Research Article

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The NSAIDs Ibuprofen and Celecoxib and the TNF-α Blocker Etanercept Prevented Cyclosporine A-Induced Depression-Like Behavior in Mice

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ABSTRACT

Cyclosporine A (CYA), is used to prevent graft rejection, but it may cause depression in individuals. Anti-inflammatory drugs are associated with antidepressant effects, the aim was evaluating the effect of nonsteroidal anti-inflammatory drugs (NSAID) (ibuprofen, celecoxib), and tumor necrosis factor-α blocker (etanercept) pretreatment on depressive behavior induced by CYA (20 mg/kg) in male mice (25±2 g). The pretreatment with ibuprofen (50 mg/kg), or celecoxib (25 mg/kg) were applied intraperitoneal for 3 days. Etanercept (1 mg/kg) subcutaneously was injected on days 1 and 3. After the locomotor test, immobility during the forced swimming test (FST), and sucrose preference (SP) were evaluated. Pretreatment with each of the drugs ibuprofen, celecoxib, and etanercept reversed the increased immobility time during FST induced by CYA after the first dose (149±7.07 s vs. control 100±10.4 s, $p<0.01$) and the last dose (179±6.4 s vs. control group 101±16 s, $p<0.01$). The SP increased following pretreatment with the selected drugs. While, the treatments did not cause significant changes in the locomotor test. The NSAIDs, and etanercept reversed CYA despair behavior during FST and anhedonia in SP test. Therefore the co-administrating of these drugs with CYA may be useful in preventing CYA psychological side effects that warrants precise evaluations.

Keywords: nonsteroidal anti-inflammatory drugs (NSAID), tumor necrosis factor-α, depression, cyclosporine

Introduction

Calcineurin inhibitors, such as cyclosporine A (CYA) and tacrolimus, are immunosuppressive drugs widely used to prevent organ transplant rejection (1). However, treatment with CYA is associated with neuropsychiatric problems in individuals, including anxiety and depression (2). Following inhibition of calcineurin, the transcription of many cytokines, and T lymphocytes are inhibited (2). CYA, can also directly control responses mediated by innate immune cells including macrophages, neutrophils and dendritic cells. That is why CYA shows the possibility for novel targeted strategies to treat inflammatory diseases (3). Indeed, calcineurin highly exists in amygdala, the main brain region related to mood disorders and anxiety. Clinical studies suggest that calcineurin activity is connected with psychiatric disorders. Because, calcineurin can regulate basal neuronal functions, neuronal transmission, neuronal structure, and neuronal stimulation by regulating excitability, inhibition of G protein-mediated calcium channels, and glutamatergic neurotransmission (2). In addition, preclinical studies have shown that inhibition of calcineurin by CYA induces anxiety and depressive-like behavior in mice (4,5).

The contribution of inflammation in the pathogenesis of depression has been noticed for a long time. For instance, rheumatoid arthritis, is a disorder that the immune system targets body tissues therefore it causes extensive inflammation, about 40 percent of these patients also suffer from depression (6). On the other hand, data from some studies suggest that treatment of major depression disorder with nonsteroidal anti-inflammatory drugs (NSAIDs), are effective on the relief of depressive symptoms (7). The useful effects are believed to be related to NSAIDs ability to reduce the central and peripheral pro-inflammatory state that is commonly seen in depression (8). NSAIDs perform their anti-inflammatory effect by inhibiting cyclooxygenases (COX), an important enzyme in the synthesis of prostaglandins from arachidonic acid. COX plays an important role in inflammation, cytokine-induced depression and sickness behavior (9).

Tumor necrosis factor alpha (TNF-α, cachexin) is an important protein in the cell signaling pathway to regulate the function of immune system cells, but the excessive amount of TNF-α can lead to persistence of the immune response which causes different inflammatory or autoimmune diseases (10,11). It is now known that TNF-α, and the related ligands are associated to some diseases such as cancer, cardiovascular disease, and autoimmune disorders (12, 13). In addition recently its involvement in the induction of depression, has attracted great attention (14).

Etanercept (ETN) is a recombinant dimeric protein, with anti TNF-α effects used as an immunomodulatory for the treatment of immune diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis. It has been observed in a randomized double-blind placebo-controlled phase III trial that ETN reduced the symptoms of lethargy and depression in patients with psoriasis (15). NSAIDs are common over-the-counter pain relievers, in addition they are used concomitantly with CYA to treat rheumatoid arthritis and lupus. Interactions of concomitant use of NSAIDs and CYA on cardiovascular and renal function have been previously studied but their effect on depressive behavior has not been studied (16,17). Studies have shown that ETN and CYA co-administration is useful alternative therapy for patients with persistent psoriasis and it appears to be safe (18). The concomitant effect of the administration of ETN and CYA on depressive like behavior has not been evaluated before. Therefore, in this animal study, we investigated the concomitant administration of CYA with ibuprofen (IBP; a COX nonselective inhibitor with less risk of side effects), celecoxib (CLX; a COX2 selective inhibitor), or ETN on the depression-like behavior.

Material and Methods

Animals

Totally 84 male NMRI mice (weighing 25±2 g, 6-8 weeks old) were kept at room temperature 21± 2 ºC, on a 12 h light and 12 h dark cycle (lights on at 6 AM) in cages containing six mice with free access to standard mice chow and tap-water. Cages were placed in the behavioral laboratory 24 h prior the experiments in order to acclimatize. The experiments were carried out according to the guidelines for the Care and Use of Laboratory Animals Issued by The National Ethical Committee of Iran (Ethical No: IR.MUI.RESEARCH.REC.1399.200). All the attempts were made in the research to reduce animal suffering and the number of animals used in the research.

Chemicals

CYA (Sandimmun, 50 mg/ml; Novartis, Switzerland), etanercept (AryoGen Pharmed Industry, 25 mg/0.5ml prefilled syringes, Iran), ibuprofen (Farabi Industry, Iran), celecoxib (Amin Industry, Iran), A selective serotonin reuptake inhibitors (SSRIs) fluoxetine HCl (FLX) (Sigma-Aldrich, Germany) was chosen as the reference antidepressant drug.

Experimental design

Totally 14 groups of animals consisting 6 mice in each group were studied. Groups included: group 1, animals that received CYA 20 mg/kg IP after it was diluted in 2%v/v EtOH/normal saline (4), group 2, control animals received (2%v/v EtOH/normal saline), for three consecutive days. Groups 3-5, received IBP 50, or 100 mg/kg and the vehicle group received 0.1% v/v tween 80 in normal saline, that were injected IP for three consecutive days (19). Groups 6-8, received CLX 25 or 50 mg/kg and the vehicle group received 10% w/v carboxymethyl cellulose (CMC) in normal saline, that were injected IP for three consecutive days (19). Groups 9 and 10, received ETN 1mg/kg and the vehicle group (normal saline) that were injected SC on alternate days (days 1 and 3) (20). Finally groups 11-14, that concomitantly received CYA with either IBP 50, CLX 25, ETN 1, or FLX 20 mg/kg. All the injections were adjusted for 10 ml/kg mice body weight.

The tests were performed 24 h after the first injections (day 2), and they received their daily injection after the behavioral tests, and 24 h after the last injections (day 4) on same groups of animals. Each animal was first subject to the locomotor test, then the forced swimming test (FST). Sucrose preference was measured on day 5 following 2 days habituation to the sucrose solution (2 %).

Locomotor test

The locomotor activity of mice was assessed 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 (horizontal exploration) was counted automatically while rears on back-legs (vertical exploration) were recorded manually. The total activity for each animal was calculated which was the sum of zone entries and rears on back-legs.

Forced swimming test

During FST mice were forced to swim in 25 ºC water in a 2-liter Pyrex beaker (diameter 12.5 cm, depth 12 cm) for 6 min, the first 2 min was considered for habituation. The animals' despair behavior was evaluated by measuring the immobility time during the last 4 min of the trial. It was considered when animals had no additional activity other than that required to keep the animals' head above the water. The entire experiment was recorded by a camera and analyzed later. After 6 min, the mice were dried carefully to avoid hypothermia and returned to their home cage.

Sucrose preference test

Anhedonia was measured as another depression criterion. On the first day animals had access to two bottles of sucrose solution (2 % w/v) in their cage, and on the second day there was one bottle of sucrose solution and on bottle of water (days 2, and 3). Finally, two bottles were placed one contained a 100 ml of sucrose solution and the other contained tap water after 24 h (on day 5) the percentage for sucrose preference (SP= sucrose consumption/body weight ×100) was measured (21).

Data processing and statistical analysis

Results were expressed as group mean ± SEM. All results were analyzed by one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison tests. P values less than 0.05 were considered significant. The software programs used for data analyzing and making graphs were Excel 2010 and the GraphPad Prism 8.

Results

The effect of IBP pretreatment following CYA induced depression

Figure 1a shows the FST results 24h (day 2) after each of the treatments. Following CYA single injection the immobility time during FST significantly increased (149±7.07 s vs. control 100±10.4 s, $p<0.01$) this behavioral change was observed in the absence of treatment effects on the locomotor test (table 1). Pretreatment with IBP reduced immobility time during FST (115±7.04 s vs. CYA, $p<0.05$) like fluoxetine. Pretreatment with IBP or its injection alone

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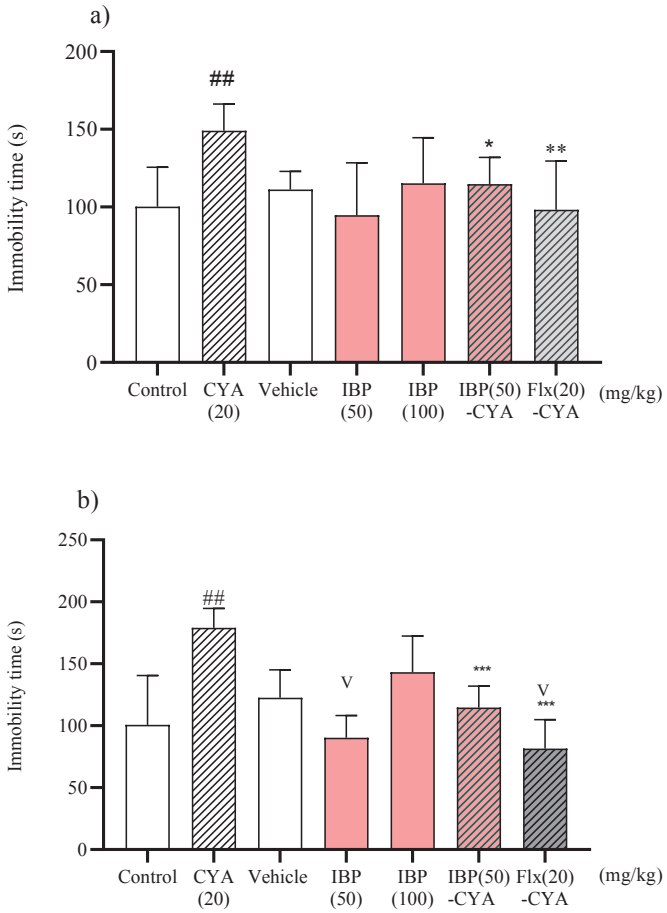

Figure 1. Effect of ibuprofen on immobility time during FST following cyclosporine administration. (a) Results of day 2, and (b) results of day 4. All treatments were administered IP, the control animals received 2%v/v EtOH/normal saline, the vehicle group received 0.1% v/v tween 80 in normal saline. Results are expressed as group mean ± SEM and analyzed by ANOVA followed by Tukey's comparison test (n=6). ##P<0.01 compared with the control; v P<0.05, compared with vehicle. ***p<0.001 compared with CYA group. CYA: cyclosporine A, Flx: fluoxetine, IBP: ibuprofen.

Table 1. Animals' locomotor activity on the second day.

Groups (n=6)	Total activity	Groups n=6	Total activity
Control	188±12	CLX25 mg/kg	189±18
CYA	169±10	CLX50 mg/kg	239±6.8 ^{vv}
Vehicle	174±18	CYA+IBP50	163±21
IBP50 mg/kg	160±19	CYA+CLX25	215±10
IBP100 mg/kg	181±11	CYC+ETN	189±5.03
ETN 1 mg/kg	115±16.5 ^{v}	CYA+FLX	152±8.5

Total activity= horizontal exploration + vertical exploration. The control animals received 2%v/v EtOH/normal saline the locomotor results for the vehicle groups are merged. Results are expressed as group mean ± SEM. ANOVA followed by Tukey's comparison tests. vv P<0.01. CYA: cyclosporine A, CLX: celecoxib, ETN: etanercept, Flx: fluoxetine, IBP: ibuprofen.

also did not cause important changes in the locomotor activity (table 1).

The immobility time during FST on day 4 is shown in figure 1b, CYA significantly increased immobility time (179±6.4 s) compared with the control group (101±16 s, $p<0.01$), while changes in the locomotor activity were negligible (table 2). Administrating IBP 50 mg/kg alone significantly reduced immobility time in FST (90±7.3 s vs. vehicle 123±9.1 s, $p<0.05$), and following its co-administrating with CYA immobility time significantly reduced compared with CYA alone (115±7 s, $p<0.001$), pretreatment with the reference drug FLX also reduced immobility time during FST (82±9.5 s vs. CYA alone, $p<0.001$). These behavioral changes were observed in the absence of treatment effects on the locomotor activity (table 2). IBP 100 mg/kg slightly increased immobility time in FST, in addition animals had less activity in the locomotor test than vehicle group ($p<0.01$) (the locomotor results for the vehicle groups are merged). Therefore depressive behavior by IBP higher dose may have been influenced by less locomotor activity. As depicted from table 3 pretreatment with IBP increased the SP up to 89.89% (the SP results for the vehicle groups are merged).

The effect of CLX pretreatment following CYA induced depression

Figure 2a shows the FST results 24h (day 2) after each of the treatments, CLX single injection reversed CYA immobility time (102.3±9.05 s vs. CYA alone 149±7.07 s, $p<0.01$), while not influencing the locomotor activity (table 1). The table also shows that only CLX 50 mg/kg significantly increased the

Table 2. Animals' locomotor activity on the fourth day.

Groups (n=6)	Total activity	Groups n=6	Total activity
Control	115±18	CLX25 mg/kg	171±11
CYA	138±21	CLX50 mg/kg	172±16
Vehicle	145±15	CYA+IBP50	145±17
IBP50 mg/kg	129±12	CYA+CLX25	158±17
IBP100 mg/kg	89±9.8 vv	CYC+ETN	158±10
ETN 1 mg/kg	93±14vv	CYA+FLX	105±11 v

Total activity= horizontal exploration + vertical exploration. The control animals received 2%v/v EtOH/normal saline the locomotor results for the vehicle groups are merged. Results are expressed as group mean ± SEM. ANOVA followed by Tukey's comparison tests. vv $P<0.01$. CYA: cyclosporine A, CLX: celecoxib, ETN: etanercept, Flx: fluoxetine, IBP: ibuprofen.

Table 3. Sucrose preference in the treatment groups.

Groups (n=6)	% Sucrose consumed to body weight	Groups n=6	% Sucrose consumed to body weight
Control	69.66	CLX25 mg/kg	79.80
CYA	65.58	CLX50 mg/kg	91.37
Vehicle	63.13	CYA+IBP50	89.87
IBP50 mg/kg	59.42	CYA+CLX25	91.30
IBP100 mg/kg	57.73	CYC+ETN	91.75
ETN 1 mg/kg	40.5	CYA+FLX	78.13

Sucrose solution (2 % w/v), percentage for sucrose preference (SP= sucrose consumption/body weight ×100) was measured. The SP results for the vehicle groups of are merged. CYA: cyclosporine A, CLX: celecoxib, ETN: etanercept, Flx: fluoxetine, IBP: ibuprofen.

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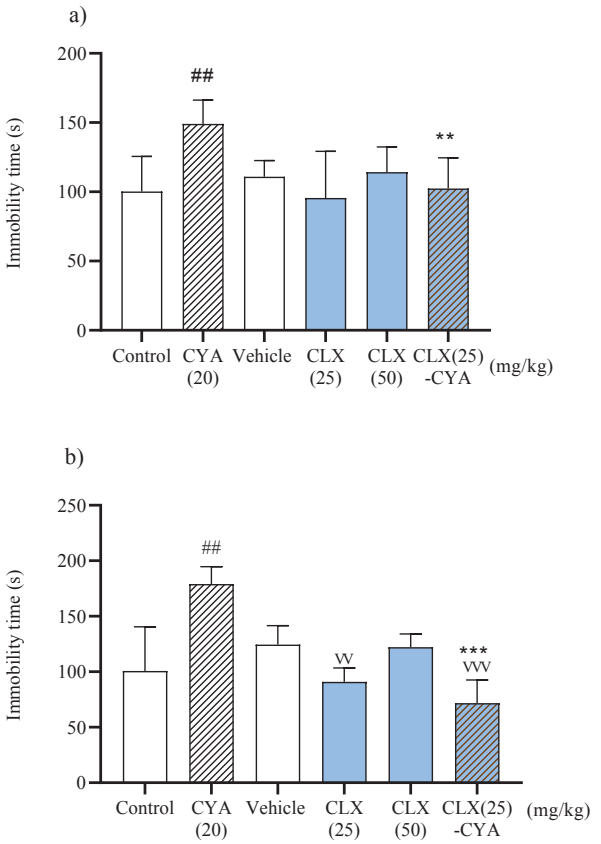

Figure 2. Effect of celecoxib on immobility time during FST following cyclosporine administration. (a) Results of day 2, and (b) results of day 4. All treatments were administered IP, the control animals received 2%v/v EtOH/normal saline, the vehicle group received 10% w/v CMC in normal saline. Results are expressed as group mean ± SEM and analyzed by ANOVA followed by Tukey's comparison test (n=6). ##P<0.01 compared with the control; vv P<0.01, vvv P<0.001 compared with vehicle; ***p<0.001 compared with CYA group. CYA: cyclosporine A, CLX: celecoxib.

locomotor activity (p<0.01 vs vehicle). As shown in figure 2b, CLX 25 mg/kg alone significantly reduced immobility time on day 4 (91.0±5.11 s vs. vehicle 124±6.06 s, p<0.01), while CLX 50 mg/kg was not effective. These behavioral changes were observed in the absence of treatment effects on the locomotor test (table 2). The co-administration of CLX25 mg/kg with CYA significantly reducing the immobility time in FST (71.7±8.55 s vs. CYA alone 179±6.4 s, p<0.001), this value was also significantly lower than vehicle immobility time (p<0.001) (figure 2b). As shown in table 2 CLX alone or during pretreatment with CYA did not cause significantly changes in the locomotor activity compared with the vehicle group. Table 3 also shows that pretreatment with CLX increased SP to 91.30%.

The effect of ETN pretreatment following CYA induced depression

Figure 3a shows the FST results 24h (day 2) after each of the treatments, ETN reversed CYA immobility time during FST (106.5±7.44 s vs. CYA alone 149±7.07 s, p<0.01). Table 1 shows that ETN alone decreases the locomotor activity compared to vehicle on day 2, however this was not observed following ETN and CYA concomitant administration. According to figure 3b, ETN significantly reduced immobility time compared with vehicle group in FST on day4 (79.5±6.26 s, p<0.001) and following the pretreatment with CYA the immobility time reduced (96.3±7.60 s, vs. CYA alone 179±6.4 s, p<0.001), the value was significantly lower than the vehicle group (p<0.05). The results of locomotor activity on day 4 are shown in table 2, ETN alone or its co-administration with CYA did not initiate significantly changes in the locomotor activity compared with the vehicle

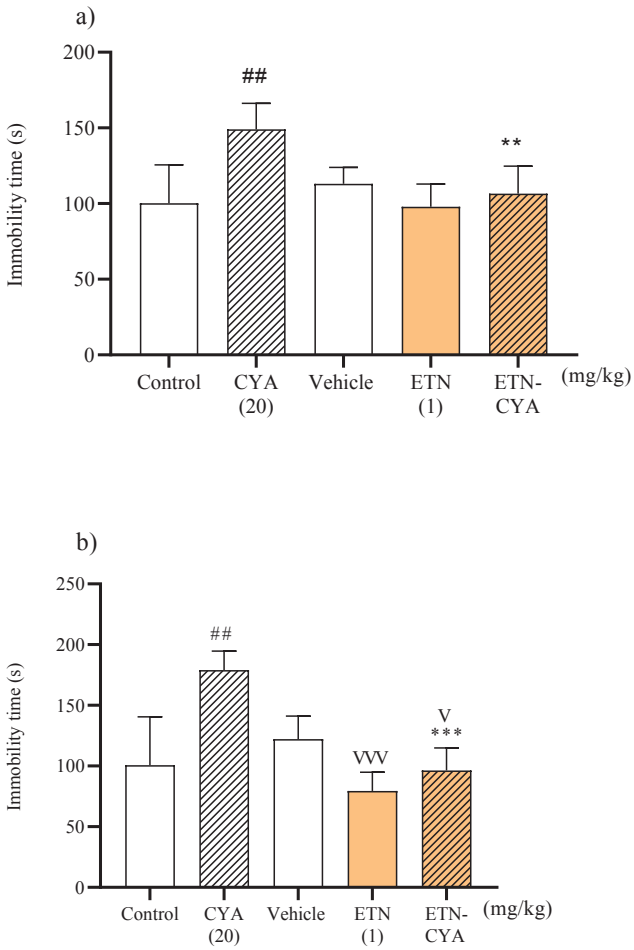

Figure 3. Effect of etanercept on immobility time during FST following cyclosporine administration. (a) Results of day 2, and (b) results of day 4. CYA and control animals that received 2%v/v EtOH/normal saline were injected IP, vehicle group (normal saline), and etanercept were injected SC. Results are expressed as group mean ± SEM and analyzed by ANOVA followed by Tukey's comparison test (n=6). ##P<0.01 compared with the control; v P<0.05, vvv P<0.001 compared with vehicle; **p<0.01, ***p<0.001 compared with CYA group. CYA: cyclosporine A, ETN: etanercept.

group. Following pretreatment with ETN there was an increase in the SP result as shown in table 3.

Discussion

This study for the first time revealed that IBP, CLX, and ETN pretreatment reduced CYA immobility time during FST in mice, even after injecting one dose of each drug. Animals' locomotor activity were assessed in order to distinguish immobility during FST from drug induced impairment in animal movement. As it was observed the changes in the immobility time during FST were in the absence of any important alteration of the locomotor activity. FST is a common test for evaluating despair behavior, an endophenotype of depression, by measuring the immobility time when the animal challenges an inescapable situation (22). Sucrose consumption also increased following pretreatment with IBP, CLX, and ETN indicating improvement of another endophenotype of depression that is anhedonia. Naïve animals prefer palatable foods or solutions, while in animals with anhedonia there is no preference (22).

CYA induced depression-like behavior in mice that was in agreement with previous results (4, 23). One possible mechanism for emotional disturbance in patients treated with calcineurin inhibitors is mediated by blocking the *mechanistic target of rapamycin* (mTOR) signaling pathway (24). Thus it was assumed that mTOR stimulation in brain could be effective in reducing the risk of depression in these patients (24). MTOR activation stimulates synapse

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protein synthesis that induces development, and function of new synaptic branches (25). N-Methyl-D aspartate glutamate (NMDA) receptors can regulate mTOR function (25). It was shown that dextromethorphan an antitussive drug that has NMDA receptor antagonist effect prevented CYA induced depression in mice (4).

In agreement with previous finding regarding the beneficial antidepressant effects of NSAIDs (19), we observed that IBP, and CLX pretreatment were useful in preventing the depression-like effect induced by CYA. Following the first doses of IBP, or CLX alone there was no important difference in the immobility time during FST compared with vehicle but they prevented CYA from initiating depressive-like behavior. After three days of injecting IBP, or CLX each alone the immobility time was less than vehicle, and also reversed CYA induced despair effect. Therefore, NSAIDs have more effective antidepressant-like benefit when accompanied with CYA. Apart from the neurotransmitter and hormonal contribution in the pathogenesis of depression inflammation is also an effective factor. A meta-analysis study proved the efficacy of anti-inflammatory treatment on depressive symptoms (8). However it is not clear that the antidepressant effect of NSAIDs is mediated via their effects on underlying somatic diseases or it is independent of the pain killing effect. For instance, rofecoxib (a COX2 selective inhibitor) increased serotonin in the frontal and the temporo-parietal cortex in rats (26). In addition, based on previous literature at least part of antidepressant-like effect of IBP is mediated through inhibiting nitric oxide (NO) and prostaglandin E2 synthesis. Since after IBP administration brain NO level decreased in BCG inoculation induced depression in mice, and it was reversed by L-arginine co-administration (27). It has been shown that the short term (less than 6 weeks) NSAIDs administration are not associated with gastrointestinal or cardiovascular adverse effects (8). Therefore the concomitant administration of CYA and NSAIDs is suggested for clinical evaluation in inflammatory diseases like rheumatoid arthritis, because in addition to their clinical benefit effects NSAIDs may reduce the risk of CYA psychological side effects.

The pretreatment with ETN prevented CYA induced depressive-like behavior that was measured on days 2 and 4. Only after the second dose of ETN alone the anti-immobility effect was detected during FST. Previously, it was observed that ETN treatment in an animal model of chronic mild stress reduced the depression-like effects similar to the tricyclic antidepressant drug, imipramine (28). It was speculated that the antidepressant effects of ETN is related to augmentation of neurotransmitters (noradrenaline, serotonin), or regulation in secretion of the stress hormone (28). On the other hand, since ETN cannot cross the blood-brain barrier following the peripheral injection of ETN, peripheral TNF-α function reduces that can only indirectly affect central TNF-α expression. Therefore, it is hypothesized that drugs such as ETN can only indirectly reduce central inflammation as a result of decreased peripheral TNF-α activity, and this reduction in inflammation can also reduce depressive symptoms (29). Peripheral ETN by preventing some of the main effects of central TNF-α, such as its effects on hippocampal activity and neurogenesis, induces antidepressant and restoration of cognitive effects (20).

In conclusion, the selective and non-selective COX inhibitors (CLX, and IBP), and the TNFα inhibitor (ETN) prevented depressive-like behavior induced by CYA. Therefore the concomitant use of NSAIDs or TNFα inhibitors with CYA are not only useful in conditions related with inflammation, they might also prevent CYA depression side effects, that warrants further clinical evaluations.

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Conflict of Interest

The authors confirm there is no conflict of interest in relation to this article.

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