Research Article

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Melatonin Prevented Depressive-Like Behavior Following Cyclosporine A or Interferon-α Administration in Mice

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ABSTRACT

Cyclosporine A (CYA) is prescribed to prevent graft rejection after transplantation. Interferon-α (IFN-α), a natural cytokine, is prescribed for some types of malignancies, and hepatitis C virus. But both may cause neurologic complications such as depression following their chronic use. Melatonin is a hormone that helps regulate the circadian rhythm, additionally the melatonin system is connected to depression. The goal was evaluating the antidepressant effect of melatonin following IFN-α, and CYA administration in mice. Male NMRI mice (25-30 g) were used, IFN-α (1600000 IU/kg, sc), CYA (20 mg/kg, ip), melatonin (50 mg/kg, ip), and fluoxetine (20 mg/kg, ip) were administered daily. After evaluating the locomotor activity, depression was assessed by splash test, forced swimming test (FST), and the sucrose preference test. There was no significant difference in the locomotor activity amongest different animal groups. Following melatonin and IFN-α co-administration immobility time in FST decreased (58.50±19.4s, $p<0.01$); and during the splash test grooming time increased significantly (114.3±15.3s, $p<0.01$) compared to the IFN-α alone group, and sucrose preference rose up to 70%. After melatonin and CYA co-administration immobility time during FST decreased (42.33±9.9s, $p<0.001$); and grooming time increased significantly (103±10.5s, $p<0.001$) compared to the CYA alone group, sucrose preference also increased up to 93%. The changes induced by melatonin in these experiments were similar to changes made by fluoxetine. Melatonin prevented depression behavior (despair, apathy, and anhedonia) induced by IFN-α, or CYA in mice. The mechanism involved in melatonin antidepressant-like effect warrants further investigations.

Keywords: depression, cyclosporine A, interferon-α, melatonin, animal models

1. Introduction

Cyclosporine A (CYA) is a calcineurin inhibitor that has been accepted for preventing graft rejection in kidney, heart, and liver transplants [1]. Other indications of the drug include treating autoimmune disorders and rheumatic diseases [2]. Neurological complications such as tremor, nervousness, and depression have been reported as side effects of chronic use of the drug [3–5]. It has been noted that the Ca^{2+}-dependent protein phosphatase, calcineurin, is involved in neurotransmission, neuronal plasticity, and memory [6]. Studies show that calcineurin inhibitors induced depressive-like effect is mediated by blockade of a signaling pathway the mammalian target of rapamycin (mTOR); a serine/threonine protein kinase that controls synaptic protein synthesis; thus, it is related to depression [7,8]. Critical roles of the glutamate ionotropic receptor N-methyl-d-aspartic acid (NMDA) receptors and the mTOR signaling pathway are recognized for control of dendritic protein synthesis in hippocampal neurons [9].

Interferon alpha (IFN-α) is a cytokine naturally produced by the immune system, that is mostly used to manage some types of malignancies such as melanoma, and hepatitis C virus [10]. Chronic use of IFN-α can cause psychological side effects such as depression, even followed by suicidal attempts [11]. One mechanism suggested for depression initiation by IFN-α is the increased activity of indoleamine 2,3-dioxygenase (IDO) that produces a shift in metabolizing tryptophan to kynurenine, and by hydroxylase, it is converted to quinolinic acid which is an NMDA receptor agonist [12,13]. As a direct result, the kynurenine level rises while the accessible level of tryptophan required for serotonin (5-HT) synthesis declines [14]. Excessive glutamate receptors (NMDA receptor) activation by excitatory amino acids has various damaging consequences, as a result of impairment of calcium buffering, including production of free radicals, initiation of the mitochondrial permeability transition, secondary excitotoxicity, and loss of neurons in the hippocampus [15].

Melatonin is a hormone that regulates the circadian rhythm, and it is secreted mainly from the pineal gland during the dark period and synthesized from 5-HT [17]. There is a close connection between the melatonin system and symptoms of depression, since in depressed individuals suffering from sleep disorders, there are signs of irregular circadian rhythms [18]. Recently, melatonin receptors MT1 and MT2 have been introduced as promising therapeutic targets for controlling depression [18]. Literature reviews have proved that melatonin exerts antidepressant effects in clinical and preclinical studies [19]. Melatonin has immunomodulatory and anti-inflammatory effects, and its tissue-protective effect during inflammatory processes is by directly scavenging toxic free radicals [20], and preventing pro-inflammatory cytokines upregulation such as interlukin-1 and tumor necrosis factor-α [21]. In addition, in spinal cord neurons, it has been shown that melatonin would dose-dependently inhibited NMDA-induced current. There is a mutual connection between inflammation-induced mechanical hyperalgesia and depressive-like effect in rats; therefore, the central melatonin system has an essential part in the comorbidity between pain sensation and depression by NMDA receptor regulation [22].

These two drugs (CYA and IFN-α) are examples of drugs that can initiate depression by different mechanism, through blockade of mTOR by CYA, or increase IDO activity and excessive NMDA receptor stimulation by IFN [7,8,12,13]. On the basis that melatonin can have antidepressant effects, the goal was to evaluate its effect on depressive behavior following IFN-α, or CYA administration in mice. Therefore, first depression was induced by IFN-α or CYA; later, depressive-like effects were evaluated following melatonin administration prior IFN-α or CYA each day.

2. Materials and Methods

2.1. Animals

Male NMRI mice that weighed 25-30 g (6-8 weeks old) were provided, six animals were kept in each cage, and free pellet food and water were available. They were kept in standard humidity, temperature (21-23 ºC), and light/dark (12h/12h) cycle. All animal experiments were performed according to the guidelines for handling laboratory animals provided by Iran National Committee for Ethics in Biomedical Research (Ethics code: IR.MUI.REC.1399.762 approval date: 2021-03-02). Determinations were made for animal welfare and reduced the number of animals used during experiments.

2.2. Chemicals

IFN-α (PDferon, Pooyesh Darou 3×10^6 IU, Iran), CYA (Sandimmune, 50 mg/mL; Novartis, Switzerland), melatonin (Nutralab, Canada), and fluoxetine HCl (Sigma-Aldrich, India) were purchased for this study.

2.3. Experimental Design

Totally 11 groups consisting of six mice in each group were used. Six day IFN-α administration has induced depression [12,23], therefore, the following animal groups received their treatments daily for 6 consecutive days: IFN-α group (1600000 IU/kg, subcutaneously; sc) [23] and the control group (normal saline, sc); melatonin group (25 mg/kg intraperitonealy; ip, the dose was according to a pilot study and literature [24]) or the vehicle (2% EtOH in normal saline, ip); a group received melatonin (25 mg/kg) with IFN-α; and a group received the standard antidepressant drug fluoxetine (15 mg/kg, ip) with IFN-α.

According to previous studies a single dose CYA has induced depression in mice [3], but in order to perform the sucrose preference (SP) test CYA was administered for 3 days. Therefore, the following animal groups received their treatments daily for 3 consecutive days: CYA group (dispersed in 2% EtOH and diluted with normal saline, 20 mg/kg, ip) [3] and the vehicle group; melatonin group (50 mg/kg, ip; the dose was according to a pilot study and literature [25]); melatonin (50 mg/kg) prior CYA administration group; fluoxetine (15 mg/kg, ip) prior CYA administration group. The volume considered for the injections was 10 ml/kg.

The behavioral tests involved, the locomotor activity test, splash test, and forced swimming test (FST) were performed consecutively on the day after the last injection (i.e., on day 7 for the 6-day protocol or on day 4 for the 3-day protocol), SP was measured for each group before conducting the behavior experiments.

2.4. Locomotor Test

A locomotor test was conducted to evaluate the possible sedative or stimulant activity of different treatments. In an open-field apparatus (Borj Sanat, I.R. Iran) ($40\times40\times40$ cm^3), with a white floor that was divided into 15 zones by red beams. Mice were carefully placed in one corner of the field to explore it for 3 min freely. By crossings, the red beams, the device counted horizontal movements, and vertical movements (number of rearing on hind legs) were counted manually. The total activity for each mouse was evaluated (the sum of horizontal and vertical movements) [3,26]. The apparatus was cleaned between experiments.

2.5. Splash test

A feature of depression is the apathy that could be evaluated in rodents by assessing grooming behavior. Animals were placed separately in a transparent apparatus, and a viscose sucrose solution (10%) was sprayed on the dorsal coat, after feeling sticky fur at the back, animals started the grooming behavior. Two items were evaluated during 5 min: grooming latency and grooming time. The apparatus was cleaned between the tests [23,27].

2.6. Forced swimming test

Despair behavior was measured by FST. In a cylindrical beaker filled with 12 cm of 25 °C water, mice were forced to swim for six minutes. The first 2 minutes was considered as habituation time, and in the last 4 minutes, animal activity was recorded using a camera, and later, the immobility time was measured in different groups. Finally, mice were taken out of the water and dried carefully to avoid hypothermia [3]. If the water temperature changed or if there were signs of dirt in it the water was restored.

2.7. Sucrose preference test

SP test measured anhedonia, another depression endophenotype. The test was conducted in three days, including two days for habituation. While animals were in their cages on the first day, they had access to two sucrose solution (2 % w/v) bottles, and on the following day, one bottle was replaced with water. On the last day, there were two bottles with exact amounts of sucrose solution or tap water, and after 24 h, the amount consumed from each bottle was measured, and the SP percentage was calculated [28]. SP was calculated for each animal group cage (6 animals in a cage).

2.8. Statistical analysis

Results are presented as group mean ± SEM (standard error of the mean). GraphPad Prizm 8 and Excel

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2020 were the software programs used for analyzing the results by using one-way analysis of variance (ANOVA), and Tukey's post-hoc test. P values less than 0.05 were considered significant.

3. Results and Discussion

3.1. The effect of melatonin prior administration on depressive-like effects of IFN-α

As shown in Figure 1a, melatonin significantly reduced the immobility time during FST compared to the control group (since the results for the vehicle group and the control group were close they are merged, n=9) (55.17±4.4s vs. 119±4.6s, $p<0.001$) while IFN-α significantly increased the immobility time compared to the control group (184.0±12.9s, $p<0.01$). Treatment with melatonin significantly reduced immobility time compared to the IFN-α alone group (58.50±19.4s, $p<0.01$), the results were similar to fluoxetine treatment. These changes were in the absence of substantial variation in the locomotor activity (Table 1). The SP level less than 65 % was considered; as anhedonia. Table 1 shows that melatonin treatment increased sucrose preference to 70 %, while the value was 49 % for IFN-α alone.

The splash test results are shown in Figure 2, while IFN-α alone significantly reduced grooming time (8.14±3.8s vs. the control group 40.6±5.2s, $p<0.001$) (Fig. 2a), following melatonin prior treatment, the value significantly increased to 114.3±15.3s ($p<0.01$ vs. the IFN-α alone group). The delay before grooming also reduced following melatonin prior treatment compared to the IFN-α alone group (42.4±20s vs. 146.1±40.7s, $p<0.05$) (Fig.2b). The changes in the splash test were similar to the fluoxetine treatment group.

3.2. The effect of melatonin prior treatment on depressive-like effects of CYA

As it is depicted from Figure 1b, CYA significantly increased immobility time during FST compared with the control group (146.0±6.9s vs. 117.0±4.65s, $p<0.01$). After treatment with melatonin immobility time was significantly lower than the CYA alone group (42.33±9.9s, $p<0.001$). In contrast, there were no essential changes in the locomotor activity results between groups (Table 1). As shown in Table 1, the SP that was 38% in the CYA alone group increased to 93% after treatment with melatonin. These changes were similar to the fluoxetine prior treatment group.

During the splash test, by administrating CYA alone, grooming time was significantly lower than the control group (14.14±5.7s vs. 47.8±7.4, $p<0.01$) (Fig 2c), the grooming time increased significantly after treatment with melatonin (103.0±19.5s vs. the CYA alone group, $p<0.001$), and the latency time decreased (29.0±7.08s vs. the CYA alone group 136.4±29.5s, $p<0.001$) (Fig 2d). These changes observed in the splash test were similar to the fluoxetine prior treatment group.

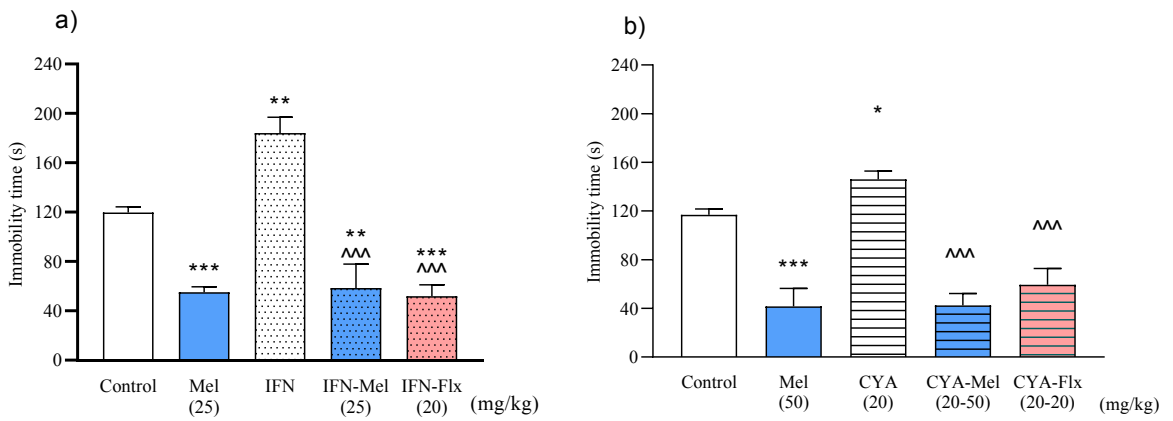

Figure 1. Effect of melatonin prior treatment on immobility time during the forced swimming test following (a) IFN-α administration for 6 days, (b) CYA administration for 3 days. All the treatments were ip except for IFN-α (1600000 IU/kg; sc). The results present mean ± SEM, and analyzed by ANOVA followed by Tukey's multiple comparison tests. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared with the control group, ^^^ $p<0.001$ compared with the IFN-α group (a) or the CYA group (b). Flx: fluoxetine, CYA: cyclosporine A, IFN: interferon-α, Mel: melatonin.

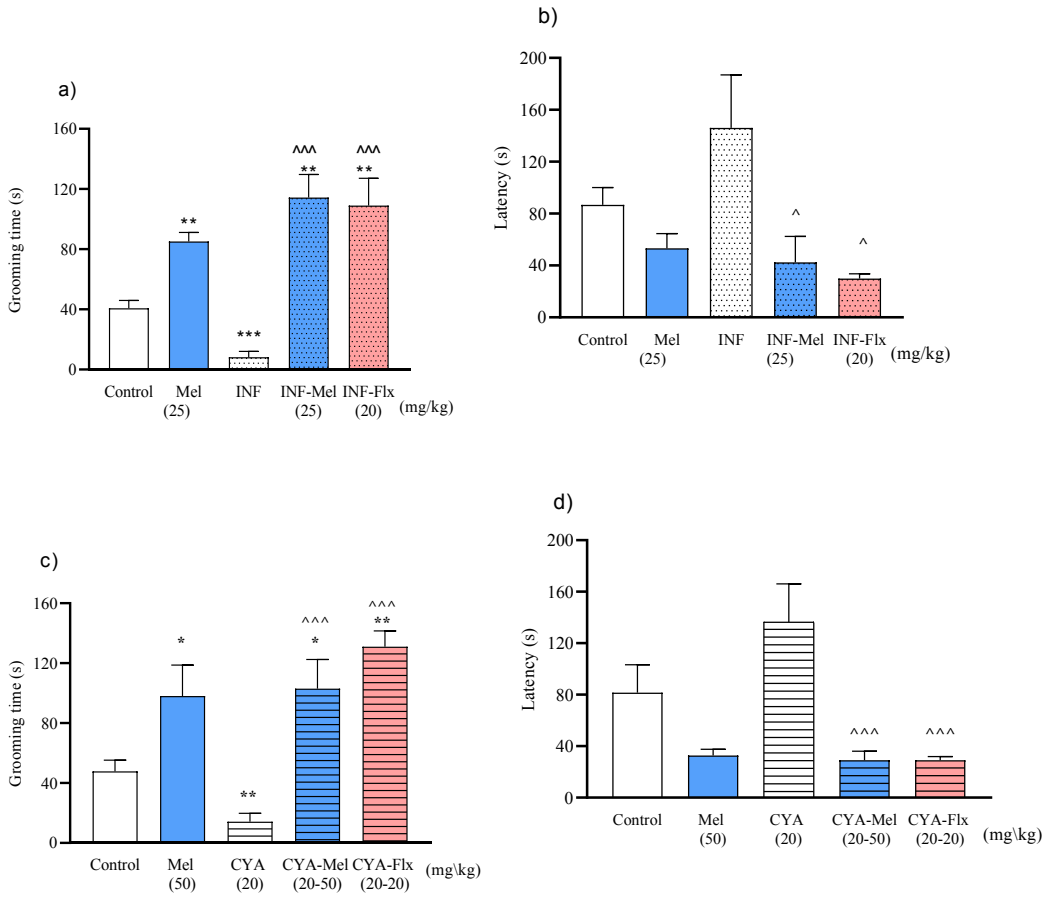

Figure 2. Effect of melatonin prior treatment on grooming time and latency during the splash test (a, b) IFN-α administration for 6 days, (c, d) CYA administration for 3 days. All the treatments were ip except for IFN-α (1600000 IU/kg; sc). The results present mean ± SEM, and analyzed by ANOVA followed by Tukey's multiple comparison tests. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared with the control group, ^ $p<0.05$, ^^^ $p<0.001$ compared with the IFN-α group (a) or the CYA group (b). Flx: fluoxetine, CYA: cyclosporine A, IFN: interferon-α, Mel: melatonin.

3.3. Discussion

In this study, it was observed for the first time that melatonin prior treatment decreased immobility time during FST, increased SP, and improved grooming in splash test during depression induced by IFN-α or CYA in mice. Locomotor activity test is essential before evaluating the behavioral experiments in rodents [29]. The total activity count proved regular animal locomotor activity however, any noticeable variation in animals' locomotor activity may influence the FST and splash test results. Depressive-like behavior was measured by different tests that evaluated different depression phenotypes in rodents: despair behavior was assessed by the measuring immobility time during FST, apathy was evaluated by measuring grooming time during splash test, and anhedonia was evaluated by measuring the sucrose preference test [30].

Melatonin administration alone clearly showed the antidepressant-like effects, by reducing the immobility time in FST, increasing the grooming time, and increasing SP. That was in agreement with previous results that showed melatonin decreased the immobility time during the tail suspension test in mice [31]. The antidepressant-like effect of melatonin was liked to its interaction with NMDA receptors and the l-arginine-NO pathway [22,31].

Depression was initiated following IFN-α administration, by the rise in the immobility time in FST, decreased sucrose preference, and the reduced grooming time. That was in accordance with earlier research that measured the effect of a soybean or flaxseed diet following depression initiated by IFN-α [12,32]. Findings have shown that following IFN-α treatment in hepatitis C patients, the brain-derived

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Table l. The results of locomotor activity and sucrose preference tests.

Groups (n=6)	Total activity (number)	Sucrose preference (%)
Control (6 days)	174.7 ± 10.1	64
Mel (25 mg/kg)	168.8 ± 11.1	82
IFN (16×10^5 IU/kg)	190.3 ± 17.1	49
IFN-Mel (16×10^5 IU/kg-25 mg/kg)	188.5 ± 14.7	70
IFN-Flx (16×10^5 IU/kg-20 mg/kg)	158.3 ± 8.2	74
Control (3 day)	177.2 ± 19.8	65
Mel (50 mg/kg)	165.8 ± 20.1	93
CYA (20 mg/kg)	193.0 ± 13.6	38
CYA-Mel (20-50 mg/kg)	177.0 ± 11.6	93
CYA-Flx (20-20 mg/kg)	148.5 ± 11.4	79

Total activity = (horizontal activity + vertical activity). Sucrose preference= (sucrose solution/ sucrose solution + water consumption×100) calculated for each animal group cage (n=6); values below 65% were considered as anhedonia. Control animals; 2% EtOH normal saline solution. All the treatments were ip except for IFN-α (1600000 IU/kg; sc). The total activity count results are presented by group mean ± SEM, and were analyzed by ANOVA followed by Tukey's post- hoc test; ($p>0.05$). Flx: fluoxetine, CYA: cyclosporine A, IFN: interferon-α, Mel: melatonin.

neurotrophic factor (BDNF) levels in circulation reduced that may reflect an alteration in the brain BDNF synthesis [33]. In addition, IDO induction by IFN-α, causes 5-HT deficiency as the main result of the shift of tryptophan metabolism to kynurenine formation [13]. 5-HT deficiency could also compromise the melatonin synthesis in the brain [17]; these changes can disturb not only the circadian rhythm but also mood. By melatonin treatment following IFN-α administration, depressive-like effects waned; ie. Immobility decreased in FST, grooming time increased in splash test, and SP increased. This could be a direct effect of an increased melatonin level in the brain that can readily pass the blood brain barrier [34]. Alternatively, by indirectly preventing the harmful neurotoxic effects of quinolinic acid overproduction in the kynurenine pathway, by antagonizing the NMDA receptor [22]. Depression following IFN-α administration often necessitates stopping the treatment or reducing the dosing schedule which may compromise the treatment results [35]. Although IFN-α induced depression can be effectively treated or prevented with antidepressant drugs [36,37], preventing depression with a safe alternative natural product would be crucial.

CYA administration induced depressive effects in mice observed by increased immobility time during FST, decreased SP, and decreased grooming in the splash test. That was in agreement with previous studies as CYA dose-dependently increased immobility time in FST in mice [3]. Likewise, it has been reported that CYA (60 mg/kg) in C57BL/6J mice prefrontal cortex has reduced serotonin and dopamine release and induced hypo-functioning, augmented anxiety behavior, and interrupted with social behavior [4]. These results are pathologically similar in patients treated with CYA [5,38], in addition, a critical problem, according to the medical and community points of view is the suicide of individuals who received organ transplants [39,40]. One suggested depression-induced mechanism is mediated by inhibition of the mTOR signaling pathway [7]. Mitochondrial function alterations are another reason for CYA induced toxicity [41], since following a drop in mitochondrial energy production, anaerobic glycolysis becomes activated which cause an increase in nitric oxide and free radical production, leading to apoptotic or necrotic cell death that depends on how serious is the injury [42]. In our animal study, melatonin prevented CYA depressive-like effects.

This antidepressant preventive effect of melatonin could be related to the melatonin effect on NMDA receptors [22,43]. Previous studies have shown that the fast antidepressant efficacy of ketamine that is an NMDA receptor antagonist is related to its effect in activating the mTOR pathway [44]. On the other hand, melatonin has a strong free radical scavenger [20], that could probably prevent the injuries induced by the decline in mitochondrial functioning initiated by CYA [41]. Although antidepressant drugs could be effective in patients receiving CYA, they could cause complicated drug interactions that can be harmful to the newly transplanted organs [45]. Therefore, melatonin as an alternative medication should be considered for further research in individuals treated with CYA to prevent depression.

The following study only aimed at evaluating the animal behavioral changes without considering the molecular changes, as a study limitation, that should be considered for future studies.

4. Conclusion

This animal study showed the beneficial antidepressant efficacy of melatonin in preventing IFN-α, or CYA-induced depression despite different mechanisms. Melatonin efficacy in preventing depression could be the direct effect of increased melatonin level in the brain, melatonin potent antioxidant capability, and its effect on NMDA receptor. More studies are suggested for evaluating the exact mechanism involved in melatonin preventing depressive-like effects following IFN-α or CYA administration.

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Conflict of interest

Authors certify that no conflict of interest in relation to this article exists.

Author Contributions

Azadeh Mesripour: supervisor, contribution in the conception, design, execution and interpretation of the results, and interpretation of data, and writing and editing the manuscript. Mehdi Aghamohseni: contribution in the conception, pharmacology experiments, execution of the results collecting the data, and writing the manuscript.

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