

Full Length Research Paper

Effect of nifedipine, imipramine and sertraline on the antidepressant-like actions of furosemide in forced swim (FST) and tail suspension (TST) tests models of depression in mice

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The objective of the study was to determine the effect of nifedipine, imipramine and sertraline on the acute and long-term antidepressant-like responses of furosemide in the forced swim (FST) and tail suspension (TST) tests in mice. Groups of mice of six in each group were treated for 30 days with Tween 80, furosemide (10 mg/kg) + nifedipine (5 mg/kg), furosemide (10 mg/kg) + imipramine (10 mg/kg) and furosemide (10 mg/kg) + sertraline (5 mg/kg), respectively. Experiments were done on day 1, 15 and 31 in the FST and TST. In the FST and TST, results showed that in the test groups, sertraline, imipramine and nifedipine enhanced the reduction of immobility of furosemide significantly when 15-days values were compared with acute values ($F(3, 20) = 14.21, P < 0.05, < 0.01$) and when 30-days values were compared with 15-days values ($F(3, 20) = 24.26, P < 0.05, < 0.01$). Duncan multiple range (DMR) post-hoc test showed that the furosemide + sertraline combination gave the most significant response. In conclusion, results show that the antidepressant-like action of furosemide is enhanced in the FST and TST models of depression in mice by co-administration of imipramine, sertraline and nifedipine.

Key words: Furosemide, nifedipine, imipramine, sertraline, forced swim test (FST), tail suspension test (TST), antidepressant.

INTRODUCTION

Emerging evidence indicates that antidepressants (ADs) exhibit their long-term clinical actions by their effects on neuroplasticity. There is now a great appreciation of the convergence of mechanisms between stress, depression and neuroplasticity (Pittenger and Duman, 2008; Racagni and Popoli, 2008).

Evidence from a substantial collection of research works implicates the loop diuretic, furosemide, as a neurochemical with neuroprotective effects that affects neuroplasticity and the biomarkers of depression. With its effects on monoamine transporters (Lucas et al., 2007),

brain renin angiotensin system (RAS) (Wright et al., 2002), phosphodiesterase (Marcus et al., 1978), furosemide may enhance cyclic adenosine monophosphate-cAMP-response element binding protein-brain derived neurotrophic factor (cAMP-CREB-BDNF) signalling. In the peripheral nervous system, the actions of furosemide may overlap with that of cAMP (Kreydiyyeh et al., 2000). Furosemide's anti-oxidant actions (Lahet et al., 2003), its effect on cytokines (Yuengsigul et al., 1999) and its attenuation of glutamate-mediated excitotoxicity (Sanchez-Gomez et al., 2011) enhances neuroplasticity. Its upregulation of brain-derived neurotrophic factor (BDNF) (Szekeres et al., 2010) which is deficient in depression, its enhancement of long-term potentiation (LTP) and neurogenesis being a KCC₂ blocker (Wang et al., 2006; Roitman et al., 2002)

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and favourable effects on Bcl-2/Bax ratio being a Bax blocker (Lin et al., 2005) enhances the neurotrophic signaling cascade of brain derived neurotrophic factor-early signal regulated kinase-cAMP-response element binding protein-B cell lymphoma 2 (BDNF-ERK 1/2-CREB-Bcl-2), an important mediator of neuroplasticity, which is impaired by stress (Trentani et al., 2002).

Recently, the induction of salt appetite by furosemide has been reported to activate the endogenous enkephalin system (Grondin et al., 2011) and could activate the cocaine-amphetamine regulated transcript (CART) peptides that have antidepressant effects (Peizhong, 2011).

The calcium channel blocker, nifedipine, enhances neuroplasticity through its anti-oxidant actions (Warner et al., 2004) and anti-excitotoxic actions in attenuating the effects of hyperglutamatergic excitotoxicity (Paul, 2001). Sustained Ca^{2+} increase generates reactive oxygen species (ROS) and the formation of ROS causes the disruption of Ca^{2+} homeostasis and cell death (Manzl et al., 2004). Nifedipine, by its actions on monoamine transporters (Padmanabhan et al., 2008) and phosphodiesterase (Moore et al., 1985) enhances cAMP-CREB-BDNF signaling (Sasaki et al., 2007), an important factor in neuroplasticity.

The aim of the study was to investigate the enhancement of the antidepressant-like responses of furosemide acutely, at day 15 and 31 by nifedipine, imipramine and sertraline in the FST and TST models of depression in mice.

MATERIALS AND METHODS

Consent for animal experimentation was obtained from the Animal Experimentation Ethical Committee of the University. Male albino mice (25 to 35 g) were used. Groups of mice, six in each group, were housed in the animal house in separate labelled metal cages for 14 days. Animals were housed at room temperature of 25 to 27°C in a 12-h light/dark cycle. They had access to food and water *ad libitum* and on the day of the test (days 1, 15 and 31), they were transported to the sound-proof testing area in their own cages.

All drugs were supplied by Sigma-Aldrich through Rovet Chemicals, Benin City, Nigeria. All the drugs were dissolved in 10% Tween 80 in distilled water because of furosemide's solubility. The mice were injected intraperitoneally (i.p.). The doses of drugs were chosen from previous studies (Eraly et al., 2006; Luszczki et al., 2003; Cryan et al., 2004; Kosuda et al., 1997; Hesdorffer et al., 2001; Mogilnicka et al., 1987).

Drug studies with the forced swimming test

The mice, after acclimatisation and care in the animal house were transported to the sound-proof testing area in their own labelled cages. They were allowed to adapt for one hour before the intraperitoneal (i.p.) injections after which there was a wait-period of 60 min before the tests of immobility.

A behavioural model of immobility first postulated by Porsolt et al. (1977) and named the behavioural despair model was used. In this model, mice were forced to swim for four minutes in a restricted space (a vertical glass cylinder of 27 cm height, 16.5 cm diameter and containing fresh tap water to a depth of 15 cm at 27°C) (Abel, 1994) from which escape is not possible. Following an initial period

of vigorous activity, the mice became helpless and adopted a characteristic immobile posture with no further attempt to engage in escape-related behaviour; and this reflects a state of despair or lowered mood. The period of on-set of immobility is timed by an observer unaware of the drug given and recorded. The mice were dried and kept warm after each test session.

In the experiment, the control group received 0.25 ml of 10% Tween 80 i.p. daily for 30 days. The second group received furosemide (10 mg/kg) + nifedipine (5 mg/kg) i.p. daily for 30 days. The third group received furosemide (10 mg/kg) + imipramine (10 mg/kg) i.p. daily for 30 days and the fourth group received furosemide (10 mg/kg) + sertraline (5 mg/kg) i.p. daily for 30 days. On the test days, (days 1, 15 and 31), doses remained unchanged except the furosemide dose which was increased to 100 mg/kg because this dose was found in a preliminary experiment to give the most significant antidepressant response. Doses below 25 mg/kg were found not to give antidepressant response. For the acute single drug experiment, separate groups of mice received 100 mg/kg of furosemide, 5 mg/kg of nifedipine, 10 mg/kg of imipramine and 5 mg/kg of sertraline i.p. before experimentation in the FST.

Drug studies with the tail suspension test

The mice, after acclimatisation and care in the animal house, were transported from the housing room to the sound-proof testing area in their own cages and allowed to adapt to the new environment for one hour before testing. The groups of mice were treated with the test compounds by intraperitoneal (i.p.) injection one hour prior to the test of immobility. In the TST first formulated by Steru in 1985, the mice were suspended on the edge of a shelf 58 cm above a table-top by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was recorded for a period of 5 min by an observer unaware of the test compound.

In the experiment, the control group received 0.25 ml of 10% Tween 80 i.p. daily for 30 days. The second group received furosemide (10 mg/kg) + nifedipine (5 mg/kg) i.p. daily for 30 days. The third group received furosemide (10 mg/kg) + imipramine (10 mg/kg) i.p. daily for 30 days and the fourth group received furosemide (10 mg/kg) + sertraline (5 mg/kg) i.p. daily for 30 days. On the test days, (days 1, 15 and 31), doses remained unchanged except the furosemide dose which was increased to 100 mg/kg because this dose was found in a preliminary experiment to give the most significant antidepressant response. Doses below 25 mg/kg were found not to give antidepressant response. For the acute single drug experiment, separate groups of mice received 100 mg/kg of furosemide i.p., 5 mg/kg of nifedipine i.p., 10 mg/kg of imipramine i.p. and 5 mg/kg of sertraline i.p. before experimentation in the TST.

Statistical analysis

In the results, data were presented as mean \pm SEM seconds. One-way ANOVA was applied to compare the means followed by DMR as post-hoc test. Mann-Whitney non-parametric test was used to compare only two groups. The difference was considered to be significant at $P < 0.05$, < 0.01 .

RESULTS

In the acute condition of the FST, it was 43.02 ± 1.04 s before the control mice became immobile. Still in the acute condition, the single agents of furosemide (100 mg/kg), nifedipine (5 mg/kg), imipramine (10 mg/kg) and

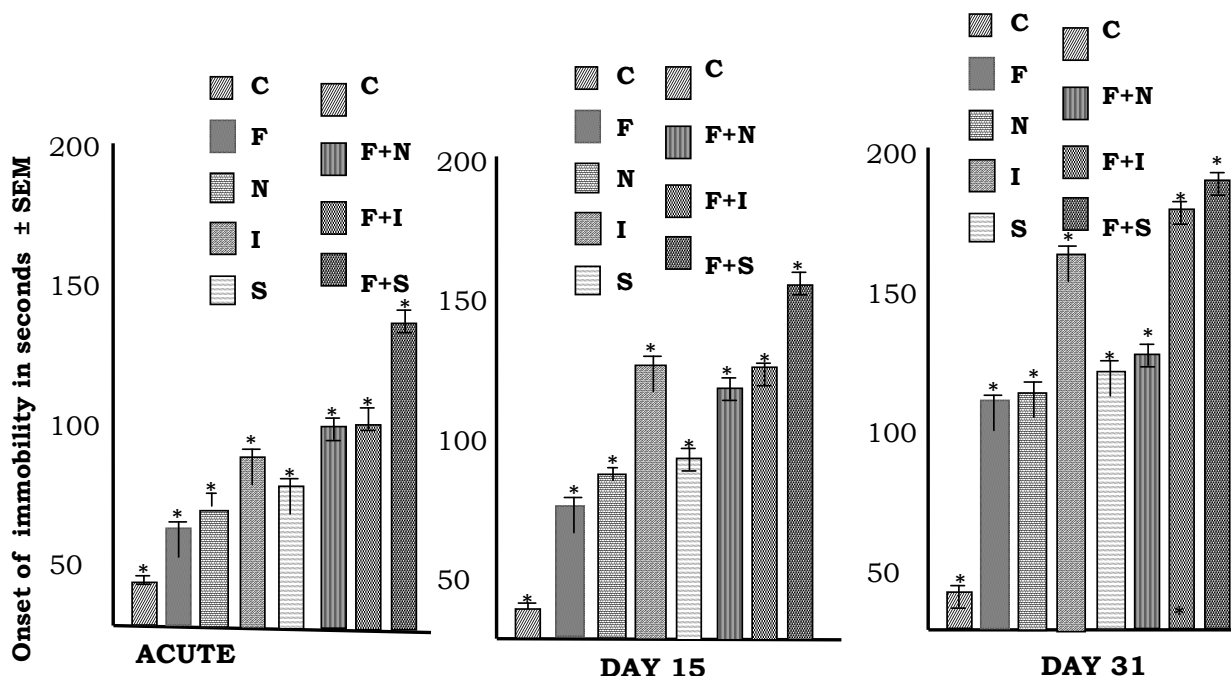


Figure 1. Effect of acute, 15 and 30-days administration of furosemide + nifedipine, furosemide + imipramine, furosemide + sertraline on onset of immobility period in the FST. Furosemide (10 mg/kg) + nifedipine (5 mg/kg); furosemide (10 mg/kg) + imipramine (10 mg/kg); Furosemide (10 mg/kg) + sertraline (5 mg/kg) were administered to mice for 30 days. Experiments were done on days 1, 15 and 31 in the FST; drug doses remained unchanged except for furosemide which was increased to 100 mg/kg. The drug combinations enhanced responses significantly when 15-day values were compared with acute values ($F(3, 20) = 15.47$; $P < 0.05$; < 0.01); and when 30-day values were compared with 15-day values ($F(3, 20) = 10.53$, ($P < 0.05$; < 0.01). Post-hoc DMR tests showed the furosemide + sertraline response as the most significant.

sertraline (5 mg/kg) prolonged the onset of immobility of mice to 63.78 ± 1.08 s, 70.86 ± 0.55 s, 84.43 ± 1.13 s and 75.30 ± 1.11 s, respectively; and the values were significant ($P < 0.01$) when compared with controls. At day 15, it became 39.40 ± 1.35 , 73.98 ± 1.52 , 88.33 ± 0.08 , 121.05 ± 1.90 and 91.94 ± 1.05 s, respectively; and at day 31, it became 41.92 ± 1.57 , 110.39 ± 1.53 , 112.62 ± 0.90 , 168.64 ± 2.00 and 114.10 ± 0.63 s, respectively (Figure 1).

In the acute condition of the FST (Figure 1), the furosemide (10 mg/kg) + nifedipine (5 mg/kg) combination prolonged the period of onset of immobility in the FST to 79.04 ± 1.02 s, and this became 101.14 ± 3.68 s and 114.10 ± 0.63 s at 15 and 31 days, respectively. The furosemide (10 mg/kg) + imipramine (10 mg/kg) combination gave 79.25 ± 1.19 s acutely, 105.50 ± 4.36 s at days 15 and 170.79 ± 0.50 s at day 31. The furosemide (10 mg/kg) + sertraline (5 mg/kg) combination gave 125.90 ± 1.33 s acutely, 150.00 ± 2.00 s at day 15 and 177.90 ± 2.89 s at day 31. The drug combinations significantly enhanced responses when the subchronic values were compared with the acute values ($F(3, 20) = 14.21$, $P < 0.05$, < 0.01), and when chronic values were compared with subchronic values ($F(3, 20) = 24.26$, $P < 0.05$, < 0.01). Post-hoc DMR test showed that the furosemide + sertraline combination gave the most significant

response. This combination displayed synergy because the values at days 15 and 31 were more than the sum of the individual acute values. The furosemide + imipramine combination only showed synergistic response on day 31 (after chronic administration).

In the acute condition of the TST, the duration of immobility was 211.72 ± 4.39 s for the control mice. Still in the same condition, the single agents of furosemide (100 mg/kg), nifedipine (5 mg/kg), imipramine (10 mg/kg) and sertraline (5 mg/kg) reduced the period of immobility of mice to 132.65 ± 2.38 , 130.81 ± 4.89 , 101.10 ± 4.89 and 110.10 ± 4.89 s, respectively; and the values were significant ($P < 0.01$) when compared with the controls. At day 15, duration of immobility was 211.72 ± 4.39 s for control, 117.18 ± 2.45 s for the furosemide group, 105.58 ± 3.11 s for nifedipine, 88.25 ± 4.34 s for imipramine and 103.28 ± 3.20 s for sertraline. At day 31, this became 220.25 ± 1.52 , 93.48 ± 1.44 , 85.05 ± 0.73 , 79.40 ± 1.00 , 81.67 ± 1.02 s, respectively (Figure 2).

In the acute condition of the TST (Figure 2), the furosemide (10 mg/kg) + nifedipine (5 mg/kg) combination reduced the period of immobility in the TST to 108.62 ± 5.40 s, and this became 101.11 ± 5.79 and 100.46 ± 0.42 s at 15 and 31 days, respectively. The furosemide (10 mg/kg) + imipramine (10 mg/kg) combination gave 207.83 ± 6.92 s acutely, 83.42 ± 1.01 s

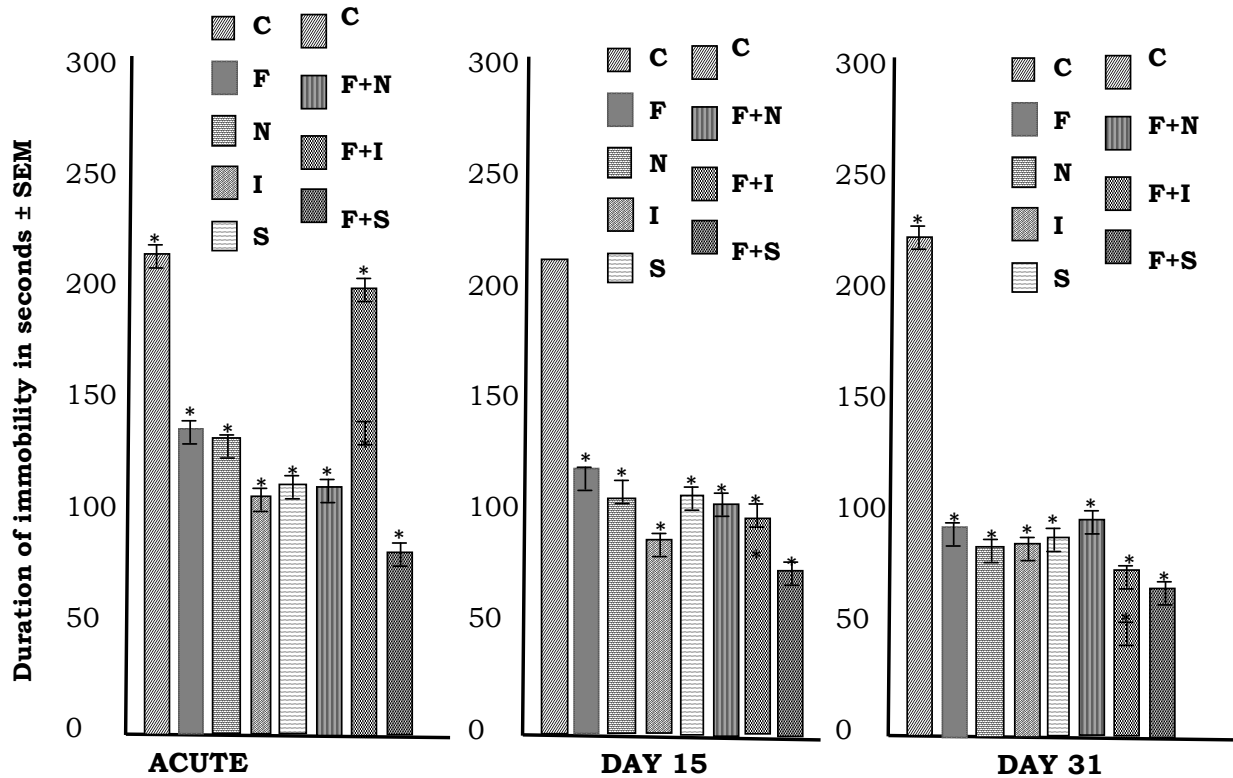


Figure 2. Effect of acute, 15 and 30-day administration of furosemide + nifedipine, furosemide + imipramine, furosemide + sertraline on duration of immobility in the TST. Furosemide (10 mg/kg) + nifedipine (5 mg/kg); furosemide (10 mg/kg) + imipramine (10 mg/kg); Furosemide (10 mg/kg) + sertraline (5 mg/kg) were administered to mice for 30 days. Experiments were done on days 1, 15 and 31 in the TST; drug doses remained unchanged except for furosemide which was increased to 100 mg/kg. Values were expressed in seconds \pm SEM (vertical bars). The drug combinations (furosemide + imipramine) and (furosemide + sertraline) reduced the duration of immobility significantly when 15-day values were compared with acute values ($F(3, 20) = 9.70$; $P < 0.05$, < 0.01); and when 30-day values were compared with 15-day values ($F(3, 20) = 16.42$; $P < 0.05$, < 0.01). Post-hoc DMR tests showed that the furosemide + sertraline (F+S) combination produced the most significant response.

at day 15 and 77.90 ± 0.73 s at day 31. The furosemide (10 mg/kg) + sertraline (5 mg/kg) combination gave 79.39 ± 7.50 s acutely, 77.80 ± 1.31 s at day 15 and 61.01 ± 0.88 s at day 31. The drug combinations significantly enhanced responses when the subchronic values were compared with the acute values ($F(3, 20) = 9.70$, $P < 0.05$, < 0.01), and when chronic values were compared with subchronic values ($F(3, 20) = 16.42$, $P < 0.05$, < 0.01). Post-hoc DMR test showed that the furosemide + sertraline combination gave the most significant response. In the acute condition, the furosemide + imipramine combination did not significantly reduce the duration of immobility when compared with the control values.

DISCUSSION

The present results are in line with previous reports (Mogilnicka et al., 1987) that nifedipine possess antidepressant actions in rodents. Results also demonstrate

that furosemide has antidepressant-like effects in mice and that the combinations of furosemide + nifedipine, furosemide + imipramine and furosemide + sertraline enhanced the antidepressant-like effects of furosemide in the FST and TST models of depression in mice on days 15 and 31 significantly different from acute values ($P < 0.01$). The furosemide + sertraline combination displayed synergy on days 15 and 31. While acute combination of furosemide + imipramine displayed antagonism, 15-day administration of furosemide + imipramine showed enhancement of response over acute values and 30-day administration showed synergy. Furosemide + nifedipine combination displayed only enhancement of response over acute values in the FST. Furosemide could enhance its acute antidepressant-like actions by enhancing cAMP-CREB-BDNF signaling. It could enhance this downstream signalling by its effect on angiotensin (Charron et al., 2002), its anti-oxidant effects (Lahet et al, 2003), its effect on adenosine (O'Connor et al., 1991), phosphodiesterase (Marcus et al., 1978) and cytokines (Yuengsigul et al., 1999). Its effect in down-regulating

the dopamine transporter (Lucas et al., 2007) and norepinephrine transporter (Habecker et al., 2003) could also enhance cAMP-CREB-BDNF signalling. Furosemide antagonizes GABAergic transmission (Mantovani et al., 2011) and chronic furosemide administration upregulates BDNF mRNA (Szekeres et al., 2010) and these mechanisms could explain the antidepressant-like effects of furosemide demonstrated in these experiments.

Additionally, furosemide's anti-apoptotic effect as a Bax blocker (Lin et al., 2005), its antioxidant status and overlapping role with Bcl-2 (Wang et al., 2007), could enhance BDNF-ERK1/2-CREB-MAP kinase-Bcl-2 signalling, the dysregulation of which is a key mechanism by which prolonged stress induces atrophy of select vulnerable neuronal subpopulations (Trentani et al., 2002).

With its effect as a KCC_2 down-regulator (Wang et al., 2006), an attribute it shares with BDNF (Wardle and Poo, 2003), furosemide may enhance CREB-BDNF signaling, enhance LTP and induce neurogenesis (Roitman et al., 2002), important biomarkers of antidepressant effect.

The synergistic effect (furosemide + sertraline) displayed from our experiments over the furosemide + imipramine combination may be explained at a downstream level involving BDNF since furosemide upregulates BDNF production which can synergise with serotonergic agents (Deltheil et al., 2009) and secondly, the serotonergic system has been found (Kozisek et al., 2004) to mature earlier than the noradrenergic system and desipramine, the metabolite of imipramine has been observed not to increase BDNF and TrkB levels in juvenile rats which were used in this study.

The present results show that while acute furosemide administration antagonizes imipramine, implicating a significant cholinergic signalling for the acute effects of imipramine, 15-day imipramine administration is not antagonized by furosemide, while 30-day furosemide and imipramine administration have a synergistic effect in reducing immobility in the FST and TST in mice. It has been reported, however (Vaillant, 1969) that discrete cholinergic mechanisms do not play an important role in endogenous depression.

Results show that nifedipine enhances the effect of furosemide in reducing immobility of mice in the FST and TST and the FST appeared to be more sensitive to the effects of this combination. Both could down-regulate the monoamine transporters to enhance cAMP-CREB-BDNF signaling and both could enhance BDNF-CREB-ERK1/2-CREB-MAP kinase-Bcl-2 signalling by attenuating the effects of hyperglutamatergic activity which can cause sustained Ca^{2+} increase to generate reactive oxygen species that may lead to disruption of Ca^{2+} homeostasis and cell death (Manzl et al., 2004; Sanchez-Gomez et al., 2011).

In conclusion, 15 and 30-day administration of nifedipine, imipramine and sertraline facilitates the effect of 15 and 30-day administration of furosemide in reducing

immobility of mice in the FST and TST models of depression in mice, while the effect of acute administration of imipramine in the reduction of immobility is antagonized by acute administration of furosemide.

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Abbreviations

SEM, Standard error of mean; **SSRI**, selective serotonin reuptake inhibitor; **TCA**, tricyclic antidepressant; **CCB**, calcium channel blocker; **SERT**, serotonin transporter; **NET**, nor-epinephrine transporter; **DAT**, dopamine transporter; **NKCC1**, isoform 1 of the sodium-potassium-chloride co-transporter; **KCC2**, isoform 2 of the potassium-chloride co-transporter; **GABA**, gamma-amino butyric acid; **cAMP**, cyclic adenosine monophosphate; **CREB**, cAMP-response element binding protein; **BDNF**, brain-derived neurotrophic factor; **ERK 1/2 (Classical MAP Kinases)**, extracellular signal-regulated kinase, isoform 1/2; **MAP**, mitogen activated protein kinase; **FST**, forced swim test; **TST**, tail suspension test.

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