Metabolic Brain Disease (2019) 34:775–787
https://doi.org/10.1007/s11011-019-00401-8

ORIGINAL ARTICLE

Protocatechuic acid attenuate depressive-like behavior in olfactory bulbectomized rat model: behavioral and neurobiochemical investigations

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Received: 12 August 2018 / Accepted: 25 February 2019 / Published online: 8 March 2019

Abstract

The main objective of the present study is to investigate potential effects of PCA in OBX induced depressive-like behavior in rat model. PCA was administered at a dose of 100 mg/kg and 200 mg/kg, by per oral in OBX and sham operated rats. Behavioral (ambulatory and rearing activity and immobility time), neurochemical [serotonin (5-HT), dopamine (DA), norepinephrine (NE) and brain derived neurotrophic factor (BDNF) expression], biochemical (MDA formation, IL-6, TNF-α and antioxidants) changes in hippocampus and cerebral cortex along with serum corticosterone were investigated. Experimental findings reveals that OBX subjected rats showed alteration in behaviors like, increase in immobility time, ambulatory and rearing behaviors significantly, reduced BDNF level, 5-HT, DA,NE and antioxidant parameters along with increased serum corticosterone, MDA formation, IL-6, and TNF-α in hippocampus and cerebral cortex compared to sham operated rats. Administration of PCA significantly attenuated behavioral and neurobiochemical alterations, thus, its antidepressant-like activity is largely mediated through modulation of neurotransmitter, endocrine and immunologic systems, mainly by improvements of BDNF, 5-HT, DA, NE, reduced MDA, IL-6, and TNF-α in hippocampus and cerebral cortex.

Keywords PCA · Olfactory bulbectomy · Neurobiochemical alterations · Oxidative stress

Introduction

Olfactory bulbectomized (OBX) induced depression is largely employed rodent method for screening of drugs in depressive mood behavior (Song and Leonard 2005). OBX rats exhibits behavioral and neurobiochemical alterations, mainly, explorative changes which are mainly seen in agitated depression (Song and Leonard 2005). Brain neurogenesis is mainly routed via modulation of brain-derived neurotrophic factor (BDNF), a member of nerve growth factor. The BDNF expression and its level found to be altered during OBX, while antidepressant therapy improve such level in various brain regions of rodents (Duman 2004; Shimizu et al. 2003; Antunes et al. 2016). Further, OBX subjected rats elicited higher proinflammtory cytokines level mainly tumor necrosis factor (TNF-α) and interleukin-6 (IL-6) the brain areas (Antunes et al. 2016) suggesting that these cytokines participate in the development of depressive state. OBX model of depression exhibited significant impairment of behavioral changes like increased immobility time, exploratory activity, biochemical alterations mainly, attenuation of monoamines, BDNF, TNF-α and IL-6 along with impaired endogenous defense system (Thakare et al. 2017a, b). The antidepressants like activity of these drugs probably mediated via neuroprotection mechanism produce by attenuation of neuroinflammatory effects.

Protocatechuic acid (PCA) induced neuroprotection in stress animals by improving endogenous antioxidant enzymatic activity (Shi et al. 2006) and antidepressant activity was by enhancing brain monoamines (Kim et al. 2014). PCA ameliorates neurocognitive dysfunction induced by

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chronic intermittent hypoxia; increased 5-HT in the brain tissues of rats along with decreased MAO-B activity (Kim et al. 2014). In our earlier findings, we observed that PCA prevented the elevation of malondialdehyde (MDA) formation, and improved endogenous antioxidant system in cerebral ischemic rats (Muley et al. 2012 2013). In addition, administration of PCA attenuates lipid peroxidation and subsequently restored the antioxidant enzymes (Zhang et al. 2015). We recently documented antidepressant potential of PCA in acute restraint stress by attenuation of MDA formation and improved antioxidant defense system, thus control oxidative stress (Thakare et al. 2016). However, effects of PCA in OBX induced depressive-like behavior are not available in literature. Hence, the work presented in this communication attempts to demonstrate the antidepressant potential of PCA in OBX induced depression, and to explore associated mechanism(s) of action.

Materials and methods

Animals

Wistar rats of either sex weighing 200–250 g, 80–100 days old were procured from Institute of Biosciences, India. Rats were housed separately in groups of 8 per cage (polycarbonate cage size: 29 cm × 22 cm × 14 cm) under standard laboratory conditions with alternating light and dark cycle of 12 h each. The animals had free access to food and water unless specified. Experimental protocol was approved (SIPS/IAEC/2014–15/01) by the Institutional Animal Ethics Committee and experiment is complying with the guidelines in accordance of National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

Drugs and chemicals

Test drug PCA and standard fluoxetine, Enzyme-linked immunosorbent assay (ELISA) kits for estimation of brain derived neurotrophic factor, corticosterone and cytokines were obtained from various repute vendors. The other chemicals utilized in the research studies were obtained from local vendors.

Olfactory bulbectomy (OBX)

Olfactory bulbectomy (OBX) surgery was carried out as per the method described by Van Reizen and Leonard (1990) and also employed at our lab earlier (Thakare et al. 2017a, b). Briefly, anaesthetized rats (Anaesthesia consist of ketamine and xylazine at the ratio of 10:1). Anesthetized rats were incised as 1-cm on midline of rat head by steriotaxically (Inco, Ambala, India) and OBX done with use of coordinates, from bregma, AP +6 mm, ML ±1 and DV 2 mm. Olfactory bulbs were ablated by use of suction and haemostatic sponge was introduced into bulb cavity in order to prevent the excessive hemorrhage, and finally incision was sutured. In Sham animals, same process was performed except olfactory bulbs removal. The model was corroborated by study of behavioral changes like, hyperactivity, duration of immobility time. The OBX/Sham rats were housed singly in cages for 15 days for rehabilitation. Pictogram of the study is shown in Fig. 1.

Experimental design

Two weeks of surgical rehabilitation, animals were grouped as per following approach-

Sham control group: Vehicle (Carboxy Methyl Cellulose (CMC), 10 ml/kg, per oral (po)
Sham standard group: Fluoxetine 20 mg/kg, po
Sham drug treated group 1 and 2- treated with PCA 100 and 200 mg/kg,po respectively
OBX control group: Vehicle, 10 ml/kg, po
OBX standard group: Fluoxetine 20 mg/kg, po
OBX drug treated group 1 and 2- treated with PCA 100 and 200 mg/kg, po respectively

Selection of PCA doses

The doses of PCA were chosen from previous documented findings of our lab (Muley et al. 2012, 2013; Thakare et al. 2016, 2017a, b). In the present studies we have chosen 100 and 200 mg/kg by oral route in order to study the dose dependent effects on various depressive behaviors in OBx rats.

In addition, As a safety measure we did not observed any significant unwanted behavioral changes with the employed doses of PCA viz. excitement and/convulsion with and itching, skin rashes, tremors etc. which was significantly observed with tricyclic antidepressants and fluoxetine respectively (Rang et al. 2007).

PCA and fluoxetine was suspended in CMC (1%, (*w*/*v*) and maximum volume was administered as 10 ml/kg by oral route. PCA treatment was given once a daily at 9.00 AM for 14 days post surgical rehabilitation period.

Behavioral studies

Forced swimming test (FST)

The duration of immobility time in FST was determined as per the procedure documented earlier by Porsolt et al. (1977).

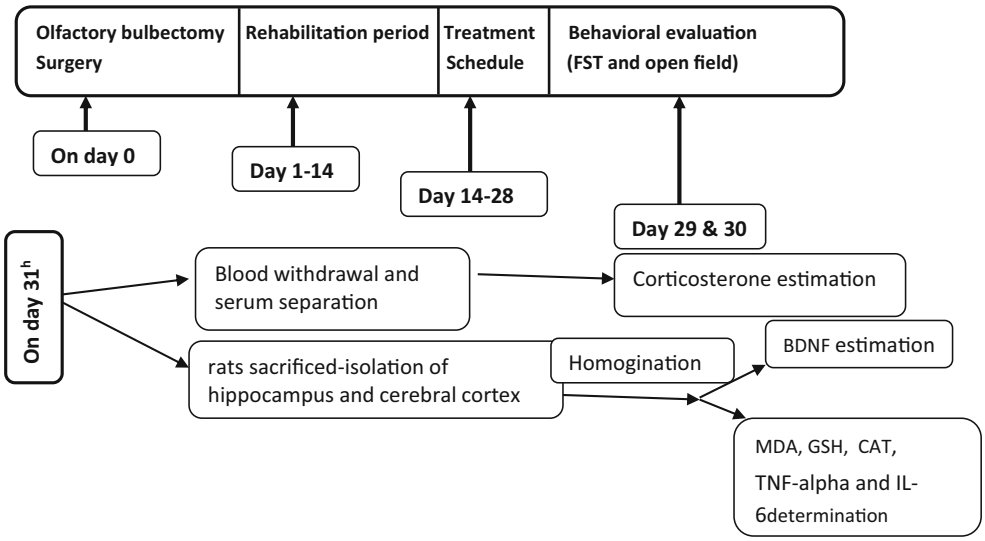

Fig. 1 Schematic presentation of the study is shown in Fig.1

Open-field test (OFT)

Ambulatory behaviors were recorded in the OFT as per the method previously employed by Rodrigues et al. (1996). The number of section crossed and rearing frequency were determined as ambulatory behavior in 6 min time period. The equipment was cleaned with a solution of 10% ethanol between tests in order to hide animal clues.

Biochemical studies

Post behavioral investigation, blood was withdrawn from retro-orbital plexus under light isoflurane anaesthesia at 8.30 am and serum was separated and used in corticosterone (CORT) measurement. Animals were sacrificed, brain samples were quickly isolated, and hippocampus and cerebral cortex were separated and homogenized in 0.1 M PBS (p*H* 7.4) and utilized for measurement of malondialdehyde (MDA) an index of lipid peroxidation process. The residual brain homogenate further centrifuged (10,000×g) at 4 °C for 15 min, resulting supernatant was employed for measurement of various neurobiochemical.

Estimation of malondialdehyde (MDA) formation

The MDA formation was estimated in homogenates of hippocampus and cerebral cortex as per the method of Ohkawa et al. (1979).

Antioxidant studies

The catalase (CAT) activity and reduced glutathione (GSH) was measured as per the procedure described by of Aebi (1984) and Ellman (1959) respectively.

Neurochemicals estimation

The monoamines, serotonin (5-HT), norepinephrine (NE) and dopamine (DA) were estimated in the tissue homogenates as per the method of Kent Shellenberger and Gordon (1971).

Determination of BDNF, and cytokines

BDNF, IL-6 and TNF-α levels were investigated by ELISA techniques by the methodology mentioned in the manufacturer's kit.

Determination of serum CORT

Serum CORT was measured by ELISA techniques by the methodology mentioned in the manufacturer's kit.

Statistical analysis

Data was expressed as the mean ± SEM. Statistical data was analyzed by two-way ANOVA followed by Bonferroni post hoc test. Probability value $p < 0.05$ was considered to be statistically significant.

Results

Effects of PCA or fluoxetine on immobility time

Experimental data suggested that rats underwent OBX elicit significantly ($p < 0.0001$) higher immobility time compared to sham control vehicle group. Treatment with PCA and fluoxetine attenuated the immobility time ($p < 0.0001$) when compared to vehicle treated OBX group (Fig. 2).

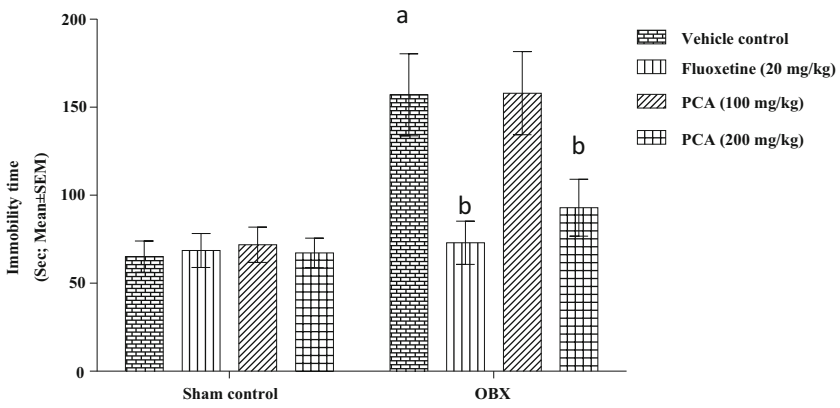

Fig. 2 Effect of PCA (100 and 200 mg/kg) or fluoxetine (20 mg/kg) on immobility time by FST in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$); $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

Effects of PCA or fluoxetine on open field behaviors

In open file test, we found increased exploratory behaviors, mainly ambulation and rearing in OBX group as compared to sham control group. Administration of PCA and significantly ($p < 0.0001$) attenuated these behavior when compared to vehicle treated OBX rats (Fig. 3a and b).

Effects of PCA or fluoxetine on monoamines level

In monoamines studies, we found significant reduction ($p < 0.0001$) of 5-HT, DA and NE level were observed in OBX operated group as compared to sham operated group. PCA and fluoxetine treatments significantly ($p < 0.0001$) improved levels of these monoamines in hippocampus (Figs. 4a, 5a and 6a). Similarly, in cerebral cortex too, we observed that, OBX rats exhibits significant decrements in levels of 5-HT, DA and NE compared to sham control. Treatment with PCA and fluoxetine significantly ($p < 0.0001$) prevented decline in these monoamines compared to OBX group (Figs. 4b, 5b and 6b).

Effects of PCA or fluoxetine on BDNF level

The experimental data reveals that OBX rats showed significant $p = 0.0036$) reduction in BDNF level in hippocampus

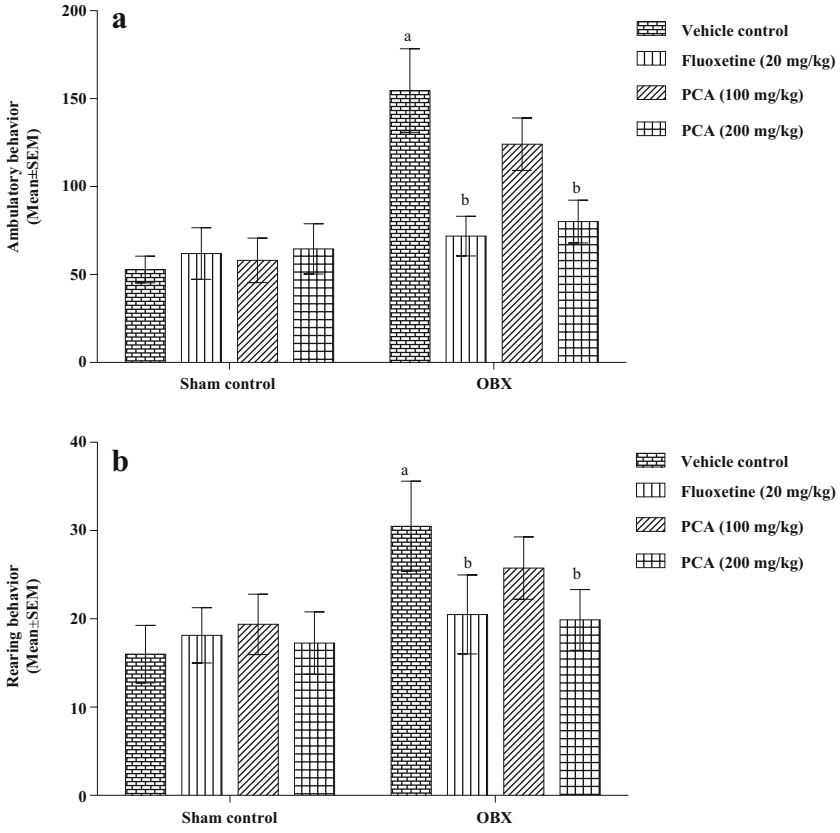

Fig. 3 Effect of PCA (100 and 200 mg/kg) or fluoxetine (20 mg/kg) on exploratory behavior by open field test in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

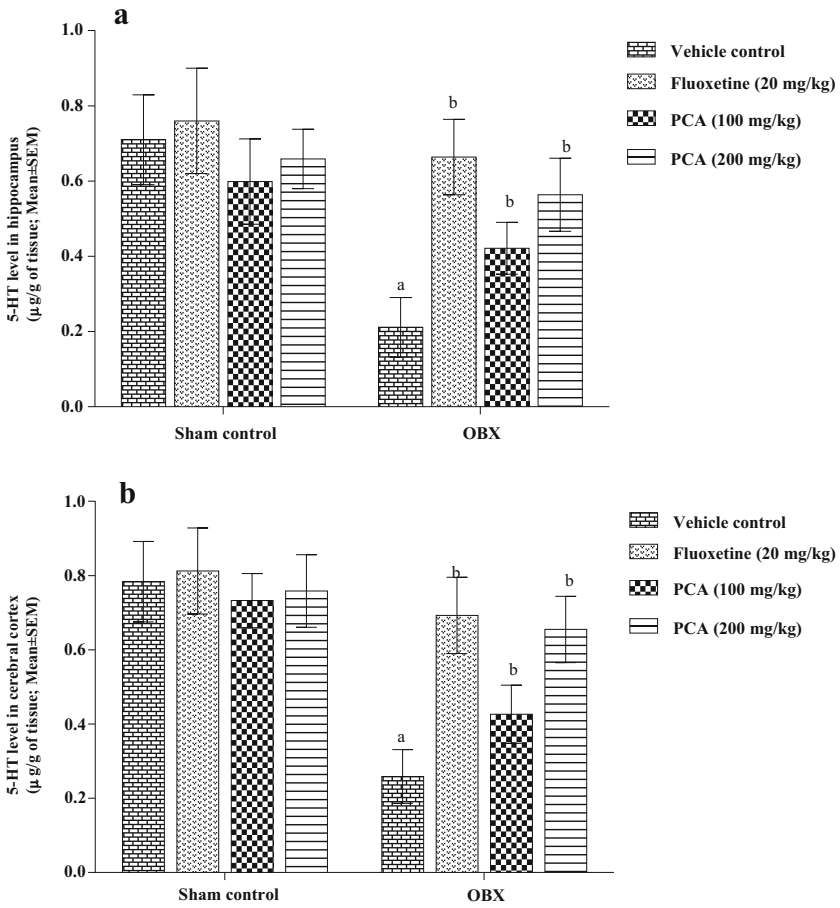

Fig. 4 Effect of PCA (100 and 200 mg/kg) or fluoxetine (20 mg/kg) on5-HT level in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

compared to sham operated group (Fig. 7a). Administration of PCA significantly prevented the decline in BDNF contents in hippocampus of compared to OBX rats. Likewise, in cerebral cortex, treatment with PCA and fluoxetine prevented decrement in BDNF level due to OBX (Fig. 7b).

Effects of PCA or fluoxetine on cytokines

There was significant increase ($p < 0.0001$) cytokines TNF-α and IL-6 in hippocampai of OBX subjected rats compared to sham group (Figs. 8a, 9a). PCA administration significantly attenuated the both cytokines levels compared to vehicle treated OBX rats. For cerebral cortex, *PCA* treatment significantly ($p < 0.0001$) prevented the elevation of TNF-α and IL-6 levels compared to OBX operated rats (Figs. 8b, 9b).

Effects of PCA or fluoxetine on serum CORT level

OBX subjected rats elicited significant ($p < 0.0001$) elevation of serum CORT level compared to sham operated group. Administration of PCA at both doses significantly prevented after serum CORT elevation compared to OBX subjected rats. (Fig. 10).

Effects of PCA or fluoxetine on MDA formation

OBX rats exhibited increased hippocampal (Fig. 11a) and cerebral cortex (Fig. 11b) MDA formation compared to sham control group which was subsequently attenuated with the PCA treatments.

Effects of PCA or fluoxetine on CAT and GSH

OBX subjected rats showed significant decrement in both CAT activity and GSH contents in hippocampus compared to sham operated group (Figs. 12a, 13a). Treatment with PCA significantly improved antioxidants CAT and GSH compared to vehicle treated OBX group. Similarly, GSH content in cerebral cortex (Figs. 12b, 13b) was reversed with PCA treatment compared to OBX treated rats.

Discussion

In the present study we proposed that, PCA could able to attenuate OBX induced depressive-like behaviors by improving behavioral and neurobiochemical alternations. Ablation of olfactory bulb in rats elicits increased hyperactivity, loss of

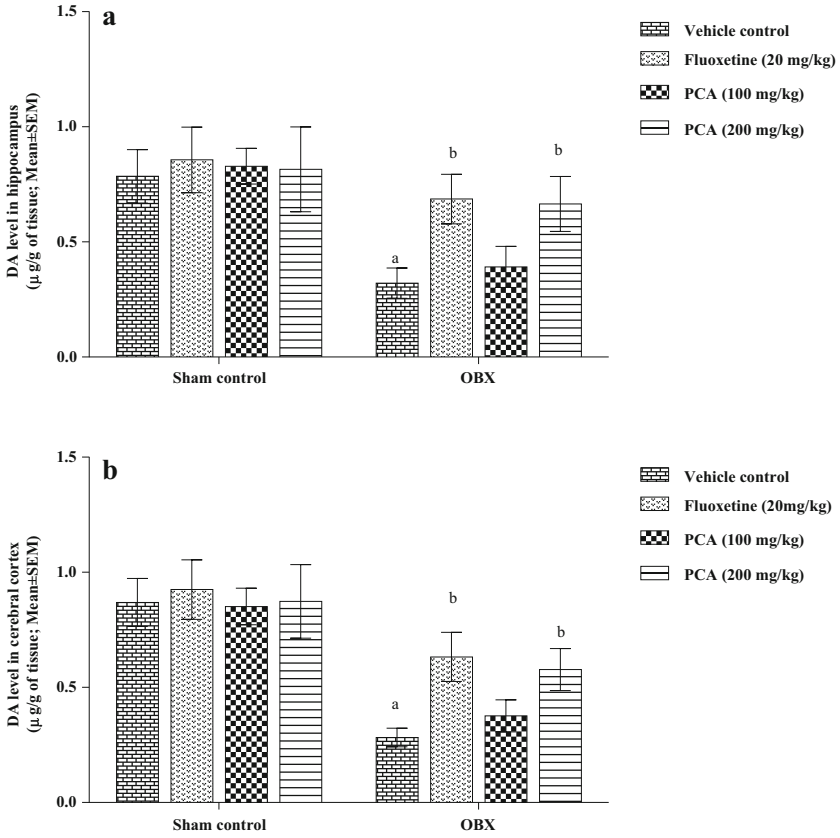

Fig. 5 Effect of PCA (100 and 200 mg/kg) or fluoxetine (20 mg/kg) on DA level in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

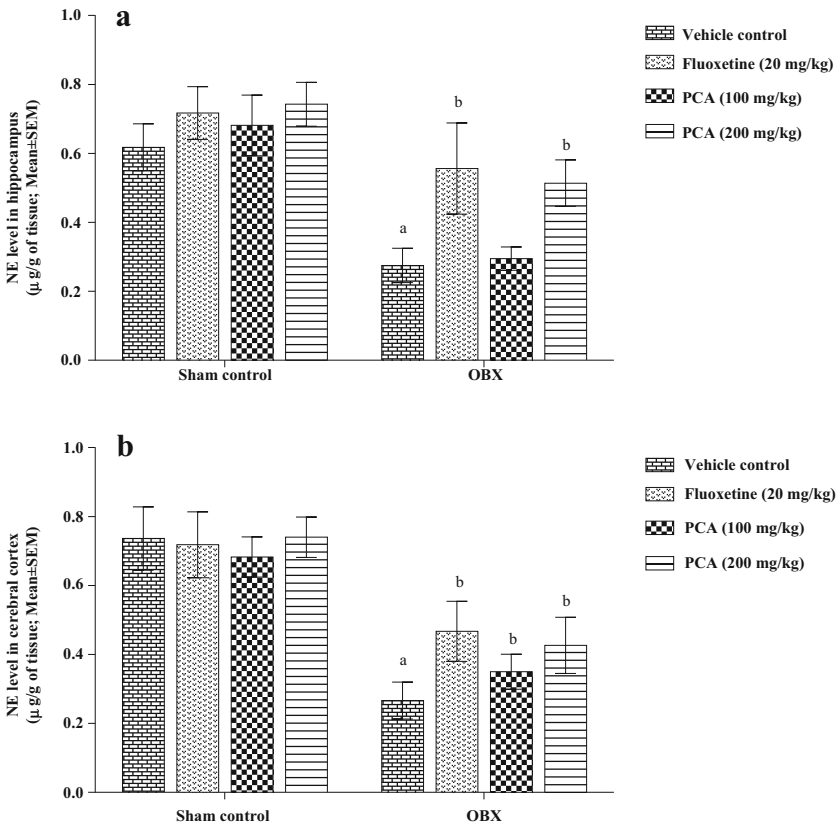

Fig. 6 Effect of PCA(100 and 200 mg/kg) or fluoxetine (20 mg/kg) on NE level in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

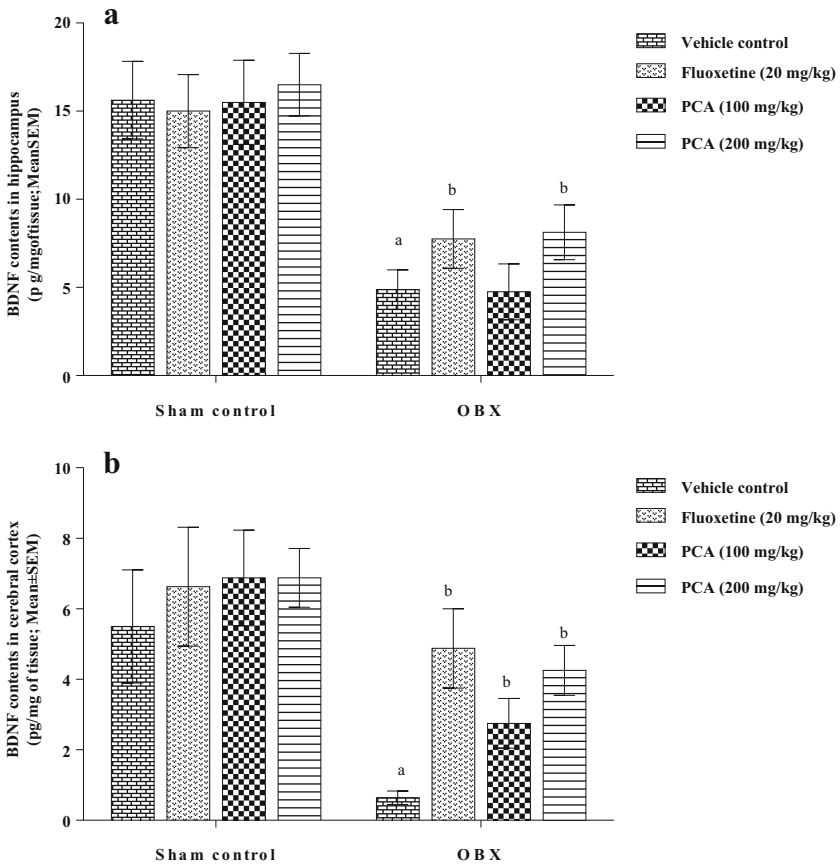

Fig. 7 Effect of PCA(100 and 200 mg/kg) or fluoxetine (20 mg/kg) on BDNF level in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

pleasure which manifested to depressive state (Song and Leonard 2005; Thakare et al. 2017a, b). Our experimental findings revealed that, OBX rats elicited increase immobility time which was subsequently attenuated with PCA administration. Further, we have measured exploratory activity, ambulatory and rearing behavior in OBX rats to identify the effects of PCA on depressive state that might augment such behaviors. We observed that, rats subjected to OBX exhibited increase ambulation and rearing behavior, suggested agitated depressive which was subsequently prevented with administration PCA at doses dependent manner.

Further, in order to understand involvements of monoamines in antidepressant like activity of PCA, we measured monoamines level 5-HT, NE and DA in hippocampus and cerebral cortex of OBX and sham control rats (Mao et al. 2011). It is apparent that deficiency of monoamines in the brain is largely participated in induction of depressive-like disorders (Elhwuegi 2004; Nutt 2008). The depressive symptoms like mood alterations, anhedonia, pessimism and feeling of worthlessness are connected by deficiency of brain monoamines (Elhwuegi 2004; Nutt 2008). Similarly, in our earlier OBX model, we found that OBX rats showed lower monoamines levels in hippocampus and cerebral cortex (Thakare et al. 2017a, b). Our present data indicated that decrease 5-HT, DA and NE level in hippocampus and cerebral cortex in OBX group while PCA and fluoxetine, noticeably improved these monoamines. Our present findings are in agreements with the findings of Kim et al. (2012), who demonstrated that PCA isolated from *Gardenia jasminoides* showed significant antidepressant activity by inhibiting MAO-A and MAO-B enzymes. As MAO-A is involved in the metabolism of serotonin, noradrenaline and to lesser extent dopamine, whereas, MAO-B metabolize the dopamine (Youdim and Weinstock 2004). Thus, we believed the improvements in monoamines levels with PCA in hippocampus and cerebral cortex in OBX rats is might be due to that ability of PCA to inhibit the MAO-A and MAO-B enzymes. However, we did not investigate the inhibitory effects of PCA on these enzymes in the present studies.

The documented literature reveals that, there is substantial correlation between depression and neuronal degeneration or damage at brain regions (Fuchs et al. 2004; Manji and Duman 2001). The chief action of BDNF is stimulation of development and subsequently formation of neurons and synapses mainly in the hippocampus, cortex (Fuchs et al. 2004). Documented reports revealed that depressed patients showed lower BDNF level (Matrisciano et al. 2009; Fernandes et al. 2011). In addition, it was noted that reduce BDNF content in hippocampus and prefrontal cortex of mice in chronic stress induce depressive behavior (Mao et al. 2014; Shen et al. 2016;

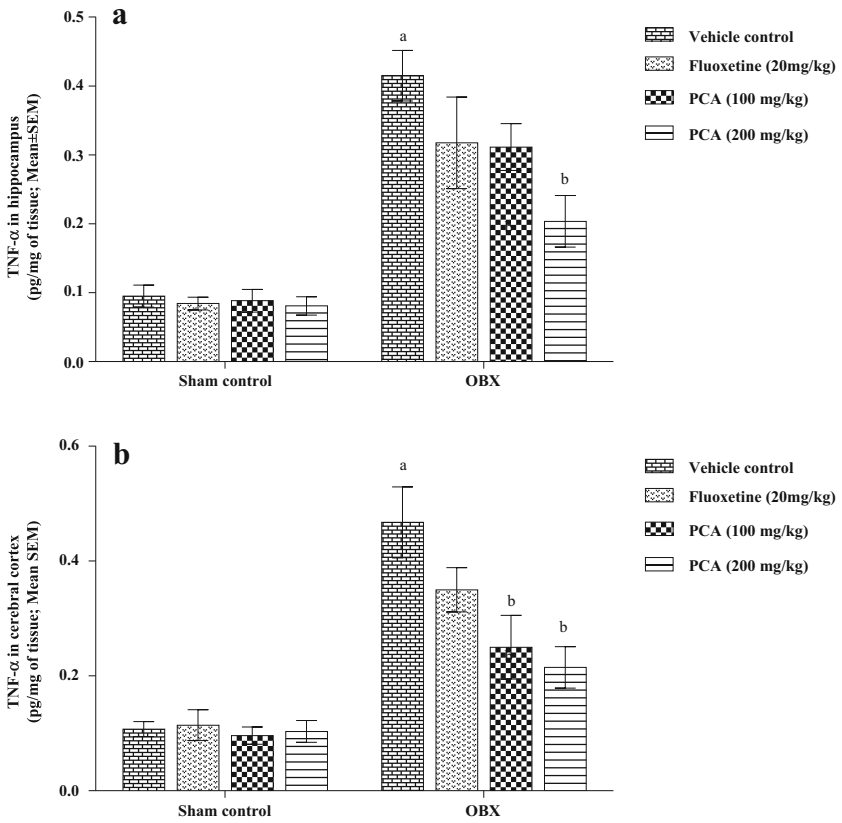

Fig. 8 Effect of PCA(100 and 200 mg/kg) or fluoxetine (20 mg/kg) on TNF-α level in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

Thakare et al. 2017a, b) and subsequent antidepressant treatment reversed the BDNF contents. In our findings too, OBX rats showed decrement in BDNF which is presumably due to increased free radicals formations due to oxidative stress and finally that induce neuronal damage. Thus, it is possible that prevention of BDNF decrement with PCA is largely through its scavenging or/neutralizing of generated free radicals, which are known to cause neuronal damage and subsequently attenuate depressive like behavior in OBX rats. Our findings are in agreement with Numakawa et al. (2011), where in they demonstrated that BDNF can significantly prevent neuronal damage caused due to oxidative stress, as found in neurodegenerative diseases. Furthermore, their findings showed that PCA administration to significantly increase the level of BDNF expression during a period of chronic intermittent hypoxia, in the hippocampus and prefrontal cortex.

Inflammatory cytokines, the immune system and neuroendocrinological components are largely participated in the development of mood related behavior (Schiepers et al. 2005). Tang et al. (2016) demonstrated that elevated TNF-α and IL-6 implicated in the pathophysiology of depression; intracerebroventricular injection of TNF-α known to exhibited depressive-like state in FST in mice (Kaster et al. 2012). Furthermore, it was found that the alteration in hippocampal neurogenesis was interrelated to the behavioral performances, as evidenced as relationship of depressive state and the dysfunctional neurogenesis. Hence, it might possible that OBX causes neuroinflammation due to increased production of pro-inflammatory cytokines, TNF-α and IL-6 in hippocampus are thought be culprit in neurogenesis process and subsequently induction of depressive like behavior. Administrations of PCA induce reduction in IL-6 and TNF-α in hippocampus and cerebral cortex. The ability of PCA due to its anti-inflammatory potential attenuates the neuroinflammation and thus subsequently prevented the elevation of IL-6 and TNF-α in hippocampus and cerebral cortex due to OBX.

It was observed that dysfunction of hypothalamic-pituitary-adrenal axis (HPA) results into increased CORT level and related alterations were also noticed post OBX in rodents (Cairncross et al. 1977; Pariante and Lightman 2008; Thakare et al. 2017a, b). Elevation of CORT level induce significant behavioral and neurochemical alterations that results in the development of depressive state were documented previously (Mao et al. 2010; Thakare et al. 2016, 2017a, b) and subsequently reduction of serum CORT suggested to induce antidepressant like effects. Likewise, we also observed that, OBX rats showed elevated serum CORT level pointing out impairment in the HPA axis. Our findings also substantiated with the documented studies of Jindal et al. (2015a, b) and Rinwa and Kumar (2014), wherein they demonstrated increased serum CORT in OBX animals which were

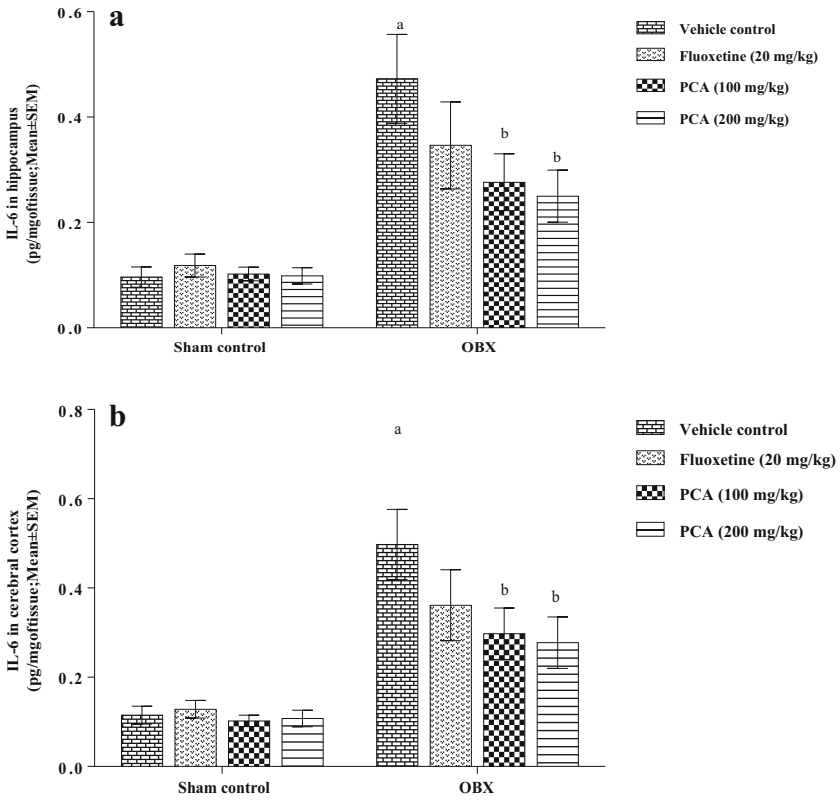

Fig. 9 Effect of PCA(100 and 200 mg/kg) or fluoxetine (20 mg/kg) onIL-6 level in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

attenuated with rolipram and *Panax quinquefolium* respectively. In the present studies, we observed that administration of PCA attenuated the elevated serum CORT level in dose dependent manner indicating normalization HPA axis and consequently antidepressant activity.

In order to understand the participation/involvement of oxidative stress in mood alterations in OBX; we measured MDA formation, CAT and GSH as endogenous antioxidants markers. We earlier reviewed that significant correlation between oxidative stress and depressive disorder, as corroborated by free radicals generation due to peroxidation process (Thakare and Patel 2015). Hence, oxidative stress is considered as main cause in the development of depressive behavior and consequently improvement of antioxidant paradigms. PCA exhibited significant neuroprotection through attenuation of the elevated MDA formation in the brain of ischemic rats (Muley et al. 2012, 2013). In present study, OBX rats elicited lipid peroxidation by higher MDA level which was consequently prevented significantly with PCA treatment thus protects hippocampal and cerebral cortex damage.

Reduced glutathione (GSH) is an important a non-enzymatic antioxidant component in biological tissue, that modulate oxidative stress via scavenging formed free radicals in biological reactions. The decrement in GSH contents are

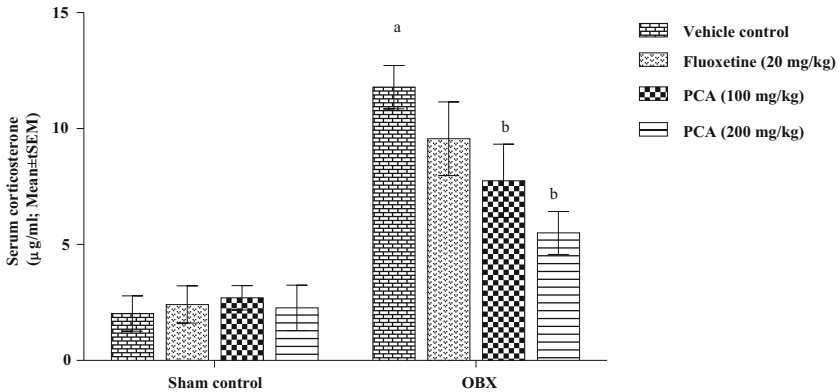

Fig. 10 Effect of PCA(100 and 200 mg/kg) or fluoxetine (20 mg/kg) on serum corticosterone level in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

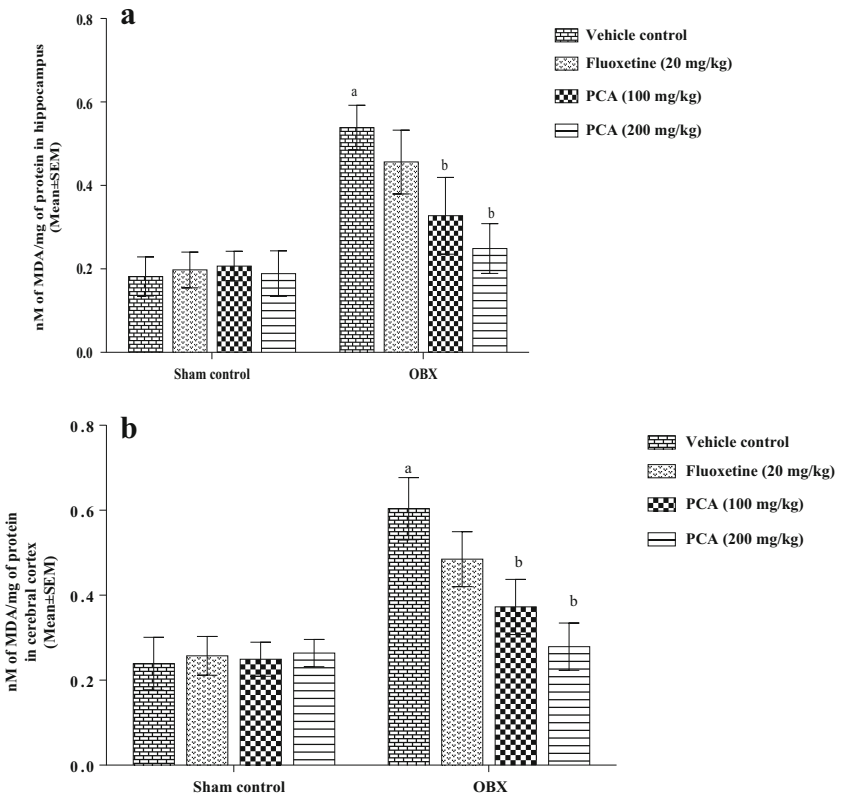

Fig. 11 Effect of PCA(100 and 200 mg/kg) or fluoxetine (20 mg/kg) on MDA formation in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

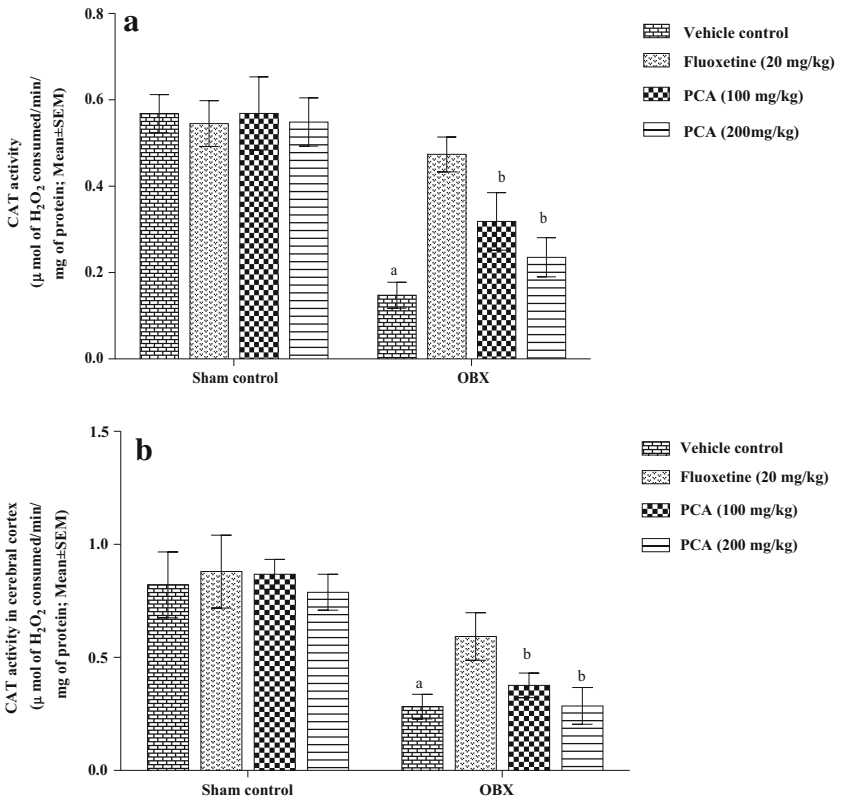

Fig. 12 Effect of PCA(100 and 200 mg/kg) or fluoxetine (20 mg/kg) on CAT activity in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

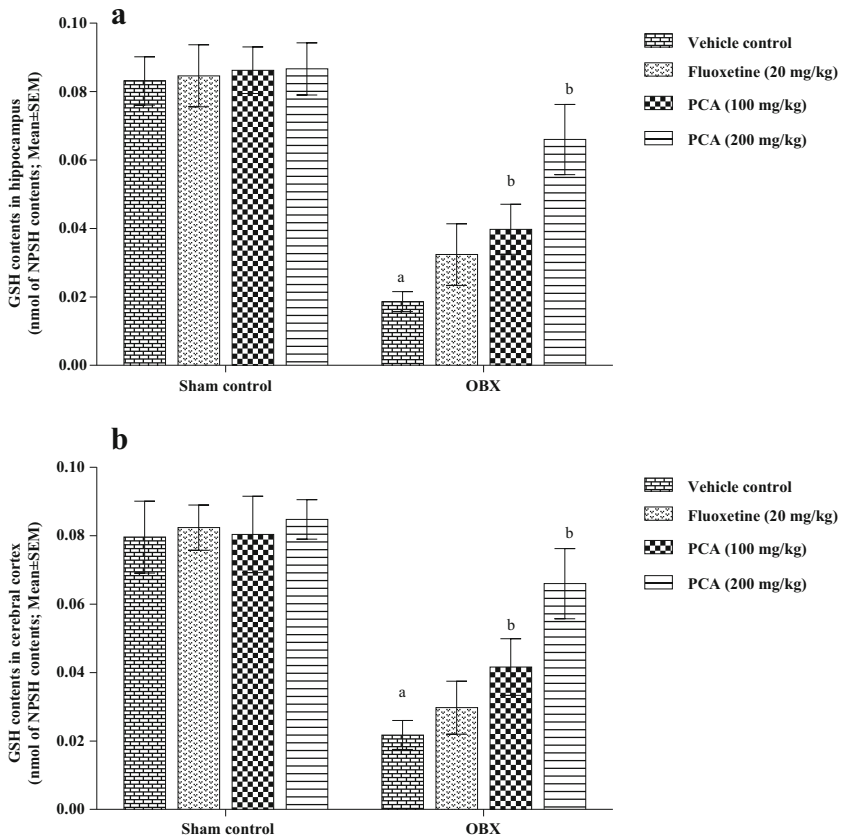

Fig. 13 Effect of PCA(100 and 200 mg/kg) or fluoxetine (20 mg/kg) on GSH content in hippocampus (**a**) and cerebral cortex (**b**) in sham and OBX rats. Experimental data expressed as mean ± SEM ($n = 8$), $^{a}p < 0.0001$ compared to sham control vehicle group, $^{b}p < 0.0001$ compared to OBX + vehicle control group

known to participate in the various neuropathological changes (Lovell et al. 1998) including mood related behavior. To validate such action, GSH treatment showed antidepressant potential in experimentally induced depressive like behavior (Rosa et al. 2013). The SOD and CAT activity involved in scavenging free radicals, thus, oxidative stress might results into disturbances in their activities. We in the present study showed that significant declined in CAT activity and GSH contents in hippocampus and cerebral cortex, PCA and fluoxetine treatment for 21 days significantly prevented alterations of these antioxidants. In addition, removal of olfactory bulb causes impaired endogenous antioxidants, CAT and GSH in the brain of OBX rats (Jindal et al. 2015a, b). The impaired antioxidants, CAT and GSH in OBX groups were found to return almost to normal with the PCA or fluoxetine treatments.

Therefore, we presumed herewith, scavenging and or neutralization free radicals mainly accomplished by phenolic group of PCA, it is possible that PCA due to its antioxidant nature participate in the antidepressant activity by scavenging free radicals which are subsequently abrogate oxidative stress and thereby improved the BDNF and antioxidant biomarkers and, attenuate neuroinflammation (reduced IL-6, and TNF-α). Our present data further substantiate with our earlier findings that PCA promote the improvement antioxidant marker levels/activities in ARS and OBX models of depression (Thakare et al. 2016, 2017a, b) which is subsequently responsible for antidepressant like activity.

As safety measure, PCA at 200 mg/kg did not induce any significant unwanted behavioral changes viz. excitement and/ convulsion with and itching, skin rashes, tremors etc. and thus found to be safe.

Conclusion

In conclusion, our data indicate that PCA mainly at 200 mg/kg exhibited antidepressant activity in OBX model by attenuation of oxidative stress through prevention of MDA formation, restoration of antioxidants, and augmentation of neurotransmitter, neurotrophic factor, and attenuation of proinflammatory cytokines IL-6, and TNF-α in hippocampus and cerebral cortex. However, further experiments are needed to warrant the antidepressant potential of PCA in mood disorders.

Acknowledgements Authors are grateful to Prof. M. N. Navale, Founder President, STES, Pune, and Dr. R.N. Kane, Principal, Sinhgad Institute of Pharmaceutical Sciences, Lonavala for providing necessary infrastructural facility, and support in the completion of present research work.

Compliance with ethical standards

Conflict of interests The authors declare that there are no conflicts of interest.

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