaviors.[35] Our results showed that the adrenergic system has a minor effect on the antidepressant-like effect of minocycline in animal models; nevertheless, chemical analysis of neurotransmitters is suggested to confirm this.

## REFERENCES


1. Holsboer F. Prospects for antidepressant drug discovery. Biol Psychol 2001;57:47-65.
2. Domercq M, Matute C. Neuroprotection by tetracyclines. Trends Pharmacol Sci 2004;25:609-12.
3. Kim HS, Suh YH. Minocycline and neurodegenerative diseases. Behav Brain Res 2009;196:168-79.
4. Morimoto N, Shimazawa M, Yamashima T, Nagai H, Hara H. Minocycline inhibits oxidative stress and decreases *in vitro* and *in vivo* ischemic neuronal damage. Brain Res 2005;1044:8-15.
5. Levkovitz Y, Levi U, Braw Y, Cohen H. Minocycline, a second-generation tetracycline, as a neuroprotective agent in an animal model of schizophrenia. Brain Res 2007;1154:154-62.
6. Hashimoto K. Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res Rev 2009;61:105-23.
7. Pae CU, Marks DM, Han C, Patkar AA. Does minocycline have antidepressant effect? Biomed Pharmacother 2008;62:308-11.
8. Vogt MA, Mallien AS, Pfeiffer N, Inta I, Gass P, Inta D, *et al*. Minocycline does not evoke anxiolytic and antidepressant-like effects in C57BL/6 mice. Behav Brain Res 2016;301:96-101.
9. Molina-Hernández M, Tellez-Alcántara NP, Pérez-García J, Olivera-Lopez JI, Jaramillo-Jaimes MT. Antidepressant-like actions of minocycline combined with several glutamate antagonists. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:380-6.
10. Arakawa S, Shirayama Y, Fujita Y, Ishima T, Horio M, Muneoka K, *et al*. Minocycline produced antidepressant-like effects on the learned helplessness rats with alterations in levels of monoamine in the amygdala and no changes in BDNF levels in the hippocampus at baseline. Pharmacol Biochem Behav 2012;100:601-6.
11. Mitani H, Shirayama Y, Yamada T, Kawahara R. Plasma levels of homovanillic acid, 5-hydroxyindoleacetic acid and cortisol, and serotonin turnover in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:531-4.
12. Maletic V, Eramo A, Gwin K, Offord SJ, Duffy RA. The role of norepinephrine and its α-adrenergic receptors in the pathophysiology and treatment of major depressive disorder and schizophrenia: A systematic review. Front Psychiatry 2017;8:42.
13. Hein L. Adrenoceptors and signal transduction in neurons. Cell

Tissue Res 2006;326:541-51.
14. Atzori M, Cuevas-Olguin R, Esquivel-Rendon E, Garcia-Oscos F, Salgado-Delgado RC, Saderi N, *et al.* Locus ceruleus norepinephrine release: A central regulator of CNS spatio-temporal activation? Front Synaptic Neurosci 2016;8:25.
15. Isingrini E, Camus V, Le Guisquet AM, Pingaud M, Devers S, Belzung C, *et al.* Association between repeated unpredictable chronic mild stress (UCMS) procedures with a high fat diet: A model of fluoxetine resistance in mice. PLoS One 2010;5:e10404.
16. Mesripour A, Alhimma F, Hajhashemi V. The effect of vitamin B6 on dexamethasone-induced depression in mice model of despair. Nutr Neurosci 2019;22:744-9.
17. Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: Recent developments and future needs. Trends Pharmacol Sci 2002;23:238-45.
18. Souza LC, de Gomes MG, Goes AT, Del Fabbro L, Filho CB, Boeira SP, *et al.* Evidence for the involvement of the serotonergic 5-HT(1A) receptors in the antidepressant-like effect caused by hesperidin in mice. Prog Neuropsychopharmacol Biol Psychiatry 2013;40:103-9.
19. Brocardo PS, Budni J, Kaster MP, Santos AR, Rodrigues AL. Folic acid administration produces an antidepressant-like effect in mice: Evidence for the involvement of the serotonergic and noradrenergic systems. Neuropharmacology 2008;54:464-73.
20. Kaster MP, Raupp I, Binfaré RW, Andreatini R, Rodrigues AL. Antidepressant-like effect of lamotrigine in the mouse forced swimming test: Evidence for the involvement of the noradrenergic system. Eur J Pharmacol 2007;565:119-24.
21. Strekalova T, Gorenkova N, Schunk E, Dolgov O, Bartsch D. Selective effects of citalopram in a mouse model of stress-induced anhedonia with a control for chronic stress. Behav Pharmacol 2006;17:271-87.
22. Vieira C, De Lima TC, Carobrez Ade P, Lino-de-Oliveira C. Frequency of climbing behavior as a predictor of altered motor activity in rat forced swimming test. Neurosci Lett 2008;445:170-3.
23. El Mansari M, Guiard BP, Chernoloz O, Ghanbari R, Katz N, Blier P, *et al.* Relevance of norepinephrine-dopamine interactions in the treatment of major depressive disorder. CNS Neurosci Ther 2010;16:e1-17.
24. Hopwood SE, Stamford JA. Noradrenergic modulation of serotonin release in rat dorsal and median raphé nuclei via alpha(1) and alpha(2A) adrenoceptors. Neuropharmacology 2001;41:433-42.
25. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br J Pharmacol 2007;151:737-48.
26. Invernizzi RW, Garattini S. Role of presynaptic alpha2-adrenoceptors in antidepressant action: Recent findings from microdialysis studies. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:819-27.
27. Rivero G, Gabilondo AM, García-Sevilla JA, La Harpe R, Callado LF, Meana JJ, *et al.* Increased α2-and β1-adrenoceptor densities in postmortem brain of subjects with depression: Differential effect of antidepressant treatment. J Affect Disord 2014;167:343-50.
28. Diguet E, Fernagut PO, Wei X, Du Y, Rouland R, Gross C, *et al.* Deleterious effects of minocycline in animal models of parkinson's disease and huntington's disease. Eur J Neurosci 2004;19:3266-76.
29. Sun H, Mao Y, Wang J, Ma Y. Effects of beta-adrenergic antagonist, propranolol on spatial memory and exploratory behavior in mice. Neurosci Lett 2011;498:133-7.
30. Stone EA, Manavalan SJ, Zhang Y, Quartermain D. Beta adrenoceptor blockade mimics effects of stress on motor activity in mice. Neuropsychopharmacology 1995;12:65-71.
31. Ley EJ, Scehnet J, Park R, Schroff S, Dagliyan G, Conti PS, *et al.* The *in vivo* effect of propranolol on cerebral perfusion and hypoxia after traumatic brain injury. J Trauma 2009;66:154-9.
32. Ressler KJ, Nemeroff CB. Role of norepinephrine in the pathophysiology and treatment of mood disorders. Biol Psychiatry 1999;46:1219-33.
33. Porsolt RD, Le Pichon M, Jalfre M. Depression: A new animal model sensitive to antidepressant treatments. Nature 1977;266:730-2.
34. Henry CJ, Huang Y, Wynne A, Hanke M, Himler J, Bailey MT, *et al.* Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. J Neuroinflammation 2008;5:15.
35. O'Connor JC, Lawson MA, André C, Moreau M, Lestage J, Castanon N, *et al.* Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry 2009;14:511-22.