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Original Article

Minocycline Prevents Depression-like Behavior After Co-administration With Dexamethasone or Cyclosporine-A in Mice

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ABSTRACT

Background: In animal studies, minocycline (Mcy) has been proven to have antidepressant effects. In addition to modulating peripheral and central pro-inflammatory pathways, Mcy may regulate the hypothalamic-pituitary-adrenal (HPA) axis and the mechanistic target of rapamycin (mTOR) signaling pathway. This study aims to evaluate the antidepressant-like effect of Mcy in mice following injection of dexamethasone (Dex) or cyclosporine-A (CsA).

Methods: Male NMRI mice were randomly divided into eight groups of 6, including control, Dex 0.25 mg/kg, CsA 20 mg/kg, Mcy 40 mg/kg, Dex+Mcy, Dex+fluoxetine 20 mg/kg, CsA+Mcy, and CsA+fluoxetine. All drugs were injected intraperitoneally (except for Dex, which was subcutaneous injection) once daily for 3 days. The locomotor activity, forced swimming test (FST), and sucrose preference (SP) test were performed on day 4.

Results: Mcy alone reduced immobility time in the FST (27.0±6.4 s) compared to the control group (104±3.9 s) (P<0.001). After the co-administration of Mcy and Dex, the immobility time significantly decreased (79.5±6.5 s) compared to the Dex group (P<0.001). It also decreased following the co-administration of Mcy and CsA (67.5±20.8 s) compared to the CsA group (P<0.001). Results were similar in the groups treated with fluoxetine plus Dex or CsA. Significant differences were not observed in the locomotor activity test.

Conclusion: Mcy prevents depression-like behavior in mice during the FST when it is co-administrated with CsA or Dex. The possibility of the positive effect of Mcy on the HPA axis and the mTOR signaling pathway should be examined in further studies.

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Introduction

While monoamine-based antidepressant drugs continue to be the gold treatment for depression, therapeutic latency and the reported small number of remissions have indicated the need for more effective therapies. Minocycline (Mcy) has more lipid solubility compared to other tetracycline antibiotics, allowing for appropriate diffusion through the blood-brain barrier and into the cerebrospinal fluid [1]. It has high anti-inflammatory properties and protects against neuronal damage. The effect of Mcy is exerted possibly through reducing pro-inflammatory nitric oxide (NO) synthase and cyclooxygenase-2 (COX-2) transcription, and consequently by the release of prostaglandin E2; with a decline in NO, interleukin1-β release also declines and microglial activity is prevented [2]. A randomized, placebo-controlled clinical trial on the effect of administration of 200 mg/day Mcy along with the common drugs for major depressive disorder, showed that Mcy could be a promising adjunctive therapy [3]. In animal studies, Mcy has been proven to have antidepressant effects by reducing despair-like behavior in the forced swimming test (FST), while the noradrenergic system was little responsible for this effect [4].

The hypothalamic-pituitary-adrenal (HPA) axis has vital role in stress regulation, and there is a connection between long-term stressful stimulation and depression [5]. The increased HPA axis activity is observed in those with depression and stress that can cause important therapeutic problems. Therefore, the regulation of the HPA axis activity in patients with depression is a suitable target for drug therapy [6]. In stressful conditions, the glucocorticoid (GC) hormone cortisol is released from the adrenal gland that stimulates both mineralocorticoid receptor (MR) and central glucocorticoid receptor (GR) [7]. Many studies on human and animal studies have shown a connection between a high blood GC level and depression [8–10]. In patients that use the synthetic GCs for a long period, or in those with Cushing's syndrome, there are common symptoms [10–12]. Animal studies have shown that dexamethasone (Dex), a synthetic GC drug, can cause depression-related behaviors in a dose-dependent manner. They have proven the molecular effects of stress, and have revealed new antidepressants or supportive therapies for modulating the HPA axis receptors MR, or GR [8, 13].

The association of calcineurin activity with anxiety and depression has been observed in clinical practice, since the number of psychiatric disorders increased in patients that were chronically prescribed with calcineurin inhibitor cyclosporine A (CsA) to prevent allograft rejection [14, 15]. Preclinical studies have reported that the depression-related behavior that is initiated after administration of calcineurin inhibitors is related to preventing a cellular signaling pathway, the mechanistic target of rapamycin (mTOR). This is a serine/threonine protein kinase pathway that regulates synaptic protein production and growth, leading to altered spine density [16]. For the fast antidepressant effects of ketamine (a N-methyl-D-asparate antagonist), the mTOR is essential [17]. It has been shown that Mcy regulates the level of GCs by affecting the HPA axis. Furthermore, the antidepressant activity of Mcy may be related to Akt/mTOR signaling pathway that produces the neurite outgrowth due to nerve growth factor induction [18]. This study aims to evaluate the antidepressant effects of Mcy on depression induced by Dex or CsA in mice.

Materials and Methods

Animals

In this study, 59 samples were male NMRI mice weighed 25-30 g (6-8 weeks old). They were kept in cage with free access to pellet food and water under standard humidity, temperature (21-23°C), and light/dark (12 h/12 h) cycle. Determinations were made for animal welfare and reduction of animal number used during experiments.

Chemicals

The following chemicals were purchased for the study: Mcy hydrochloride (Sigma, Germany), 50 mg/mL Sandimmune ampoule as a CsA (Novartis, Switzerland), 8 mg/2 mL Dex ampoule (Raha Industry, Iran) and the reference antidepressant, fluoxetine HCl (Sigma-Aldrich, India).

Experimental design

The mice were divided into eight groups of 6: Group1 received Mcy 40 mg/kg intraperitoneally (IP) (according to a pilot study and reference [4]), group 2 received subcutaneous (SC) injection of Dex 0.25 mg/kg [13], group 3 as the control group, formed by merging the groups received SC and IP injection of normal saline, group 4 received CsA 20 mg/kg IP (CsA was diluted in 2% v/v ethyl alcohol/normal saline) [19], group 5 as control animals received vehicle 2% v/v ethyl alcohol/normal saline, group 6 received both Mcy 40 mg/kg (IP) and Dex

0.25 mg/kg (SC), group 7 received both fluoxetine 20 mg/kg (IP) and Dex 0.25 mg/kg (SC), group 8 received both Mcy 40 mg/kg (IP) and CasA 20 mg/kg (IP), and group 9 received both fluoxetine 20 mg/kg (IP) and CsA 20 mg/kg (IP). The volume for all injections were 10 mL/kg. All drugs were administered once daily for three successive days and the tests took place on day 4.

Locomotor activity test

The locomotor activity test was conducted to evaluate the possible sedative or stimulant activity of different treatments. In an open-field apparatus with a 40×40×40 cm^3 size (Borj Sanat, Iran) and a white floor that was divided into 15 equal parts by red beams. Mice were gently placed in one corner of the field, free to explore for three minutes. By crossing the line (the red beams), the device counted horizontal movements, and the vertical movements (number of time the animal stands on its hind legs) were counted manually. The total activity for each mouse was recorded (i.e. the sum of horizontal and vertical movements) [4, 20].

Forced swimming test

Despair-like behavior of mice was assessed by the forced swimming test (FST). In a cylindrical beaker filled with 12 cm of 25°C water, mice were forced to swim for six minutes. The initial 2-minute time was considered as the habituation time. In the last 4 minutes, animal activity was recorded using a camera. In this regard, immobility time, swimming time, and climbing time were measured for different groups [19, 21]. At the end, the mice were taken out of the water and dried carefully to avoid hypothermia.

Sucrose preference test

Sucrose preference (SP) test measures anhedonia, a depression phenotype in rodents. The test started from the first day and was performed in three days; the first two days were for habituation to the bottle of sucrose solution (2.5 % w/v) that was put in their cage. On the third day, one sucrose solution bottle and one water bottle were measured and placed in the cages. Then, the amount consumed from each bottle was measured after 24 h (on day 4), and the SP percentage was calculated for each cage [13]. Values less than 65% were considered anhedonia.

Statistical analysis

Behavioral test results were presented as Mean±SEM. The software programs that were used for drawing the graphs and interpreting the results were GraphPad Prism software, version 8 and Excel 2020. The effect of different treatment regimens were analyzed by using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. $P<0.05$ was considered statistically significant.

Results

Effect of Mcy on the despair-like behavior following Dex administration

As shown in Figure 1a, after Mcy administration, the immobility time in the FST significantly decreased (27.0±6.4 s) compared to the control group (104±3.9 s); $F_{(4, 28)}=80$, $P<0.001$, indicating an antidepressant activity. Dex alone increased the immobility time significantly (150±7 s, $P<0.001$), while after treatment with both Mcy and Dex, the despair-like behavior was reversed (79.5±6.5 s; $P=0.017$ compared to the control group, $P<0.001$ compared to the Dex alone group). These changes were similar to the group received both fluoxetine and Dex. Swimming and climbing times in the FST are presented in Table 1. As can be seen, Mcy significantly increased the swimming time while Dex prevented swimming activity. In the group with Mcy and Dex co-administration, the swimming and climbing times improved similar to the groups treated with both fluoxetine and Dex. Table 1 also shows th SP test results. As can be seem, anhedonia induced by Dex (SP=55%) was reversed by Mcy co-administration (SP=87.4%). The changes observed during the FST were in the absent of changes during the locomotor activity test, Table 1 presents the total activity during the locomotor test. Only treatment with both fluoxetine and Dex could significantly increase the total activity compared to the control group.

Effect of Mcy on the despair-like behavior following CsA administration

Following the CsA administration, the immobility time in the FST increased significantly (149±6.67s) compared to the control group (102±3.88s); $F_{(4, 27)}=16.40$, $P=0.038$ (Figure 1b). Treatment with both Mcy and CsA had anti-immobility effect such that it significantly reduced the immobility time compared to the CsA administration alone (67.5±20.8s, $P<0.001$). These changes were similar to the group received both fluoxetine and CsA. Table 1 shows that CsA alone reduced both climbing and

Table 1. The locomotor activity test, SP test, and FST results in different groups

Groups	Total Locomotor Activity, (Units)	SP %	FST	
			Swimming Time (s)	Climbing Time (s)
Control	168±13.5	69.3	97.3±6.9	43.0±4.4
Mcy 40 (mg/kg)	192±17.8	76.4	151.3±12.0***	61.7±7.5
Dex 0.25 (mg/kg)	136±22.1	55	52.6±4.4**	37.2±7.4
CsA 20 (mg/kg)	124±11.0	38	63.9±4.6	25.0±2.4
Dex+Mcy	205±10.7	87.4	113.5±11.2vvv	47.0±13.4
Dex+Flx	228±9.8*	88.8	126.7±9.5vvv	75.8±10.0v
CsA+Mcy	166±5.3	77.1	99.7±11.0^	61.0±15.0
CsA+Flx	178±18.5	76.3	92.3±9.7	88.0±7.1^^^,**

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Total locomotor activity: Horizontal activity+vertical activity; SP%: Sucrose consumption/water plus sucrose consumption)×100. Control animals received normal saline solution. Results are presented by Mean±SEM, and were evaluated by ANOVA followed by Tukey's post hoc test. Flx: Fluoxetine. *P<0.05, **P<0.01, ***P<0.001 compared to the control; vP<0.05, vvvP<0.001 compared to the Dex along; ^P<0.05, ^^^P<0.001 compared to the CsA alone.

swimming times during the FST, although the changes were not significant. Administration of both CsA and Mcy significantly increased the swimming time compared to the CsA administration alone. Administration of both fluoxetine and CsA increased the climbing time significantly compared to control and CsA alone groups. As shown in Table 1, the anhedonia induced by CsA injection was also reversed after administration of Mcy (SP=77.1%). There was no significant change in the locomotor activity according to the results in Table 1.

Discussion

In this study, Mcy administration reduced immobility time during the FST, and had anti-immobility effect when co-administrated with CsA or Dex. Therefore, it can be said that Mcy caused anti-despair behavior and prevented depression-like effect induced by CsA or Dex, indicating that the immobility time in the FST was a direct result of animal's dispaire behavior. There was an exeption for the group received Dex with fluoxetine which may have influenced the FST results. FST is one of the popular tests for evaluating the despair-like behavior in rodents, and is used globally for evaluating antidepressant effect of drugs and for screening antidepressant products [22] and to poor response to antidepressant therapy. Progress in this area requires valid animal models. Current models are based either on manipulating the environment to which rodents are exposed (during the developmental period or adulthood. While the increased immobility time in this test presents the despair-like behavior as a type of depression-like behaviors, the swimming and climbing times may indicate the involvement of the serotonergic or catecholaminergic system, respectively [23] which suggest it might be taken as a predictor of motor activity in rat FST. To investigate this proposal, the frequency, duration, as well as the ratio duration/frequency for each behavior expressed in the FST (immobility, swimming and climbing. Although the administration of Mcy reduced immobility time in the FST, the animals' total activity in the locomotor activity test remaind normal, indicating the antidepressant effects of Mcy. Swimming time was significantly increased after Mcy administration that may be related to the increased serotonin activity. This results is supported by a previous animal study that proved the trivial role of noradrenergic system in antidepressant-like effects of Mcy, since after administration of α-methyl-p-tyrosine (a selective inhibitor of the tyrosine hydroxylase, an enzyme necessary for epinephrine synthesis), there was no change in Mcy antidepressant-like effect in the FST [4]. Another mechanism for the antidepressant effects of Mcy is the exertion of anti-inflammatory and neuroprotective effects by inhibiting COX-2 and suppression of microglial activation [3].

The administration of Dex increased the immobility time in the FST, while locomotor activity was in the normal range, indicating the initiation of depression-like behavior. Previous animal studies also have reported the

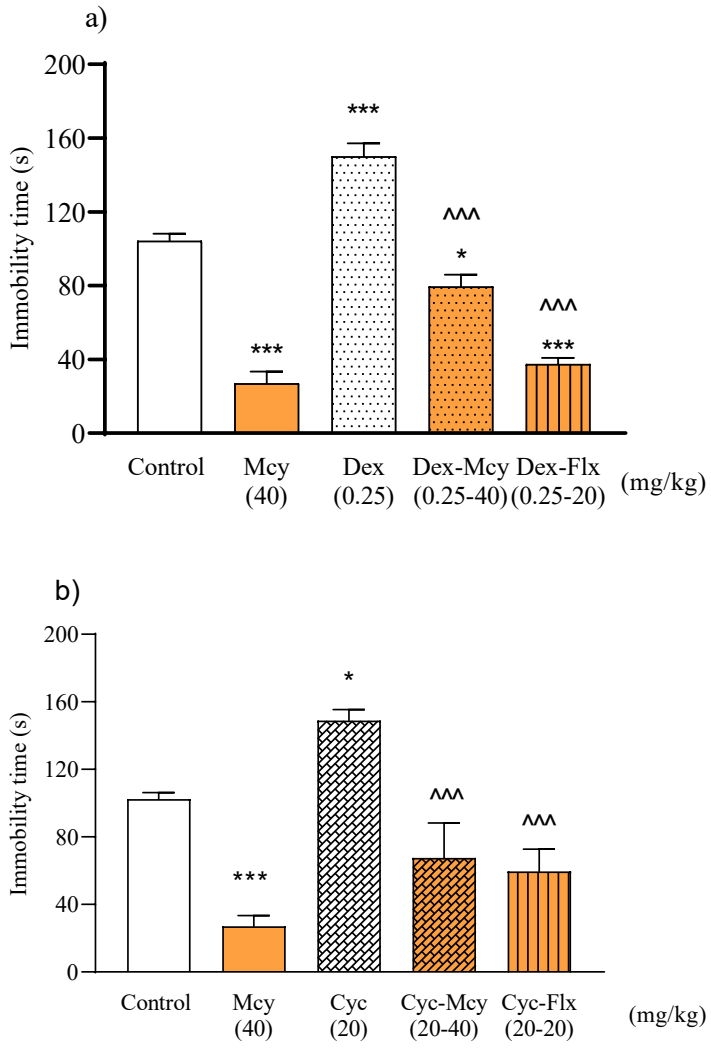

Figure 1. Effect of Mcy administration plus (a) Dex or (b) CsA injection for 3 days on the immobility time in the FST test

The results are presented by Mean±SEM, and analyzed by ANOVA followed by Tukey's post hoc test. $^{*}P<0.05$ and $^{***}P<0.001$ compared to the control group, $^{\wedge\wedge\wedge}P<0.001$ compared to the Dex alone or CsA alone. Flx: Fluoxetine.

depression-like behavior induced by Dex or corticosterone administration, and also following the induction of water avoidance stress in mice [13, 24, 25]. After oral Dex administration in healthy individuals and its binding to the GR and activating the HPA axis feedback system, the cortisol secretion decreases under the Dex suppression test. However, in depressed individuals, cortisol secretion cannot be inhibited by Dex consumption, which proves the GC resistance due to the impaired feedback of the HPA axis caused by altered function of GR in these patients [7] possibly caused by altered function of the receptor for glucocorticoid hormones, the glucocorticoid receptor (GR). However, in depressed subjects cortisol secretion cannot be inhibited following Dex consumption, that proves GC resistance since the negative feedback on the HPA axis mediated by GR is damaged in these patients [8]. In our experiment, fluoxetine was able to prevent depression-like behaviors induced by Dex injection. This was also observed after injection of Mcy. The effect of Mcy on the HPA axis can be the reason for preventing depression induced by Dex. This finding was supported by a previous study where Mcy treatment during different periods of postnatal days in mice significantly reduced depression-like symptoms and the HPA axis hyperactivity induced by lipopolysaccharide administration [26].

Our study in consistent with previous studies that showed CsA administration could induce depression-like behavior in mice [19]. Clinical studies as well as animal studies have revealed that calcineurin inhibition has a relationship with

psychologic illness and depression [27, 28]. The calcineurin inhibitors induce depressive-like behavior through the mTOR signaling pathway, and the increased mTOR activity in medial prefrontal cortex may prevent the risk of depression in people that use calcineurin inhibitors [14]. An in-vitro study on PC12 cell line suggested that Mcy significantly initiated the nerve growth factor-induced neurite outgrowth in a concentration-dependent manner, which was not observed after tetracycline demonstration. They found out that, in addition to several common signaling molecules, mTOR signaling pathway was involved in the activity of Mcy [18]. Therefore, the possible activity of Mcy on the mTOR signaling pathway can be the reason for preventing CsA-induced depression.

Conclusion

This study provides convincing evidence about the antidepressant effects of Mcy when it is co-administrated with CsA or Dex. The possibility of the positive effect of Mcy on the HPA axis and the mTOR signaling pathway should be examined in further studies.

Ethical Considerations

Compliance with ethical guidelines

All experiments were performed in accordance with the guidelines for the care and use of laboratory animals of Isfahan University of Medical Sciences (Code: IR.MUI.REC.1399.821).

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Authors' contributions

Supervision, conventionalization, design, methodology, interpretation of data: Azadeh Mesripour; Investigation, pharmacological experiments, data collection: Sara Pezeshki; Writing, editing and final approval: The both authors.

Conflict of interest

The authors declared no conflict of interest.

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