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Original Article

Anxiolytic effect of minocycline in posttraumatic stress disorder model of Syrian hamsters

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Abstract

Objective: The objective was to study the anxiolytic effect of minocycline in resident–intruder social conflict in submissive hamsters post resident intrusion model using open field test (OFT) and elevated plus maze (EPM) and serum cortisol levels. **Materials and Methods:** Fifty-two singly housed male Syrian hamsters were used, post standardization of an animal model. Resident intrusion was done (5 min), in which smaller hamsters were placed in the cage of larger hamster, and the behavior of smaller hamster was noted. Eight submissive hamsters per group (disease control, lorazepam group as a positive control, and the test drug was minocycline) were used, and the drug was administered immediately post resident intrusion, intraperitoneally. Behavioral tests, namely OFT and EPM, were done followed by retro-orbital blood collection for serum cortisol estimation. The level of significance was set at $P < 0.05$. **Results:** The minocycline group showed a statistically significant decrease in serum cortisol levels compared to the disease control group. Among all the variables pertaining to both the behavioral tests, namely EPM and OFT, the results indicated an anxiolytic effect, which was statistically significant compared to the disease control group. **Conclusion:** As per the biochemical test using serum cortisol levels and behavioral tests in the form of EPM and OFT, the study concluded that the anxiolytic effect of minocycline is at least comparable to the positive control, lorazepam.

Keywords: *Behavioral tests, Cortisol, Neuroinflammation*

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder, characterized by recurring flashbacks, nightmares, hyperarousal, and numbing, which significantly reduces the quality of life in patients and is associated with comorbidities such as anxiety, major depression, substance abuse, and suicide [1,2].

After severe physical or psychological trauma, the first symptom in PTSD patients is hyperarousal which is characterized by severe anxiety [3,4]. Large epidemiological studies have shown a lifetime prevalence of about 8% in the US, but the prevalence increases drastically after catastrophic events [5]. There have been limited epidemiological studies of PTSD in India. As per one of the studies, the prevalence rate was documented to be as high as 12% [6,7].

There has been increased research in this field, and this has furthered our understanding of PTSD, which is reflected through the revisions in the diagnostic criteria for PTSD and its reclassification from a class of anxiety disorders to its current place in trauma- and stressor-related disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria [8].

Currently, only two drugs, paroxetine and sertraline, belonging to class of selective serotonin reuptake inhibitors (SSRIs) have been approved by the United States Food and Drug Administration for the treatment of PTSD. However, both these drugs have variable efficacy and safety and achieve full remission in <30% of patients of PTSD and provide only symptomatic relief [9]. These drugs have limited value in patients presenting with initial phase of acute anxiety and hyperarousal [10].

Benzodiazepines such as alprazolam and lorazepam are commonly used off-label to treat initial symptoms of anxiety [11]. Initially, the most common presenting symptom

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in patients suffering from PTSD is acute anxiety and hyper arousal. The most commonly prescribed drug for acute anxiety is lorazepam, as it is believed to prevent intrusion and reconsolidation of traumatic memory [12].

However, benzodiazepines have adverse effects such as sedation and dependence which impair the quality of life of the patient. Hence, there is a need for newer drugs, especially for the stage of hyperarousal and acute anxiety in PTSD [13].

The onset of stress is known to increase concentrations of various cytokines, predominantly interleukin-1 (IL-1) in the hippocampus and amygdala which are seat of memory consolidation and emotional aspects of memory, respectively. IL-1 is also responsible for enhanced release of cortisol through activation of the paraventricular nucleus (PVN) to secrete cortisol-releasing hormone (CRH). An increase in protein synthesis to secrete CRH has been observed in the PVN. The concentration of IL-1 is directly proportional to stress, and it follows a bell-shaped curve with respect to memory consolidation. Initial stress enhances memory consolidation, while in later stages, there is excessive IL-1 in the brain leading to memory impairment [14,15].

Minocycline, which is a commonly used antimicrobial, is known to have a potent anti-inflammatory effect, as evidenced by animal studies. As there have been limited studies on anxiolytic effects of this potential drug, we decided to use this drug as the test drug.

The main objectives of our study were as follows:

To study the anxiolytic effect of minocycline in resident–intruder social conflict in submissive hamsters post resident intrusion model using

a. Behavioral tests: Open field test (OFT) and elevated plus maze (EPM)
b. Biochemical test: Serum cortisol levels.

Materials and methods

Animal ethics committee permission

The Institutional Animal Ethics Committee permission was taken before the commencement of the study under reference number AEC/17/2017. Animals randomly bred in the Centre for Animal Studies of the National Institute of Nutrition, Hyderabad, were used. The study was conducted in accordance with the Committee of Purpose of Control and Supervision of Experimentation in Animals (CPCSEA) guidelines.

Experimental animals

The study was carried out with a total of 52 male Golden Syrian Hamsters (*Mesocricetus auratus),* of which 12 hamsters were large weighing >160 g and aged 4–9 weeks, while 40 hamsters were small weighing 90–140 g and aged >12 weeks. The larger hamsters were used as dominant hamsters, while the smaller ones were used as submissive hamsters during the study. Out of 40 submissive hamsters, we used 16 hamsters for standardization and 24 hamsters for actual study (Phase 2).

Husbandry conditions

Animals were maintained in the Central Animal House of Seth GSMC and KEMH in conditions prescribed as per the CPCSEA guidelines. Animals were quarantined for a couple of weeks and then handled daily for acclimatization.

Drug procurement

Two drugs, namely minocycline hydrochloride and lorazepam, were procured from Sigma Aldrich, Mumbai, in pure powder form as an actual pharmacological ingredient. Lorazepam was used in the dose of 0.3 mg/kg, while minocycline was used in the dose of 42 mg/kg. The doses were based on the conversions of doses used in previous studies, as shown in Table 1.

Serum cortisol kits

Serum cortisol kits for hamsters were manufactured by Arbor Assays and imported from the USA. Serum cortisol was estimated using noncompetitive ELISA test [16].

Study procedure

The model was initially standardized. Animals were strictly maintained in adequate environment as prescribed by the CPCSEA guidelines and with a dark-light cycle of 14:10.

a. Each hamster was individually housed in their home cages
b. After period of quarantine, all the hamsters were handled daily for 10 min. The handling consisted of gently picking up the animal by its scruff and keeping it back in the cage so that handling does not act as a confounding factor
c. After 2 weeks of daily handling, the procedure of resident intrusion was done by placing smaller hamster in cage of larger hamster, either for 5 min or the period till which the larger hamster physically injured the smaller hamster, whichever was earlier and behavior of smaller hamster was noted based on behavioral inventory by Huhman *et al.* [Table 2]. The submissive behavior was assessed with respect to behaviors such as tail lift, fleeing behavior, and full submissive posture [Figure 1]
d. Only submissive hamsters were used and divided into three groups of 8 animals
e. Submissive hamsters were given respective drugs depending on the group stat intraperitoneally [Table 1]. The animals were coded, and the investigator performing behavioral tests and serum cortisol estimation was blinded and was thus not aware regarding the nature of drug given to each group. The procedure for this study has been schematically represented in Figure 2.

Table 1: Study drugs with doses

Group name (*n*=8)	Drug	Dose
Disease control	Normal saline	1 mL IP
Positive control	Lorazepam	0.3 mg/kg in 1 mL NS IP
Test group	Minocycline hydrochloride in saline	42 mg/kg in 1 mL NS IP

Table 2: Characteristics behavior of submission in hamsters

Submissive behavioral characteristics	Description
Tail lift	Lift tail with or without hindfoot adduction
Flee	Flight, retreat, escape from cage or rapid movement away from opponent
Full submissive posture	Lies unmoving on the back even after opponent has moved away

Figure 1: Submissive hamster showing full submissive posture by lying on its back even when opponent is removed

f. Behavioral tests were done after 24 h in the form of EPM, in which time spent in open arms and percentage preference in open arms were noted, and OFT in which time spent in the central zone and number of entries in the central zone were noted. Additional variables such as latency to initial movement, total distance traveled, and number of entries in each zone were also noted
g. Post behavioral tests, retro-orbital blood collection was done as per the CPCSEA guidelines. 0.5 ml blood was collected from each animal. The blood was immediately centrifuged to separate the serum. The serum was stored at −80°C in a deep freezer till the time ELISA test was performed. The ELISA test was performed after thawing the serum at room temperature
h. Antibiotic drops (tobramycin) were inserted in both the eyes of the hamsters post retro-orbital blood collection.

All the doses were calculated using similar antianxiety studies done in rats and other rodents as no reference using similar drugs was available in hamsters. It was followed by equivalent interspecies dose conversion using standard validated references [17].

Statistical analysis

Data were analyzed using IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. The level of significance was set at $P < 0.05$. Normality was tested by Shapiro–Wilk test. Parametric data for standardization were analyzed using unpaired *t*-test and that for the study were analyzed using single-way ANOVA followed by *post hoc* Tukey's test. Nonparametric data were analyzed using Kruskal–Wallis test followed by *post hoc* Dunn's test.

Results

Results of standardization

Serum cortisol levels

As shown in Figure 3, all values represent mean ± standard deviation (SD) data and they passed the test of normality. Unpaired *t*-test was applied. *t* value of 6.92 ($P = 0.004$) was obtained after analysis, which is statistically significant. It indicates that there is a statistically significant increase in serum cortisol level in smaller submissive hamster post resident intrusion, and it is suggestive of anxiogenic effect post resident intrusion.

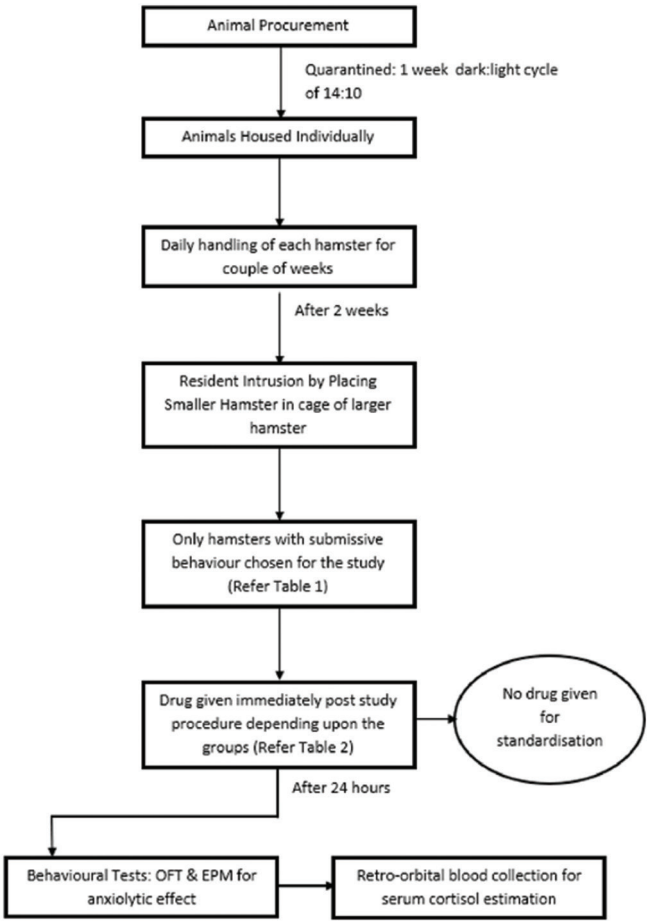

Figure 2: Schematic study flow

Elevated plus maze

All values in Figure 4a represent mean ± SD data that passed the test of normality. Unpaired *t*-test was applied for each variable, i.e., time spent in open arms and percentage preference in open arms. The level of significance was set at $P < 0.05$, and for both the variables, $P = 0.012$, $t = 8.98$ and $P = 0.002$, $t = 6.59$, respectively, were obtained. Thus, the decrease in both variables compared to negative control is statistically significant.

Open field test

All values in Figure 4b represent mean ± SD data that passed the test of normality. Unpaired *t*-test was applied for each variable, namely time spent in the central zone and number of entries in the central zone, both of which show a statistically significant decrease with $P = 0.01$, $t = 2.76$ and $P = 0.0003$, $t = 5.20$, respectively.

Study results

Serum cortisol levels

All values in Figure 5 represent mean ± SD data that passed the test of normality. Application of one-way ANOVA

followed by post hoc Tukey's test showed statistically significant difference with respect to both the variables namely, time spent in open arms and percentage preference in open arms, between disease control group and positive control group. Similar results were seen between disease control group and minocycline group. *P* values obtained were $P < 0.01$, which is indicative of high statistical significance. The *F* value is 25.36.

Elevated plus maze

All values in Figure 6a represent mean ± SD data that passed the test of normality. One-way ANOVA showed statistically significant difference between with respect to time spent in open arm and percentage preference in open arm across all three groups. Post hoc Tukey's test showed statistically significant difference for both the above-mentioned variables when positive control group and Minocycline group were compared with disease control group. The F value for time spend in open arms is 56.36 and for percentage preference for open arms is 38.32. The *P* value for both the variables, namely time spent in open arms and percentage preference in open arms, was $P < 0.001$, which is extremely significant.

Open field test

All values in Figure 6b represent mean ± SD data that did not pass the test of normality. Hence, as the data were nonparametric, Kruskal–Wallis test was used followed by *post hoc* Dunn's test. Statistically significant difference was seen between disease control group and positive control group with respect to time spent in central zone and number of entries in central zone. Similar results were seen between disease control group and the Minocycline group. The Kruskal–Wallis H value and *P* value for number of entries in the central zone and time spent in the central zone were *H* value: 10.77, *P* value: 0.004 and *H* value: 11.31, *P* value: 0.003, respectively.

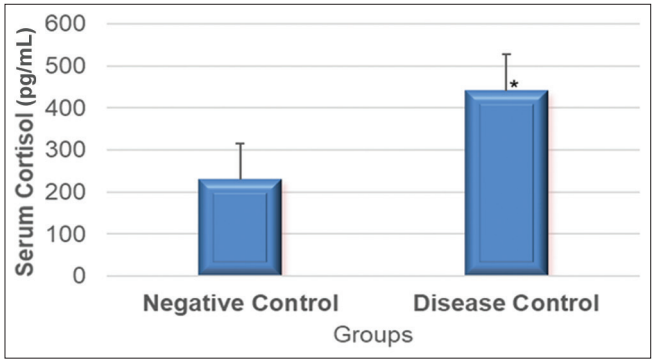

Figure 3: Serum cortisol levels ($n = 8$ per group). *$P < 0.05$ versus disease control group, using unpaired *t*-test

Results for other variables

Additional variables were measures during the procedures of both the behavioral tests. During OFT, we additionally checked for total distance traveled during 5 min of OFT. During standardization, there was a statistically significant increase in total distance traveled in the negative control group compared to the disease control group ($P = 0.04$) using unpaired *t*-test. However, no statistical significance was seen during the study period using drugs, and hence, the results were excluded. In terms of latency to the first movement, no significant differences were observed neither during standardization phase nor during the study phase.

There were no adverse events reported throughout the experimentation.

Discussion

PTSD is a common psychiatric disorder affecting the quality of life of the patients leading to both acute and chronic distress [18].

The stressful event is commonly psychological in nature without any physical harm. The commonly used models to induce stress include single prolonged stress model, chronic restraint model and hot or cold exposure model. These models induce stress through physical stressors. However, the stress induced in PTSD is mainly psychological and not physical and hence the above-mentioned models have poor translational validity. Our model induces stress psychologically and hence has better translational validity [19].

We used Syrian hamsters as they are inherently territorial and solitary in nature [20]. Second, on confrontation of smaller and larger hamsters in latter's cage, the larger hamster rarely physically injures the smaller hamster and both the hamsters exhibit characteristic ritualistic agnostic behavior (dominance and submission) [Table 2]. The induced stress is psychological in nature enhancing validity of our study.

Current management of PTSD consists of both pharmacological and nonpharmacological modalities. Nonpharmacological modalities are generally the first line of

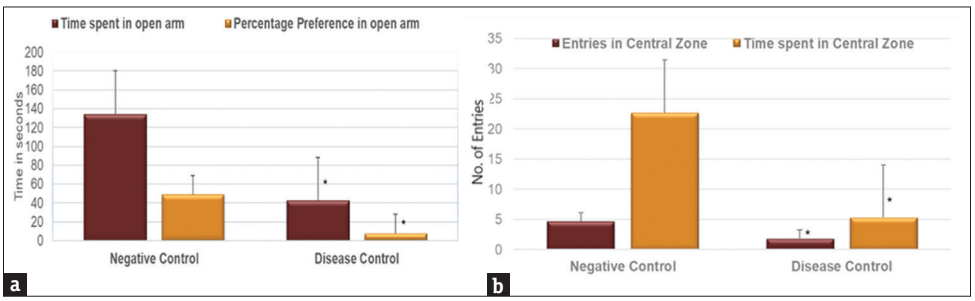

Figure 4: Graphical representation of variables of elevated plus maze and open field test on standardization ($n = 8$ per group). *$P < 0.05$ versus disease control group, using unpaired *t*-test. (a) Elevated plus maze, (b) open field test

treatment consisting primarily of psychotherapy and cognitive behavioral therapy. Pharmacological therapy consists of drugs such as SSRIs, benzodiazepines, N-methyl-D-aspartate receptor antagonists, and corticosteroids [21].

SSRIs are commonly prescribed classes of drugs, but paradoxically, they are initially anxiogenic for a couple of weeks followed by anxiolytic activity. In general, patients of PTSD come to the psychiatric OPD with acute anxiety-like symptoms and they are prescribed benzodiazepines such lorazepam and alprazolam for a week along with SSRIs. After 1 week, a patient is asked to discontinue benzodiazepines. Benzodiazepines like lorazepam account for the highest off-label prescribed drugs in PTSD on an OPD basis, and hence, we used it as our positive control. However, as per systemic review by Guina *et al*., benzodiazepines cause more harm than good. They have been shown to be ineffective both in prevention and treatment of PTSD and have been shown to worsen symptoms of PTSD in terms of recurrent flashbacks and severe nightmares [10]. Thus, there is a need for newer treatment modality, both for prevention and treatment of PTSD and ameliorating acute distress in PTSD.

All the currently used drugs generally provide only symptomatic relief, and there are no specific guidelines regarding duration of drug therapy. There is a need for development of new drugs or repurposed medications with different mechanisms of action, better safety and tolerability, and curative in nature.

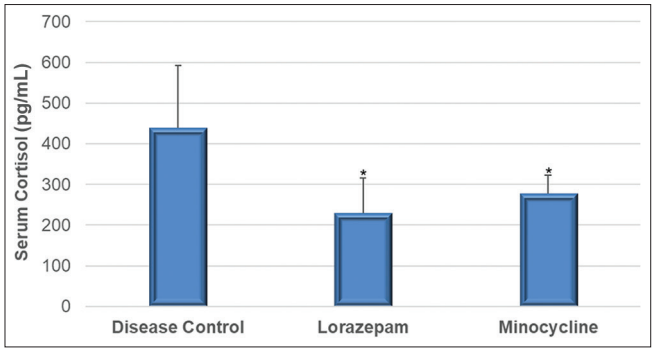

Figure 5: Graphical representation of serum cortisol levels in study (n = 8 per group). *P < 0.05 versus disease control group, using ANOVA and *post hoc* Tukey's test

Minocycline is generation tetracycline, and it acts by inhibiting bacterial protein synthesis. It is also known to possess additional anti-inflammatory effects which are hypothesized to occur due to inhibition of T-lymphocyte response and also inhibition of neutrophil migration [22]. This property is believed to responsible for therapeutic efficacy in conditions like PTSD. One of the hypotheses of PTSD suggests that it is a continuous low-grade inflammatory state with imbalance in the functioning of sympathetic and the parasympathetic arm of the autonomic nervous system, along with impaired function of hypothalamic–pituitary–adrenal axis [23]. Minocycline is hypothesized to promote neurogenesis and neuroplasticity, reduce oxidative stress and glutamate excitotoxicity, and attenuate a decrease of serotonin, dopamine, norepinephrine, and their derivatives [24].

Currently, there is no treatment for preventive aspect of PTSD. Certain genotypes are more susceptible to the development of PTSD compared to others, and identification and screening of these potential phenotypes will be essential in the future [25]. Minocycline, through our study findings, may be used in these potentially susceptible phenotypes in the future when they are exposed to trauma. This drug can act for potential postexposure prophylaxis in these patients and thus greatly improve quality of life and may be curative.

Serum cortisol level in plasma is a commonly used biomarker for assessment of acute stress and anxiety. After induction of anxiety, there is activation of inflammatory cascade in the brain associated with predominant activation of IL-1. This leads to activation of PVN leading to secretion of CRH. This ultimately leads to increased secretion of cortisol, further leading to increased plasma cortisol levels [14]. We have measured serum cortisol levels post stress induction and elevation in the same is indicative of anxiety.

During standardization, there was an increase in serum cortisol levels 24 h after exposure to stress compared to the normal control. Similarly, there was anxiogenic finding in both the behavioral tests as evidenced by a decrease in time spent and percentage preference in open arms of EPM and decrease in time spent and number of entries in the central zone of OFT. Both the biochemical test and behavioral test validate our model.

Our results show acute anxiolytic effects both on biochemical tests as well the behavioral tests as evidenced by

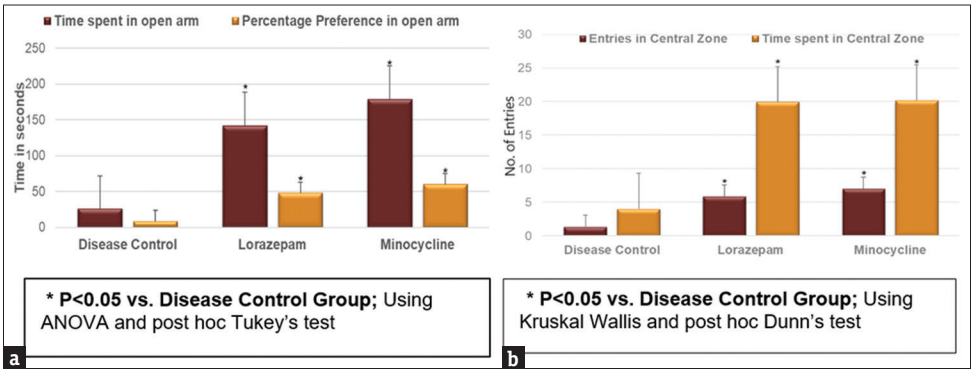

Figure 6: Graphical representation of variables of elevated plus maze and open field test in the study (n = 8 per group). (a) Elevated plus maze, (b) open field test

a decrease in serum cortisol levels in the minocycline group compared to the disease control group and an increase in time spent in open arms in EPM and increase in number of entries and time spent in OFT compared to the disease control group. This finding implies that minocycline has an immediate antianxiety effect, and if other studies validate our findings, minocycline can be used for postexposure prophylaxis of PTSD. This effect of a postexperience drug regimen could be since Minocycline blocks consolidation of the traumatic memory and thus prevents anxiety as many antibiotics may block protein synthesis which is critical for memory consolidation.

There have been limited studies regarding postexposure administration of minocycline for prevention of PTSD, and hence, our study is unique. A study done by Levkovitz *et al*. [15], using Predator Stress Paradigm (PSS) model in Sprague Dawley rats, showed similar results to our studies with significant anxiolytic effect using minocycline. In addition, the study showed a decrease in pro-inflammatory cytokines in the brain including IL-1, IL-6, and tumor necrosis factor-alpha, which consolidates the anti-inflammatory hypothesis of minocycline.

A study using chronic administration of minocycline in a Wistar rat model of intermittent foot shock was done by Wang *et al*. [26], and the results for behavioral tests were similar to our study as evidenced by an increase in time spent in central zones in OFT and increase in time spent in open arms in EPM. This study also showed a decrease in microglial cell activation in the group receiving minocycline. Microglial cells in the brain are activated by various pro-inflammatory activations, and thus, a decrease in the same can be attributed to anti-inflammatory effect of minocycline on PTSD-like states. Similar results are seen in the study by Liu *et al*. [27], which was done using chronic restraint on C57BL/6 mice and chronic administration of minocycline. In this study, the efficacy of minocycline was comparable to buspirone which had been used as a positive control.

Our results are in line with other animal studies of acute anxiety and PTSD, and thus, the drug shows promising results for taking it further in terms of drug development. As we are using acute single dose of minocycline, there is a lower risk of toxicity and development of antibiotic resistance seen with chronic use.

This study has further opened prospects for further studies using a similar animal model and minocycline with greater number of biochemical parameters. The main potential parameter regarding minocycline is its potential use in postexposure prophylaxis for PTSD in the future. It will greatly help in improving the quality of life of patients immediately posttrauma, and thus, more studies are needed to certify its preventive role.

The major limitations of this study include:

a. Due to insufficient funds, we had to use serum cortisol as a biochemical marker which is less specific than serum corticosterone in rodents [28]
b. We have used single resident intrusion only and thus looking only at the anxiety component of PTSD. More studies will be needed to address the role of minocycline in chronic PTSD which is often accompanied by depression
c. Animal behavioral models in psychiatry usually could only achieve face validity, not construct validity (unless the real thoughts and emotions of animals can be detected correctly), therefore, whether minocycline has anxiolytic effects in human remains unknown
d. Blood levels of the drugs were not tested in this study, so it is not clear how much amount of the drugs left in animals after 24 h.

Conclusion

The anxiolytic effect of minocycline is comparable to that of lorazepam and statistically significantly more compared to disease control as evidenced by serum cortisol levels and behavioral tests in Golden Syrian hamsters.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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