Research Article

Antidepressant Effect of Etoricoxib and Ibuprofen on chronic mild stress-induced depression in mice

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Received: 10 January 2022 Revised: 11 March 2022 Accepted: 12 April 2022

Abstract

Background: Chronic mild stress (CMS) induces behavioral changes, oxidative-stress and neuroinflammation. CMS mimics the clinical aspects of anxiety and depression. Current antidepressant drugs have slow onset of action, low response rates and problem of drug resistance. However, there is a scope of new therapy for the treatment of depression disorders. **Objectives**: The present study is aimed to assess the efficacy of ibuprofen and etoricoxib in CMS model using mice and to explore the possible mechanism for the same. **Materials and Methods:** Animals were exposed to CMS procedure for 28 days. The mice were daily treated with ibuprofen (15mg/kg p.o.), etoricoxib (5mg/kg p.o.) and venlafaxine (10 mg/kg p.o., reference standard) for 14 days, 2 h before exposure to stress procedure. The behavioural consequence of depression was measured in terms of immobility time, locomotor activity, anxiety level by elevated plus maze model and sucrose preference test respectively. The biochemical estimations included serum corticosterone, reduced glutathione (GSH), neurotransmitter estimation and quinolinic acid level measurement, serotonin, noradrenaline, and dopamine. **Results:** The animals treated with ibuprofen, etoricoxib and concomitant treatment of both ibuprofen and venlafaxine showed significant increase in sucrose preference and locomotor activity along with decrease in immobility time, corticosterone level, adrenal gland weight, and quinolinic acid levels. Further, they also significantly raised brain neurotransmitters levels viz. serotonin, nor-adrenaline, and dopamine. **Conclusion:** The anti-depressant action of these drugs can be attributed to improvement of brain neurotransmitter levels, reduction in the level of corticosterone and quinolinic acid leading to neuroprotection in the CNS.

Keywords: Ibuprofen, etoricoxib, neuro-inflammation, NSAIDs

Introduction

Depression is one of the most commonly diagnosed mental disorders around the world which causes patients to feel emotional suffering and endure a low quality of life. It is estimated that major depression will be the second most disabling condition in the world (Greenberg et al., 2003). Previous studies support that there is reciprocal link between stress, inflammation and depression (Slavich and Irwin, 2014). There is role of inflammation and deregulation of immune system in pathophysiology of depression (Leonard, 2010). Recent researches have demonstrated that the deregulation of hypothalamic-pituitary-adrenal (HPA) axis is also associated with major depression (Barden, 2004; Pariante and Lightman, 2008). Chronic stress results into sustained hyperactivity and deregulation of HPA axis which produces excessive glucocorticoids. A large number of evidences showed that chronic high concentration of glucocorticoids impaired hippocampal neurogenesis and produces depressive symptoms (Anacker et al., 2013; Anacker et al., 2011). Clinical investigations also showed significant elevation in cortisol level in depressive patients (Hinkelmann et al., 2012). Increase in serum cortisol levels might decrease serotonin levels by reducing the activity of tryptophan 2, 3 dioxygenase (Cowen, 2002).

Cytokines play a multidirectional role in information transmission between the immune system, endocrine system, and neurological system (Capuron and Dantzer, 2003). Interleukin-1 (IL-1) is one of the major pro-inflammatory cytokines involved in the regulation of HPA- axis activity in the brain (Leonard and Myint, 2009). Repeated administration of IL-1, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) shows depressive-like behaviour in animals (Miller et al., 2008;

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DOI: https://doi.org/10.31024/ajpp.2022.8.2.1

Kaster et al., 2012). Additionally, the inflammatory cytokines have a significant role in regulating synaptic plasticity in major depressive disorder in rodent models of depression (Khairova et al., 2009). Upon activation by pro-inflammatory cytokines, Indoleamine 2, 3-dioxygenase (IDO) induces up regulation of tryptophan catabolism via kynurenine pathway, which results in the production of neuroactive metabolites such as quinolinic acid (Sublette and Postolache, 2012). Increased level of quinolinic acid (QUIN) is reported to lead to dysfunctioning of neurons and eventually to neuronal death (Meier TB et al., 2016). In depression, glutamatergic hyperfunction also acts through low N-methyl-D-aspartate (NMDA) antagonism in the kynurenine pathway (Myint et al., 2006). Anti-inflammatory and non-opioid derivatives are implicated in anti-nociception (Hamza and Dionne, 2009). Antidepressant and anti-oxidative effect of ibuprofen was reported in the rotenone model of Parkinson's disease (Zaminelli et al., 2014).

Use of Celecoxib (selective COX-2 inhibitor) enhances the effect of reboxetine and fluoxetine on cortical noradrenaline and serotonin output in the rat (Johansson D et al., 2012). Clinical investigations observed efficacy of adjunctive celecoxib treatment in patients with major depressive disorder (Akhondzadeh S et al., 2009; Na et al., 2014). From previous study, it was shown that added aspirin to fluoxetine led to improvement in treatment- resistant depressive rats in experimentally induced depression in rats (Wang Y et al., 2011; Bhatt et al., 2016). The use of diclofenac also attenuates lipopolysaccharide-induced alterations to reward behaviour and corticosterone release (De La Garza II et al., 2004).

Based on above reports, present study aims at investigating antidepressant activity of ibuprofen and etoricoxib in alone and combination with established antidepressant drug (venlafaxine) using chronic mild stress model and to understand mechanism(s) of action of these drugs.

Materials and Methods

Animals

Swiss albino mice (weight 25-30gm) were selected for experiments purpose. Mice were obtained from L.M. College of Pharmacy, Department of Pharmacology, Ahmedabad, India. The animals were maintained under standard environment conditions (temperature (22 ± 2 ˚C), humidity (55 ± 5%) with 12:12 hr- light/dark cycle) and provided with feed and water ad libitum. The experimental protocol number LMCP/Pharmacology/17/06 was approved by the Institutional Animal Ethics Committee (IAEC), Ahmedabad.

Experimental protocol

In the present study, a chronic mild stress model of Swiss albino mice were used to evaluate the antidepressant effect of analgesic and anti-inflammatory drugs (etoricoxib and ibuprofen) in individual and concomitantly with established antidepressant drug (venlafaxine) using chronic mild stress model.

Drug treatments

The dose of etoricoxib (5mg/kg) p.o. and ibuprofen (15mg/kg) p.o. were selected on the basis of previous studies (Zaminelli et al., 2014; Jayaraman et al., 2010). The test drugs were prepared in 0.5% carboxymethyl cellulose solution and administered orally daily using oral gavage. Venlafaxine (10 mg/kg) p.o. via oral gavage was used as a reference standard (dissolved in distilled water), and its dose was selected as per the earlier study (Kumar et al., 2013). The animals were divided into six groups, and the drug treatments were carried out as per table 1.

Chronic mild stress (CMS) procedure

The chronic mild stress was applied for 4 weeks. The stress consisted of repeated mild physical and psychological stressors. Seven different stressors were present in table 2. On day 0, mice were evaluated for the various behavioural tests such as sucrose preference test and forced swim test, locomotor activity, elevated plus maze, tail suspension test. The stress regimens used in this study was modified version of models previously described (Sun et al., 2016; Ayuob et al., 2016; Willner et al., 1992). On day 7 of each week during CMS, sucrose preference test and behavioural test were performed to evaluate anhedonia behaviour in mice. From day

Table 1. Treatment of drug and their dose in different groups in chronic mild stress model of mice

Groups	Chronic mild stress procedure (for 4 weeks)	Drugs treatment/Dose
Group 1	Nil	Saline p.o.
Group 2	Chronic mild stress(CMS)	Saline p.o.
Group 3	CMS	Venlafaxine (10mg/kg) p.o.
Group 4	CMS	Etoricoxib (5mg/kg) p.o.
Group 5	CMS	Ibuprofen (15mg/kg) p.o.
Group 6	CMS	Venlafaxine (5mg/kg) p.o. + Ibuprofen (15mg/kg) p.o.

Table 2. Chronic mild stress (CMS) procedure

Days/week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
W- 1	Cage tilting at 45º (for 4 hrs)	Cold swimming (temperature 5ºc) (for 5 min)	Tail pinch for (60 sec)	Housing in mild damp saw dust for (6 hrs)	Wet saw dust for (4 hrs)	Overnight illumination	Food and water deprivation (4 hrs)
W-2	Cold swimming (temperature 5ºc) (for 5 min)	Tail pinch for (60 sec)	Housing in mild damp saw dust for (6 hrs)	Wet saw dust for (4 hrs)	Overnight illumination	Food and water deprivation (4 hrs)	Cage tilting at 45º for 4 hours
W-3	Tail pinch for (60 sec)	Housing in mild damp saw dust for (6 hrs)	Wet saw dust for (4 hrs)	Overnight illumination	Food and water deprivation (4 hrs)	Cage tilting at 45º for 4 hours	Cold swimming (temp 5ºc) (for 5 min)
W-4	Housing in mild damp saw dust for (6 hrs)	Wet saw dust for (4 hrs)	Cage tilting at 45º for 4 hours	Tail pinch for (60 sec)	Overnight illumination	Cold swimming (temp 5ºc) (for 5 min	Food and water deprivation (4 hrs)

1 to day 28 various stressors were applied as mentioned in table 2. The stress sequence was changed every week in order to make the stress procedure unpredictable. On 28th day, blood samples were collected for corticosterone estimation. From day 29 to day 43, treatments were given to different groups. On day 43, blood samples were collected two hours after the treatment for corticosterone estimation and then after, mice were sacrificed to collect brain for various neurotransmitter studies.

Behavioural Parameters

Sucrose preference test

The sucrose preference test was performed as documented previously with minor modifications at the end of 1st, 2nd, 3rd and 4th week of the study. Mice were first trained to drink 1% sucrose solution before starting of CMS procedure for 1 hour. Each group provided simultaneously with sucrose (1%) and water. Sucrose intake was calculated by measuring the bottle at 60 minutes (Dhingra and Valecha, 2014).

Forced swim test

Forced swim test was carried out as explained earlier (Porsolt et al., 1978). The mice were taken to a separate room and immediately placed in a cylinder (45 cm high, 20 cm diameter) filled to 30 cm depth and maintained at 25 ± 1°C. Mice were examined for the duration of 5 minutes. The oral treatments in the various groups were carried out 1 hour prior to forced swim test. Clean water was used for each behavioural trial.

Locomotor activity

Each animal was placed in a closed square (30 cm) area equipped with infrared light-sensitive photocells using a digital Actophotometer. The mice were observed for a period of 5 min and the values were expressed as counts per 5 min. The apparatus was placed in a darkened, light- and sound-attenuated and ventilated test room (Christiansen et al., 2016).

Elevated plus maze

Elevated plus maze (EPM) assesses unconditioned anxiety like behaviour in mice. EPM consisted of two open arms (30×5 cm), two enclosed arms (30×5 cm), and a connecting central platform (5×5 cm). The maze was elevated 38.5 cm above the ground. At the beginning of the 5-min session, each mouse was placed in the central neutral zone, facing one of the close arms. Percentage time in the open and central arms and number of head dips over the edge of open arms was recorded by experiments. An arm entry was defined as a mouse having entered an arm of the maze with all four legs (Lister, 1990).

Tail suspension test (TST)

TST was performed based on the previous method that the mouse hung 25 cm above the floor by the tip of the tail (1 cm) tied up to the level. The immobility time was counted during a test at period of 6 minutes (prior 1 minute to adapt and recorded the last 5 minute). The mouse may be considered immovable if it hung passively and absolutely unmoving (Steru et al., 1985).

Biochemical analysis

Estimation of brain serotonin, noradrenaline and dopamine

The estimation of serotonin, noradrenaline and dopamine rat brain was carried out according to the fluorometric method (Ciarlone et al., 1978). Brain tissue sample was homogenized in 10 volumes of cold acidified N-butanol using a glass homogenizer. Duplicate internal standard tubes were carried in parallel with the brains homogenates. After the chemical procedure as specified in the methods section, the monoamines were assayed in the aqueous phase. Excitation and emission wavelengths of 295 and 355 nm, respectively, were used for measurement of serotonin. Noradrenaline fluorescence was measured at excitation and emission wavelengths of 380 and 480 nm while dopamine fluorescence was measured at excitation and emission wavelengths of 320 and 375 nm in the same sample.

Corticosterone estimation

For extraction of corticosterone, 0.1–0.2 ml of serum was treated with 0.2 ml of chloroform: methanol mixture (2:1, v/v), followed by 3 ml of chloroform. The samples were vortexes for 30 sec and centrifuged at 2,000 rpm for 10 minutes. The chloroform extract then treated with 0.1 N NaOH by vortexes rapidly and NaOH layer was rapidly removed. The samples were treated with 3 ml of 30 N H_2SO_4 by vortexes vigorously. The tubes containing H_2SO_4 was kept in dark for 30–60 min and thereafter fluorescence measurements carried out in fluorescence spectrophotometer with excitation and emission wavelength set at 472 and 523.2 nm respectively (Zenker and Bernstein, 1958).

Estimation of reduced glutathione

1.0 ml of homogenates (10%) was precipitated with sulfosalicylic acid (4%). The samples were kept at 4˚C for 1 h and then subjected to centrifugation at 1200 rpm for 15 min. The assay mixture contained 0.1 ml of supernatant, 2.7 ml of phosphate buffer , and 0.2 ml of 5, 50-dithiobis-(2-nitrobenzoic acid) in a total volume of 3.0 ml. The development of yellow colour was read immediately at 412 nm, and GSH levels were expressed as micromole per milligram protein (Jollow et al., 1974).

Measurement of Quinolinic acid

1 ml of HRP (Horseradish Peroxidase) solution was added to serum, H_2O_2 solution (1.0 ml) and 0.1M lactate buffer solution. The mixture was incubated at 30◦C for 90min without exposure to light. The fluorescence intensity of the solution was measured with excitation and emission wavelengths at 328 and 377 nm, respectively. The fluorescence intensity of a reagent blank solution was similarly measure under the same conditions (Odo et al., 2009).

Adrenal gland weight

The animals were sacrificed using CO_2 chamber. The Adrenal gland was dissected out from animal and washed using saline. The samples were soaked on filter paper and their weight was taken using digital weighing machine (Pesarico et al., 2016).

Statistical analysis

Data were expressed as mean ± SEM. Analysis was performed with Prism software using one-way analysis of variance (ANOVA) followed by Tukey's comparison test where results showing $p < 0.05$ were considered statistically significant.

Results

Behavioural tests

In forced swim test, it was observed that disease control group showed significant increase ($p<0.001$) in immobility time as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine, and concomitant treatment of ibuprofen and venlafaxine showed significant decrease in immobility time as compared to disease control group as shown in (figure 1). It is to be noted that ibuprofen in presence of half the dose of venlafaxine showed maximum reduction ($p<0.001$) in immobility time amongst all the treatments as compared to disease control group.

The locomotor activity was observed by number of cut-off observed in the Photoactometer in the various groups. In this test, it was observed that disease control group showed significant decrease ($p<0.001$) in number of cut-off as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine, concomitant treatment of ibuprofen and venlafaxine showed significant increase in number of cut-off as compared to disease control group as shown in (figure 2). Further, it is clear from the result that concomitant group having half the dose of venlafaxine showed similar result as that of venlafaxine alone treatment

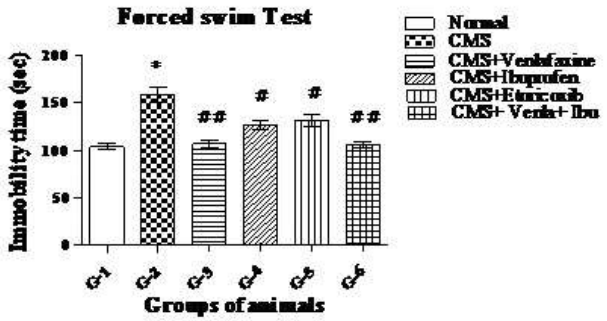

Figure 1. Effect of drugs treatment on immobility time in FST. Each bar and line represents Mean ± SEM (n=6), One-way ANOVA Followed by Tuckey's multiple comparison test. *p <0.001 when compared with the normal group. #p <0.01, ##p <0.001 when compared with the disease control group.

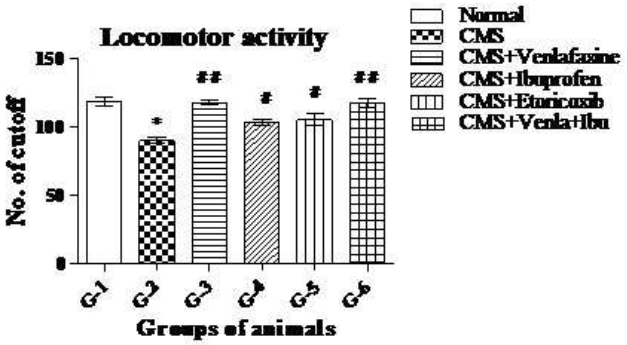

Figure 2. Effect of drugs treatments on number of cut-off in Photoactometer. Each bar and line represents Mean ± SEM (n=6), One-way ANOVA Followed by Tuckey's multiple comparison test. *p <0.001 when compared with the normal group. #p <0.05, ##p <0.001 when compared with the disease control group.

using therapeutic dose.

In tail suspension test, it was observed that disease control group showed significant increase ($p<0.001$) in immobility time as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine, concomitant treatment of ibuprofen and venlafaxine showed significant decrease in immobility time as compared to disease control group (figure 3). It is also clearly observed that concomitant group showed similar results as that of venlafaxine (10mg/kg) dose.

In plus maze model test, it was observed that disease control group showed significant decrease in time spent in arm as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine and concomitant treatment of ibuprofen and venlafaxine showed significant increase in time spent in open arm as compared to disease control group (Figure 4). Results of concomitant group were found similar as that of earlier procedures.

In sucrose preference test, it was observed that disease control group showed significant decrease ($p<0.001$) in sucrose preference as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine and concomitant treatment of ibuprofen and venlafaxine showed significant increase in sucrose preference as compared to disease control group (Figure 5).

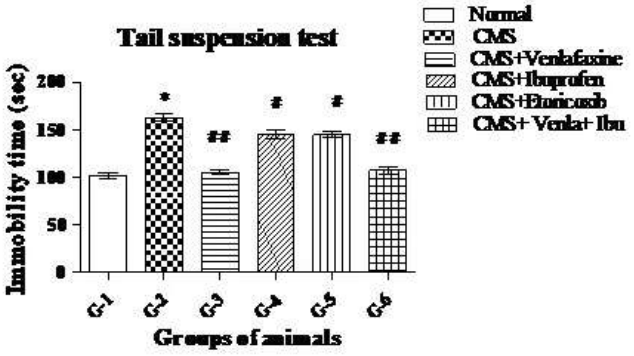

Figure 3. Effect of drugs treatment on immobility time in TST. Each bar and line represents Mean ± SEM (n=6), One-way ANOVA Followed by Tuckey's multiple comparison test. *p <0.001 when compared with the normal group. #p <0.05, ##p <0.001 when compared with the disease control group.

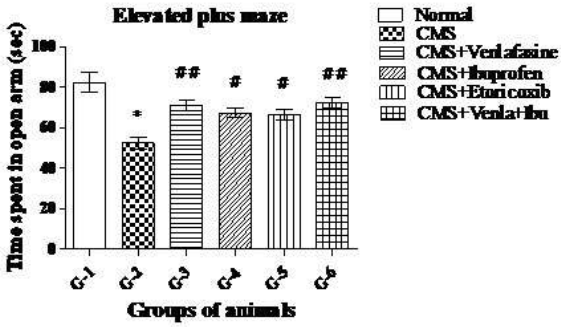

Figure 4. Effect of drugs treatment on time spent in open arm in EPM. Each bar and line represents Mean ± SEM (n=6), One-way ANOVA Followed by Tuckey's multiple comparison test. *p <0.001 when compared with normal group. #p <0.05, ##p <0.01 when compared with the disease control group.

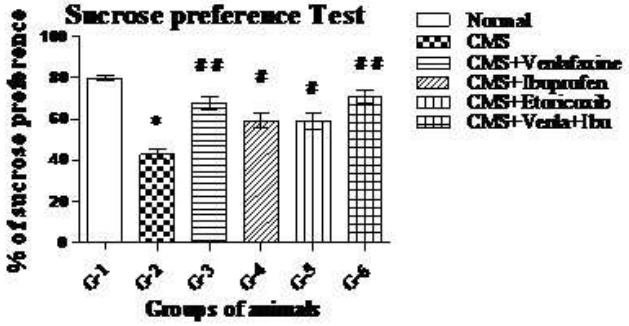

Figure 5. Effect of drugs treatment on % of sucrose preference in SPT. Each bar and line represents Mean ± SEM (n=6), One-way ANOVA Followed by Tuckey's multiple comparison test. *p <0.001 when compared with the normal group. #p <0.01, ##p <0.001 when compared with the disease control group.

Biochemical estimation

In serum corticosterone estimation, it was observed that disease control group of mice showed significant increase in serum corticosterone levels as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine, concomitant treatment of ibuprofen and venlafaxine showed significant decrease in serum corticosterone levels as compared to CMS- group as shown in Figure 6. In addition to above, reduction in serum corticosterone level was comparable in both venlafaxine and concomitant group.

In estimation of serotonin, it was observed that disease control group showed significant decrease in serotonin as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine and concomitant treatment of ibuprofen and venlafaxine showed significant increase in serotonin as compared to disease control group as shown in Figure 6. However, concomitant treatment group showed remarkable increase in serotonin levels when compared to other treatment groups. Further, it was observed that disease control group showed significant decrease in nor-adrenaline and dopamine as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine, concomitant treatment of ibuprofen and venlafaxine showed significant increase in nor-adrenaline and dopamine as compared to disease control group as shown in Figure 6.

For glutathione estimation, it was observed that disease control group showed significant decrease in GSH level as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine, concomitant treatment of ibuprofen and venlafaxine showed significant increase in

GSH level as compared to disease control group (Figure 7). Further, it was observed that disease control group showed significant increase in quinolinic acid as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine and concomitant treatment of ibuprofen and venlafaxine showed significant decrease in quinolinic acid as compared to disease control group (Figure 7). However, concomitant treatment group showed remarkable reduction in quinolinic acid levels as compared to other treatment groups. Significant increase in adrenal gland weight was observed in disease control group as compared to normal group. However, all the treatments groups have shown remarkable reduction in the adrenal gland weight as shown in figure 7.

Discussion

The mice treated with chronic mild stress for 4 weeks. CMS results in some behavioural abnormalities that parallel symptoms observed in human depression and different antidepressants reverse these symptoms (Willner et al., 1992). CMS-induced mice can effectively mimic the depressive state shown by reducing sucrose intake in SPT, decreasing locomotor activities and increasing immobility time in TST/FST, along with the reduction of neurotransmitters into brain (Wang et al., 2011).

In chronic mild stress model, different types of stressors were given to mice over the period of 4 weeks. The stress consisted of repeated mild physical and psychological stressors (Willner et al., 1992). The mice were treated with chronic mild stress after 28 days showed an increase in immobility time in forced swim test and tail suspension test, elevated serum corticosterone level and decreased sucrose intake in sucrose preference test. The behavioural change observed during chronic mild stress procedure was replicated as in previous studies (Willner et al., 1992; Muscat and Willner, 1992). Our study also showed parallel results with those of reported studies in which exposure to CMS increased immobility time and reduced the sucrose consumption in the mice. In the present study, forced swim test and tail suspension test were performed at the end of each week during CMS and end of treatment period. Stress significantly increased immobility time over the periods of 28 days indicating behaviour despair in mice. Ibuprofen and etoricoxib reversed immobility time in animal model of depression. Further, sucrose preference test was used to detect anhedonia. CMS-induced anhedonia is core symptoms of depression. Inability to experience pleasure in normally pleasurable activity is known as anhedonia (Willner et al., 1992; Muscat and Willner, 1992). Stress significantly reduced the sucrose preference as compared to normal group. Ibuprofen and etoricoxib showed significant increase in

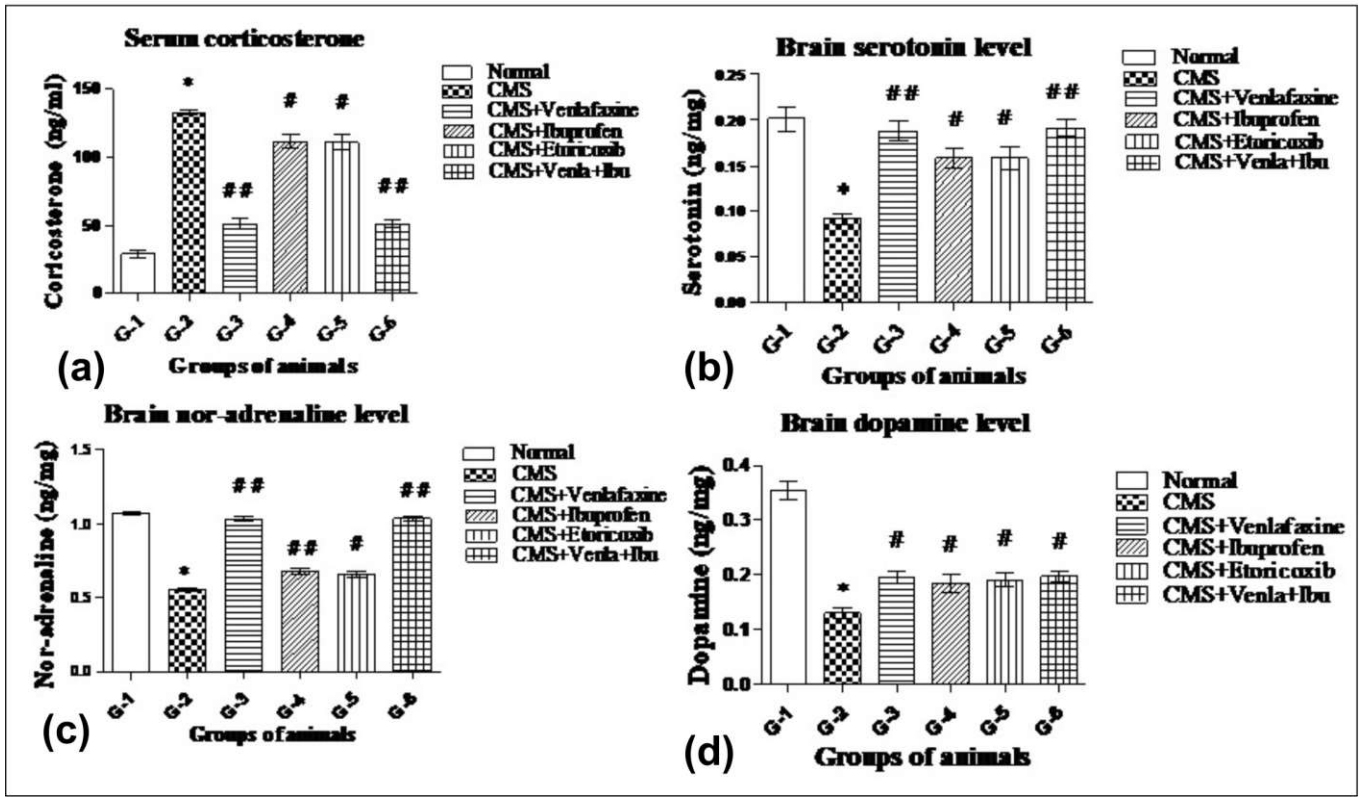

Figure 6. Effect of drugs treatment on (a) Serum corticosterone, (b) Brain serotonin level, (c) Brain nor-adrenaline level, (d) Brain dopamine level. Each bar and line represents Mean ± SEM (n=6), One-way ANOVA Followed by Tuckey's multiple comparison test. *p <0.001 when compared with normal group. #p <0.01, ##p<0.001when compared with the disease control group.

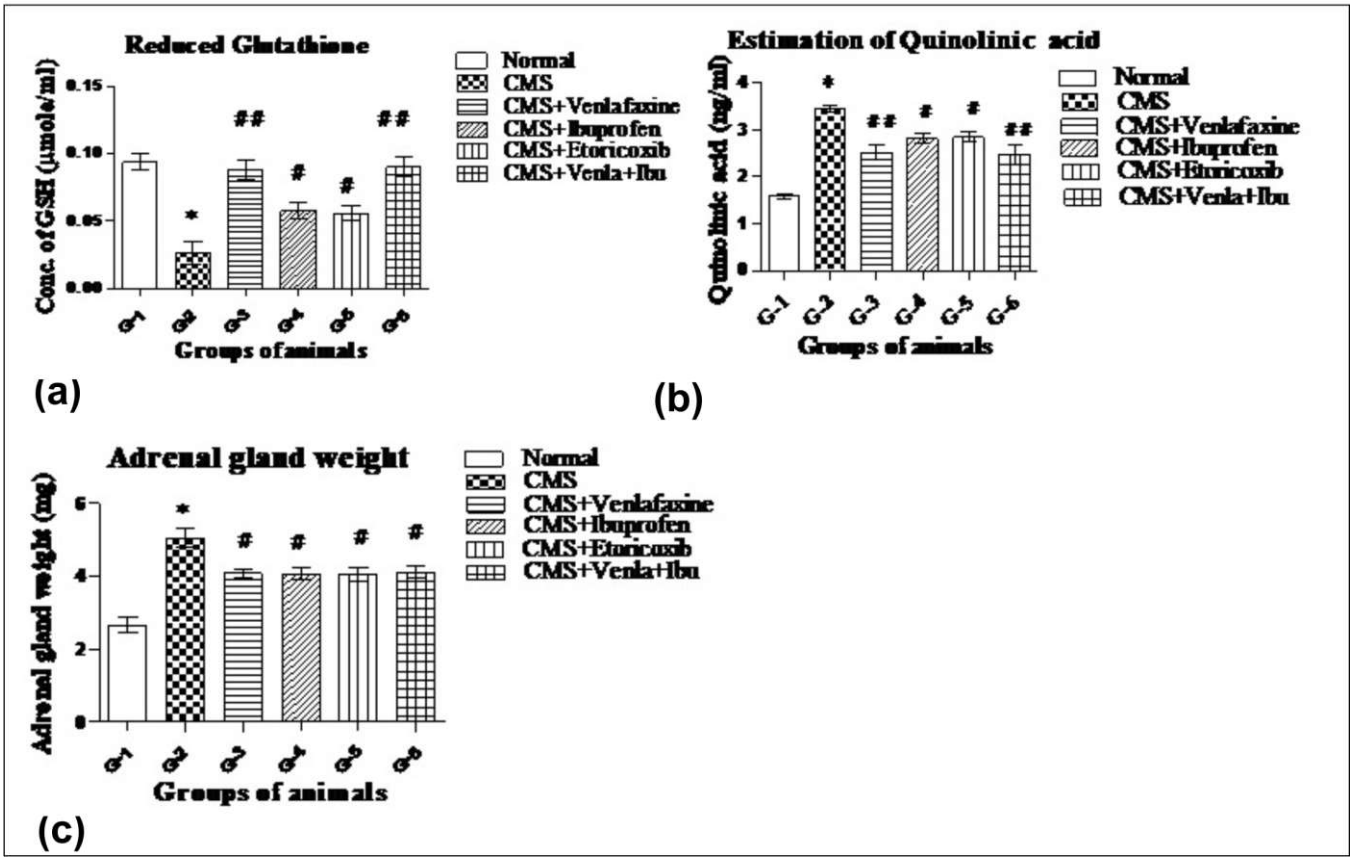

Figure 7. Effect of drugs treatment on (a) Reduced glutathione, (b) Quinolinic acid, (c) Adrenal weight. Each bar and line represents Mean ± SEM (n=6), One-way ANOVA Followed by Tuckey's multiple comparison test. *p <0.001 when compared with normal group. #p <0.05when compared with the disease control group.

sucrose preference as compared to CMS treated group.

We also observed significant reduction in time spent in open arm and decrease in locomotor activity due to repeated unpredictable chronic mild stress. Our results also showed an increase in adrenal gland weight and serum corticosterone levels in CMS-treated group after the stress procedure of CMS. In clinical study, elevated cortisol level is observed in depressed patients (Sublette and Postolache, 2012). The adrenal gland weight was used in this study as an indirect parameter of the HPA axis activation. Chronic stress results in the hyperactivity and deregulation of HPA axis and thus produces excess glucocorticoids (Kaster et al., 2012; Khairova et al., 2009). Hence, the mechanism of increase adrenal gland weight and corticosterone can be attributed hypothalamic-pituitary adrenal axis in central nervous system.

Reactive oxygen species (ROS) also play a role in the pathogenesis of neuropsychiatric disorders (Michel et al., 2012; Bilici et al., 2001; Khanzode and Dakhale, 2003). Our observation showed reduction in reduced glutathione levels in disease control group as compared to normal animals. However, pre-treatments with ibuprofen, etoricoxib and venlafaxine increased ($p<0.05$) reduced glutathione levels indicating reduction of oxidative stress. Upon activation by pro-inflammatory factors, indoleamine 2,3-dioxygenase induces up regulation of tryptophan catabolism via the KP, which results in the production of neuro-active metabolites which is quinolinic acid and reducing the formation of serotonin. Increased levels of quinolinic acid are reported to lead to dysfunctioning of neurons and cause of neuronal death (Hazari and Bhad, 2015; Smith et al., 2016; Stone et al., 2013). It has been observed that disease control group in our study showed significant increase in quinolinic acid as compared to normal group. The groups treated with ibuprofen, etoricoxib, venlafaxine and concomitant treatment of ibuprofen and venlafaxine showed significant decrease in quinolinic acid as compared to disease control group revealing neuroprotective activity of those anti-inflammatory and antidepressant drugs selected under the study.

Interestingly, it is clearly evident from the results of concomitant group where in ibuprofen alongwith half the dose of venlafaxine (5mg/kg) showed similar results to that of venlafaxine (10mg/kg) dose in almost all the test procedures. This indicates that addition of anti-inflammatory drug in patients receiving antidepressant therapy can help in better outcome of the results and also reduce the therapeutic dose of antidepressants.

Conclusion

It is suggested from our study that ibuprofen and etoricoxib

are effective in reducing the symptoms of depression based on behavioural tests. The anti-depressant action of these drugs can be attributed to improvement of brain neurotransmitter levels, reduction in the corticosterone and quinolinic acid leading to neuroprotection in the CNS. Further, the use of concomitant treatment of ibuprofen and venlafaxine showed synergistic effect suggesting possible beneficial effect of using NSAIDs in the patients suffering from depression.

Conflict of interest

None

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