RESEARCH PAPER

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The effect of bupropion augmentation of minocycline in the treatment of depression

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The aim of the current study was to analyse the augmentation of minocycline with bupropion in treating depression. 'Saline' (10 ml/kg), 'minocycline *per se*' (25 mg/kg), 'minocycline *per se*' (50 mg/kg), 'bupropion *per se*' (5 mg/kg), 'bupropion *per se*' (10 mg/kg) and 'bupropion + minocycline' (5 mg/kg + 25 mg/kg each) were administered to mice via the intraperitoneal route. In the forced swim and tail suspension test, the immobility period was analysed after 30 min of the treatment. Monoamines like dopamine, norepinephrine and serotonin levels were analysed in brain areas such as the whole brain, hippocampus and cerebral cortex using an HPLC-fluorescence detector. Euthanasia of mice was performed 1 h after treatment. Comparison between the control group and combination therapy and other standard drug groups showed a significant decrease in immobility in both antidepressant animal models. The combination of bupropion and minocycline showed greater benefits with respect to a reduction in the immobility time period and enhancement of dopamine, serotonin, and norepinephrine levels in the cerebral cortex, hippocampus and the whole brain when compared to the monotherapy treated groups. Hence, the side effects may be reduced drastically through this combination by a reduction in the bupropion/minocycline dosage.

Key words: depression, monoamines, bupropion, minocycline, hippocampus, cerebral cortex

INTRODUCTION

Depression is often considered as a common mental disorder of the brain encompassing feelings of sadness, guilt, loss of appetite, tiredness, lack of concentration, lack of self-esteem, lack of interest or pleasure, and disturbed sleep. Depression is common worldwide, with an estimated 300 million people affected. Depression adds to the global burden of disease (according to the World Health Organization). The antidepressants available are associated with adverse effects and a slow onset of action, which basically restricts their effectiveness, and hence the prerequisites of the therapy of depression are still unmet (Mojtabai, 2009; Richelson, 2013). Augmentation therapy as a second-line treatment is preferred over first-line monotherapy because the latter is associated with a lower success rate (60-70%) (Thase et al., 2007). The therapeutic potential of the new generation drugs like venlafaxine (a dual reuptake inhibitor), reboxetine (a selective NE-reuptake inhibitor) or multiple receptor-acting drugs like bupropion, mirtazapine, trazodone and nefazodone may be positively influenced by decreased adverse reactions due to decreased affinities for other systems (Bondy, 2002). Studies have demonstrated that bupropion increases monoaminergic neurotransmission in a different manner compared to several other antidepressants. In rat and mouse studies, presynaptic (by affecting serotonin release or reuptake) and postsynaptic (by binding to serotonin receptors) alteration of serotonergic neurotransmission did not take place via bupropion and its metabolites such as threohydrobupropion, erythrohydrobupropion and hydroxybupropion, but it did reduce the reuptake of dopamine and norepinephrine into rat and mouse synaptosomes (sacs formed by presynaptic neuronal membranes

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that mimic presynaptic neuronal terminal activity) (Ferris and Cooper, 1993). It acts through a negative feedback mechanism mediated by an autoreceptor (Ascher et al., 1995). Norepinephrine and dopamine reuptake is inhibited by bupropion. Due to its dual action, it is considered a drug of interest in the treatment of depression (Stahl et al., 2004). Bupropion showed antidepressant effects at 10 mg/kg in mice (Kale and Addepalli, 2014).

Minocycline showed anti-depressant activity in different preclinical and preliminary clinical studies. Minocycline is known for its neuroprotective properties by directly promoting neurogenesis, being a broad spectrum tetracycline antibiotic (Soczynska et al., 2012). It also modulates immune processes, decreases oxidative stress, and increases neuron growth. A double-blind, randomised, placebo-controlled trial showed benefits of minocycline as an adjunct treatment option to reduce the dose of known antidepressants and thereby related side effects (Dean et al., 2017). A recent review made an overall observation of significant benefits in reducing the immobility time period and in anhedonia-based parameters with minocycline treatment. The report also suggested the need for considering the assessment of antidepressant activity of minocycline in additional clinical trials (Reis et al., 2019). Minocycline is known to reduce the immobility time period in mice at 50 mg/kg (Henry et al., 2008; Zheng et al., 2015). The evidence suggests the importance of considering minocycline and bupropion combinations in the treatment of depression. Therefore, the present study considered an analysis of minocycline and bupropion combination treatment in different antidepressant animal models.

METHODS

Animals

Male Swiss Albino mice, weighing in the range of 20-30 g, procured from Bombay Veterinary, Mumbai, were housed within the animal facility. The animals were housed in polycarbonate cages at room temperature (25±2 ºC) and humidity (50~60%) with a 12:12 hour light/dark cycle. The animals were acclimatised for a week before starting experimental work where they were given free access to standard food and water. A separate set of animals were used for the forced swim test (36 animals) and tail suspension test followed by brain monoamine estimation (36 animals). In total 72 animals were considered for three experiments i.e. forced swim test - 36 animals, and the remaining 36 for the tail suspension test followed by brain monoamine estimation). Each group present had 6 animals in the set. Prior approval from the Institutional Animal Ethical Committee (IAEC) (Approval no: CPCSEA/IAEC/SPTM/P-02/2016) was granted before conducting the studies.

Drug solutions and treatment

Administration of drugs was through the intraperitoneal route. Drug solutions were prepared using saline (0.9% w/v of NaCl) as a vehicle. Each animal received treatment 30 min prior to treatment with drugs. Animals were categorised into six groups. Saline (10 ml/kg) was given to the control group. Bupropion (10 mg/kg), minocycline (50 mg/kg), bupropion (5 mg/kg), minocycline (25 mg/kg) and a combination of bupropion (5 mg/kg) and minocycline (25 mg/kg) treatment were given to groups II, III, IV, V and VI, respectively.

Antidepressant models

Forced swim test (FST)

The forced swim test or behavioural despair test was conducted as reported by (Porsolt et al., 1978). On the first day, the mice underwent a "pre-test-session" for approximately 15 min. Each mouse was forced to swim for about 15 min in a plexiglass cylinder (12 cm internal diameter; 21 cm height) which contained water up to 10 cm from the bottom at 24±1°C. On the second day, each animal was treated 30 min prior to the test session and the swimming period was recorded for 6 min. For evaluation, the last 5 min session from the total 6 min of the recorded video was utilised. Mice were regarded as immobile when no limb movements were observed during floating or when only small or slight limb movements necessary for floating were seen. The immobility time was calculated as seconds denoted by mean ± SEM.

Tail suspension test (TST)

A set of aluminium stands measuring 58 cm (high) × 30 cm (wide) were used as apparatus during the TST study. At 58 cm height on a horizontally fixed aluminium rod, adhesive tape was utilised to suspend each mouse by its tail. The tape was placed approximately 1 cm from the tip of the tail (Vogel, 2008). Mice received treatment 30 min before undergoing the 5 min test session. Recorded video of each animal was evaluated for its immobility in seconds and denoted as mean ± SEM.

Estimation of monoamines in the brain by the HPLC with fluorescence detector (HPLC-FD) method

Monoamine level analysis in the brain was carried out in 3 areas i.e. the hippocampus, cerebral cortex, and the whole brain (whole brain=hippocampus

+ cerebral cortex + remaining brain tissue). It was conducted using the HPLC (Shimadzu, LC-2010C HT) with FD (RF-20A-prominence, Shimadzu) method (Lakshmana and Raju, 1997; Choudhary et al., 2013; Kale et al., 2014). Approximately 1 h before euthanasia, mice were treated. After performing the TST at a 30 min interval, mice heads were dropped in 0.1 M perchloric acid at the 60 min interval. Perchloric acid was maintained in an ice-cold environment. Weighing of the brain was done immediately after removal. The hippocampus, cerebral cortex, and the remaining part of the brain were carefully separated, and each part was weighed individually and then homogenisation was carried out in 2 ml of 0.1 M perchloric acid. This was maintained in an ice-cold environment. Later, centrifugation of the resulting mixture at around 8000 rpm (Eppendorf 5810 R, Rotor F-45-30-11) was carried out for 20 min at 4°C. The resulting supernatant was filtered through a 0.45 µm membrane and then eventually stored at -80°C until further analysis. Injection of the samples at room temperature was carried out carefully and on a reversed-phase analytical column, the chromatographic separation was observed (Waters, C18, 5 µm, 25 mm × 0.46 mm). Processing of the gathered data was done using LC Solution software. Preparation of the mobile phase was carried out using 0.1 M Phosphate buffer at pH 3.92, which was further adjusted with phosphoric acid, and eventually filtered through a 0.45 µm membrane filter. Mobile phase flow rate was adjusted to 0.8 ml/min. At an excitation wavelength of 280 nm and an emission wavelength of 315 nm, serotonin, dopamine and norepinephrine were spotted. By comparing the retention time of the sample and the standard the monoamine peaks were recognised. According to the area under the curve and by means of the respective straight-line equation, the concentration of each respective monoamine in the sample was analysed. The linearity observed for serotonin, dopamine and norepinephrine was in the range of 0.993–0.996. The resulting data was expressed as µg/g of the weight of tissue.

Statistical analysis

GraphPad Prism 5.0. was used for statistical analysis. One-way analysis of variance (ANOVA) followed by the Tukey test was used to compare the groups and to assess the associated statistical significance in the forced swim test and tail suspension test. Two-way ANOVA followed by the Bonferroni post-test was used to compare the groups and assess the associated statistical significance of brain monoamines. Representation of the data was as the mean ± SEM.

RESULTS

Forced swim test

The immobility period was reduced significantly in groups that received treatment of 'bupropion *per se*' (10 mg/kg) and 'bupropion + minocycline' (5 mg/kg + 25 mg/kg each), in comparison to the control group (Fig. 1; $F_{5,30}$=3.4, P=0.015).

Tail suspension test

The immobility time period was significantly decreased in groups treated with 'bupropion *per se*' (10 mg/kg) and 'bupropion + minocycline' (5 mg/kg

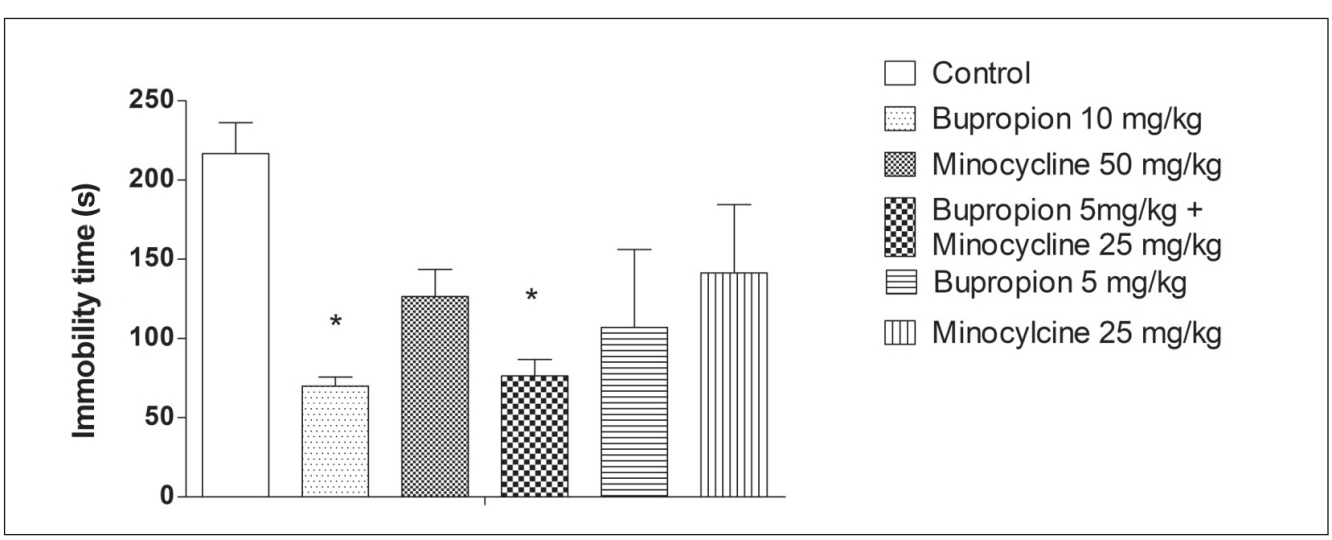

Fig. 1. Forced swim test. A significant difference is denoted by * - p<0.05, ** - p<0.01 *** - p<0.001 — as compared against the vehicle-treated group.

+ 25 mg/kg) when compared against the control group (Fig. 2; $F_{5,30}$=6.26, P=0.0004).

Estimation of the norepinephrine level

Hippocampus: A significant increase was observed in the levels of norepinephrine in 'bupropion *per se*' (10 mg/kg) and 'bupropion + minocycline' (5 mg/kg + 25 mg/kg), as compared to the control group (Fig. 3A). The combination treated group when compared with 'minocycline *per se*' (50 mg/kg) showed a significant rise in the levels of norepinephrine (Fig. 3A).

Cerebral cortex: Though the increase in norepinephrine levels was observed in 'minocycline *per se*' (50 mg/kg), 'minocycline *per se*' (25 mg/kg), and 'bupropion + minocycline' (5 mg/kg + 25 mg/kg), the difference was not statistically significant from the control group (Fig. 3A).

Whole brain: The combination treated group i.e. 'bupropion + minocycline' (5 mg/kg + 25 mg/kg) showed a significant increase in the levels of norepinephrine from the control group (Fig. 3A). The combination treated group also showed a significant increase in levels of norepinephrine from the 'bupropion *per se*' (5 mg/kg) treated group.

Estimation of dopamine level

Hippocampus: The treatment of drugs such as 'bupropion *per se*' (10 mg/kg) and the combination of 'bupropion + minocycline' (5 mg/kg + 25 mg/kg) showed a significant increase in the levels of dopamine, in comparison to the control group (Fig. 3B). The combination treated group showed a significant increase in the levels of dopamine, in comparison to the 'bupropion *per se*' (10 mg/kg) treated group, 'bupropion *per se*' (5 mg/kg) treated group, 'minocycline *per se*' (50 mg/kg) treated group and the 'minocycline *per se*' (25 mg/kg) treated group, separately (Fig. 3B).

Cerebral cortex: The combination treated group i.e. 'bupropion + minocycline' (5 mg/kg + 25 mg/kg) showed a significant increase in the levels of dopamine in cerebral cortices in comparison to the minocycline *per se*' (25 mg/kg) treated group (25 mg/kg) (Fig. 3B).

Whole brain: The levels of dopamine increased significantly in the 'bupropion *per se*' (10 mg/kg), 'minocycline *per se*' (50 mg/kg), and combination treated i.e. 'bupropion + minocycline' (5 mg/kg + 25 mg/kg) treated groups in comparison to the control group. The combination treated group showed a significant increase in the levels of dopamine, in comparison to the 'bupropion *per se*' (10 mg/kg) and 'bupropion *per se*' (5 mg/kg) treated group, 'minocycline *per se*' (50 mg/kg) treated group and 'minocycline *per se*' (25 mg/kg) treated group, separately (Fig. 3B).

Estimation of serotonin level

Hippocampus: The combination treated group i.e. 'bupropion + minocycline' (5 mg/kg + 25 mg/kg) showed a significant increase in the levels of serotonin in comparison to the control group (Fig. 3C). A significant increase in the levels of serotonin was also shown by the combination group in comparison to the 'bupropion *per se*' (10 mg/kg) treated group, 'bupropion *per se*' (5 mg/kg) treated group, 'minocycline *per se*' (50 mg/kg) treated group and 'minocycline *per se*' (25 mg/kg) treated group, separately (Fig. 3C).

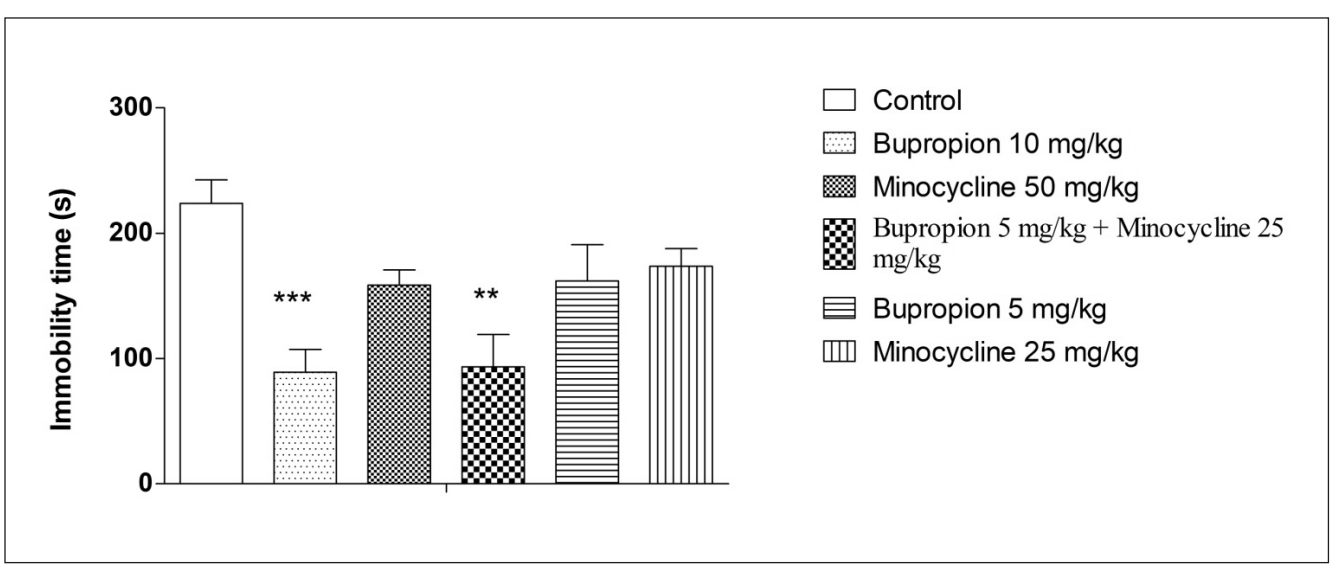

Fig. 2. Tail suspension test. A significant difference is denoted by * - p>0.05, ** - p<0.01 *** - p<0.001 — as compared against the vehicle treated group.

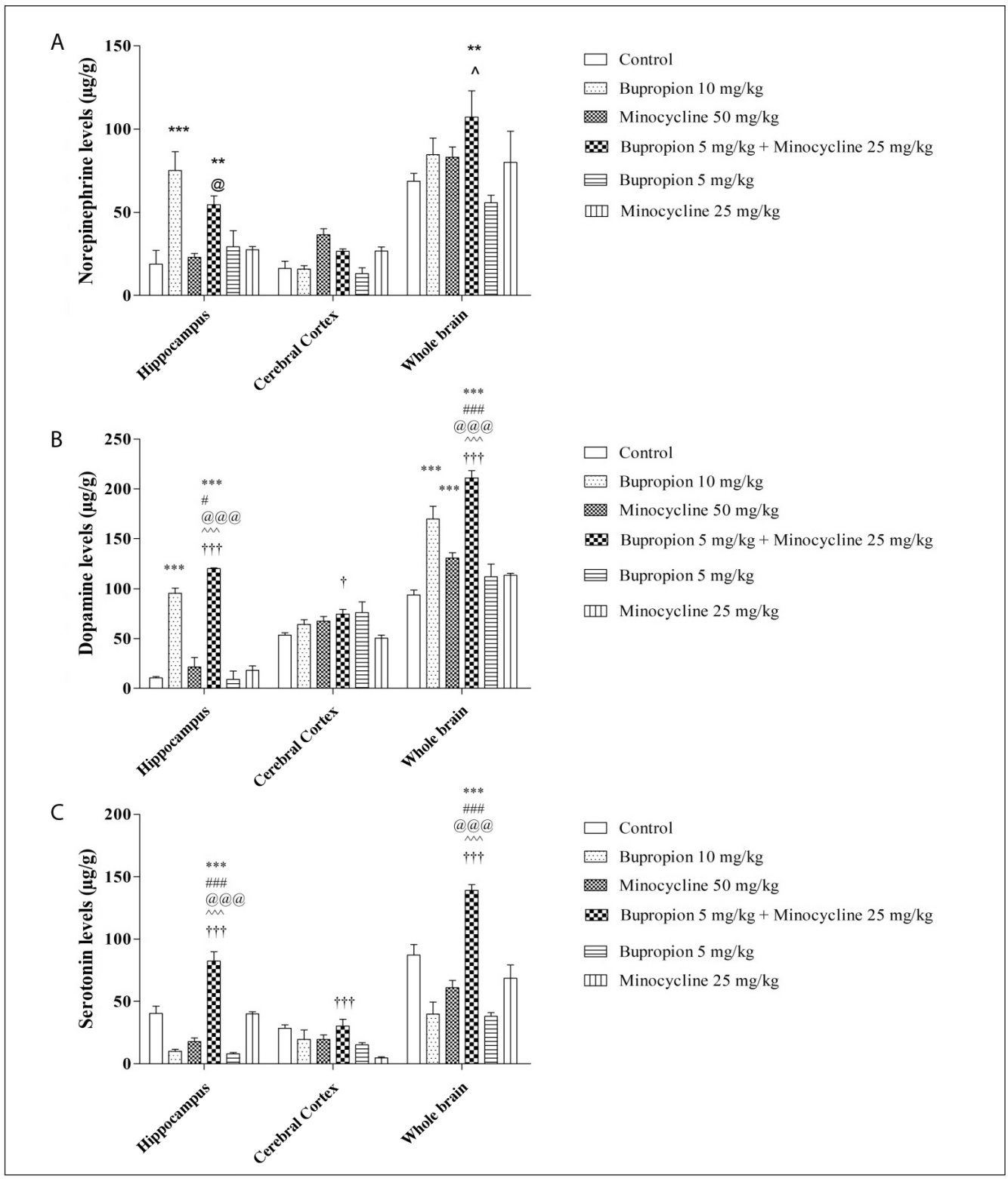

Fig. 3. Estimation of norepinephrine (A: Interaction – $F_{10,90}$=3.25, P=0.0013; Treatment – $F_{5,90}$=6.95, P<0.0001; Regions – $F_{2,90}$=82.31, P<0.0001), dopamine (B: Interaction – $F_{10,90}$=13.68, P<0.0001; Treatment – $F_{5,90}$=68.28, P<0.0001; Regions – $F_{2,90}$=311.88, P<0.0001) and serotonin (C: Interaction – $F_{10,90}$=9.85, P<0.0001; Treatment – $F_{5,90}$=53.42, P<0.0001; Regions – $F_{2,90}$=143.9, P<0.0001) levels in hippocampi, cerebral cortices and whole brain using HPLC–FD. A significant difference is denoted by * – p<0.05,** – p<0.01,*** – p<0.001 – as compared against the control group; # – p<0.05, ## – p<0.01, ### – p<0.001– as compared against the bupropion (10 mg/kg) treated group; @ – p<0.05, @@ – p<0.01, 244 – p<0.001 – as compared against the minocycline (50 mg/kg) treated group, ^ – p<0.05, ^^ – p<0.01, ^^^ – p<0.001 – as compared against the bupropion (5 mg/kg) treated group; † – p< 0.05, †† – p< 0.01, ††† – p<0.001 – as compared against the minocycline (25 mg/kg) treated group.

Cerebral cortex: A significant increase in dopamine levels was shown by the combination treated group i.e. 'bupropion + minocycline' (5 mg/kg + 25 mg/kg) in cerebral cortices in comparison to the 'minocycline *per se*' (25 mg/kg) treated group (Fig. 3C).

Whole brain: A significant increase in the levels of serotonin was observed in the combination treated group i.e. 'bupropion + minocycline' (5 mg/kg + 25 mg/kg) in comparison to the control group. The combination treated group also showed a significant increase in the levels of serotonin in comparison to the 'bupropion *per se*' (10 mg/kg) treated group, 'bupropion *per se*' (5 mg/kg) treated group, 'minocycline *per se*' (50 mg/kg) treated group and 'minocycline *per se*' (25 mg/kg) treated group, separately (Fig. 3C).

DISCUSSION

The antidepressant activity in the FST and TST is associated with the immobility period arising out of the inescapable condition. These are commonly employed tests of antidepressant activity and are also used to infer "depression-like" behaviour. In the TST, scores of immobility are taken while mice are suspended by their tails. Challenges related to thermoregulation are not encountered as water is not required in the TST (Cryan et al., 2005). Immobility in the FST or TST has been interpreted as an expression of behavioural despair or entrapment (Lucki et al., 2001; Cryan et al., 2005), and is reversed by the acute administration of almost all available antidepressants. This poses a problem for the model, since antidepressants restore mood in depressed humans only after many weeks of administration. Apart from this, the possibility of getting false positive results with drugs that enhance locomotor activity and a decrease in the immobility time period (e.g. amphetamine) is higher in the FST. The differentiation of the acute and chronic antidepressant effect is also not possible in the FST. Interestingly, the observed significant difference in performance and drug effects in rodents from different strains indicates that the FST is sensitive to genetic variation (Porsolt et al., 1978; López-Rubalcava et al., 2000). The high reliability of the FST and TST has also contributed to their use and they are both considered useful for investigating differences between different strains reactivity to stress. The FST and TST have been used extensively for this purpose, but the selectivity of these tests for monoamine-based mechanisms may limit their ability to detect novel mechanisms (Willner, 1990; Thiébot et al., 1992; Weiss and Kilts, 1995; Lucki, 1997). A recent study used the forced swim test and reported an interesting finding on the age-dependent changes in serotonin transport levels in the lateral septum and dorsal raphe of rats (Ulloa et al., 2014). Prepubertal rats had less stress-induced depressive responses, due to the higher availability of serotonin in the forced swim test, than pubertal (Ulloa et al., 2014). In animal studies, minocycline reduced immobility by increasing climbing and enhanced the anti-immobility effect of sub-threshold doses of desipramine in the forced swim test (an antidepressant-screening model) (Molina-Hernández et al., 2008). Deak et al. (2005) reported no change in climbing and swimming behaviour with minocycline. Amorim et al. (2017) showed changes in swimming behaviour with minocycline in diabetic mice. There are many preclinical studies reported by Reis et al. (2019) indicating an increase in locomotion with minocycline. Bupropion is also known to increase climbing behaviour in mice (Kale and Addepalli, 2014). Overall both drugs affect locomotion. There is a limitation in the present study due to the unavailability of swimming and climbing behaviour data to justify the immobility outcomes.

The antidepressant benefits of reducing the immobility time period with bupropion (10 mg/kg) treatment were in line with available reports (Kale and Addepalli, 2014). The unavailability of pre-clinical and clinical reports with the combination approach of minocycline and bupropion limits the discussion on benefits related to a reduction in immobility time period observed in the FST and TST, however, the same was the advantage of the present study. Though there was a reduction in the immobility time period observed with minocycline (50 mg/kg) treatment, it was not statistically significant. The observed reduction was in line with available reports (Henry et al., 2008; Zheng et al., 2015; Reis et al., 2019).

The benefits of bupropion with an increase in norepinephrine, dopamine, and serotonin levels in the considered brain regions were in line with the available reports (Piacentini et al., 2003; Kale and Addepalli, 2014). The increase in norepinephrine, dopamine, and serotonin levels with minocycline treatment were not statistically significant, however, the increment suggests benefits of minocycline treatment. Previous reports suggest a neuroprotective role of minocycline in terms of an attenuated decrease in norepinephrine, (Ahuja et al., 2008) dopamine, (Zhang et al., 2006a) and serotonin (Zhang et al., 2006b) levels.

Bupropion metabolism mainly happens through CYP2B6. Other enzymes such as CYP1A2, 2A6, 2C9, 2D6, and 2E1 also play a role in bupropion metabolism (Jefferson et al., 2005). Reports related to minocycline metabolism are sparsely available (Nelis and De Leenheer, 1982). CYP450 might be playing an important role in minocycline metabolism. An *in-vitro* study suggested a local inhibition of cytochrome p450 (Husain et al., 2017). Reports related to minocycline affecting enzymes that metabolise brain monoamines are scarcely available. Du et al. (2001)

reported no alteration in monoamine oxidase activity. Study of minocycline effects on other related enzymes could be a separate avenue for further research. There is a strong need to study the metabolism of minocycline in preclinical and clinical trials. In addition, the metabolism related interaction between minocycline and bupropion may add an advantage.

Overall, the bupropion plus minocycline treated group showed a better brain monoamine profile among the treated groups. There are no pre-clinical or clinical reports available with the consideration of the same combination approach. Bupropion is associated with one of its severe side-effects i.e. epileptic seizures with an increased dose. Other side-effects include confusion, agitation, hallucinations, and coma (Hubbard, 2005; Kara et al., 2013). This combination approach may enhance the therapeutic activity, i.e. the antidepressant effect, with a reduction in the associated side-effects, due to lowered doses, however, the present study's findings need further assessment in different preclinical and clinical conditions.

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