

Nifedipine enhances the antidepressant response of sertraline and imipramine

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Depression, a bewildering and burdensome illness, is one of the commonest psychiatric diseases. It is expected to be the second leading contributor to Global Disease Burden by 2020. The objective of the study was to determine the effect of nifedipine on the responses of imipramine, sertraline and furosemide in the forced swim test (FST) and tail suspension test (TST) in mice. Groups of mice were housed in individual metal cages for control, nifedipine + imipramine, nifedipine + sertraline and nifedipine + furosemide groups and were treated for 30 days with placebo, nifedipine (5mg/kg) + imipramine (10mg/kg), nifedipine (5mg/kg) + sertraline (10mg/kg), nifedipine (5mg/kg) + furosemide (10mg/kg) respectively. Experiments were done on Day 1 (acute), 15 (subacute) and 31 (subchronic) when drug doses were not changed except for furosemide which became 100mg/kg. In the FST and also in the TST, results showed that in the test groups, nifedipine potentiated the reduction of the period of immobility of imipramine, sertraline and furosemide significantly when subacute values were compared to acute values ($F(3, 20) = 15.47, P < 0.05, < 0.01$) and when subchronic values were compared to subacute values ($F(3, 20) = 10.53, P < 0.05, < 0.01$). DMR post-hoc test showed the nifedipine + imipramine combination as giving the most significant response. In conclusion, results show that subchronic nifedipine administration significantly potentiated the reduction of immobility in the FST and TST of subchronically-administered imipramine, sertraline and furosemide.

Keywords: Nifedipine, Imipramine, Sertraline, Furosemide, FST, TST, Antidepressant.

INTRODUCTION

Due to the down-stream neuroadaptive changes, antidepressants (Ads) currently in use have a delayed onset of action. There is a correlation between immediate early gene induction such as the activity-regulated cytoskeleton associated protein (Arc) expression in dendritic spines and the onset of synaptogenesis (Wang and Pickel, 2004). There is also now a greater appreciation of the convergence of mechanisms between stress, depression and factors that determine neuroplasticity (Pittenger and Duman, 2008; Racagni and Popoli, 2008). In depression, there is reduced level of the activity-regulated cytoskeleton associated protein (Arc) mRNA (Bramham et al., 2010) and antidepressant drug

treatment induces Arc gene expression in the brain (Yang et al., 2013; Duman and Li, 2012; Li et al., 2010; Pei et al., 2003). Through the upregulation of brain-derived neurotrophic factor (BDNF), the selective serotonin reuptake inhibitor (SSRI), sertraline which may act as selective brain steroidogenic stimulant (SBSS) (Nin et al., 2011) and imipramine (Chen et al., 2010) enhance synaptogenesis. Serotonin 1A receptor-mediated signaling through early signal-regulated kinase (ERK) is essential for normal synaptogenesis in neonatal mouse hippocampus (Mogha et al., 2012).

The calcium channel blocker, nifedipine, may enhance neuroplasticity through its anti-oxidant actions (Allanone et al., 2005; Godfraind et al., 2005; Warner et al., 2004), anti-apoptotic effects (Ares et al., 1997), antagonistic effect on cytokines (Lu et al., 2008) and anti-excitotoxic actions in attenuating the effects of hyperglutamatergic excitotoxicity (Paul, 2001). Sustained Ca^{2+} increase gen-

erates 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 inhibitory actions on monoamine transporters (Padmanabhan et al., 2008; Mogilnicka et al., 1987), GABA (Das et al., 2004), adenosine (Bartup et al., 1990) and phosphodiesterase (Moore et al., 1985) enhances cAMP-CREB-BDNF signaling (Sasaki et al., 2007), an important factor in neuroplasticity. Nifedipine's ability to decrease KCC_2 mRNA (Galanopoulou and Moshe, 2003) may contribute in preventing falls in long-term potentiation.

Nifedipine, a protein kinase C (PKC) inhibitor (Allanone et al., 2005), may also enhance synaptogenesis (Liao et al., 2008) and facilitate long-term potentiation (LTP) due to reduction of the Ca^{2+} -dependent K^+ -mediated after-hyperpolarisation (AHP) (Norris et al., 1998). It may not affect brain-derived neurotrophic factor-induced upregulation of the activity-regulated cytoskeleton-associated protein (Arc) (Zheng et al., 2009) and may lead to decreased activation of mammalian target of rapamycin complex₁ (mTORC₁) (Alexandrescu et al., 2010).

Accumulating body of evidence implicates the loop diuretic, furosemide, as a neurochemical with neuroprotective effects that affects neuroplasticity and the biomarkers of depression. By its effects on monoamine transporters (Lucas et al., 2007), brain signal angiotensin system (RAS) (Wright et al., 2002), GABA (Mantovani et al., 2011), phosphodiesterase (Marcus et al., 1978), furosemide may enhance cAMP-CREB-BDNF signaling. 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 (Yuengsrigul et al., 1999), its attenuation of glutamate-mediated excitotoxicity (Sanchez-Gomez et al., 2011) enhance 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 KCC_2 blocker (Wang et al., 2006, Roitman et al., 2002) and favourable effects on Bcl-2/Bax ratio being a Bax blocker (Lin et al., 2005) enhances the neurotrophic signaling cascade of BDNF-ERK 1/2-CREB-Bcl-2, an important mediator of neuroplasticity, which is impaired by stress (Trentani et al., 2002). Both furosemide (Liedtke et al., 2011) and BDNF (Bramham et al., 2010) may up-regulate the immediate early gene, Arc, which enables stable long-term potentiation and promotes neuronal survival. BDNF also induces the mammalian target of rapamycin-(mTOR)-dependent local activation of translation machinery and protein synthesis in neuronal dendrites (Takei et al., 2004; Slipczuk et al., 2009). Bramham et al. (2010) noted that, unlike Arc, mTOR signaling is dispensable for LTP maintenance and for enhanced initiation.

Recently, the induction of salt appetite by furosemide

has been reported to activate the endogenous enkephalin system (Grondin et al., 2011) and may activate release of the cocaine-amphetamine regulated transcript (CART) peptides that have antidepressant effects (Peizhong, 2011).

The aim of the study was to evaluate the effects of nifedipine on the antidepressant responses of imipramine and sertraline in the TST and FST models of depression in mice which has not been reported.

MATERIALS AND METHODS

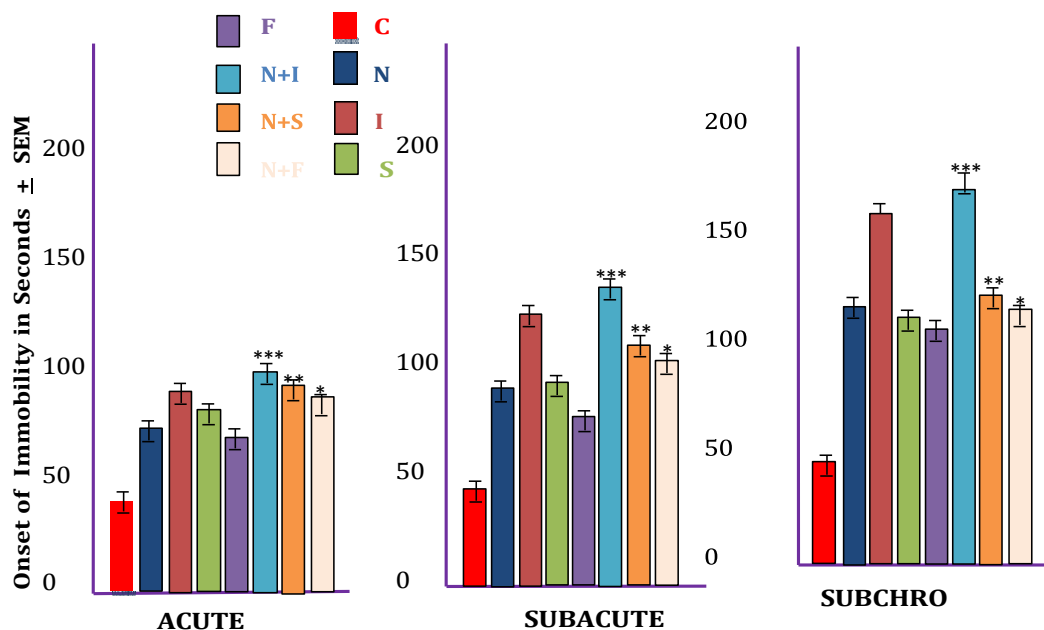
Male albino mice (25g-35g) were used. Groups of mice were housed in the departmental laboratory in separate labelled metal cages for 30 days. Animals were housed at room temperature of 25°-27°C in a 12-hour light/dark cycle. They were allowed food and water *ad libitum*, and on the day of the test (Days 1, 15 and 31) 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.). None of the animal groups exhibited hyperlocomotion or stereotypy in their home-cages which is the most basic assessment of locomotion. The doses of drugs were chosen from previous studies (Lundy et al., 2003; Eraly et al., 2006; Luszczyk 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

Male albino mice (25g-35g), after acclimatisation and care in the departmental laboratory were transported to the sound-proof testing area in their own labelled cages. They were allowed to adapt for one hour before the intraperitoneal injections after which there was a wait – period of 60 minutes before the tests of immobility.

Mice were forced to swim for four minutes in a vertical glass cylinder of height 27cm, diameter 16.5cm and containing fresh tap water to a depth of 15cm at 27°C. The mice were dried and kept warm after each test session. A behavioural model of immobility first postulated by Porsolt (Porsolt et al., 1977) and named the behavioural despair model was used. In this model, mice are forced to swim in a restricted space from which escape is not possible. Following an initial period of vigorous activity, the mice become helpless and adopt 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.

In the experiment, the control group received 0.25 ml



Values are expressed in seconds $\pm$ SEM (Vertical Bars). The drug combinations prolonged the period of onset of immobility significantly when subacute values are compared to acute values ($F(3, 20) = 15.47$; $P < 0.05$, < 0.01) and to values obtained with the single drugs; and when subchronic values are compared to subacute values ($F(3, 20) = 10.53$; $P < 0.05$, < 0.01). Post-hoc DMR tests showed the nifedipine + imipramine (N + I) combination produced the most significant response and the order of magnitude of response was $N + I > N + S > N + F$.

Figure 1. Effect of acute, subacute and subchronic administration of nifedipine + imipramine, nifedipine + sertraline, nifedipine + furosemide on onset of period of immobility in the fst.

of Tween 80 i.p. daily for 30 days. The second group received nifedipine (5mg/kg) + imipramine (10mg/kg) i.p. daily for 30 days. The third group received nifedipine (5mg/kg) + sertraline (5mg/kg) i.p. daily for 30 days and the fourth group received nifedipine (5mg/kg) + furosemide (10mg/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 100mg/kg.

Drug studies with the tail suspension test

Male albino mice weighing 25-35g were used. They were housed in the departmental laboratory in labelled metal cages for 30 days prior to testing, in a 12-hour light/dark cycle with food and water freely available. The mice 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 (Steru et al., 1985), the mice are suspended on the edge of a shelf 58cm above a table-top by adhesive tape placed approximately 1cm from the tip of the tail. The duration of immobility is recorded for a period of 5 minutes by an observer unaware of the test compound.

minutes by an observer unaware of the test compound.

In the experiment, the control group received 0.25ml of Tween 80 i.p. daily for 30 days. The second group received nifedipine (5mg/kg) + imipramine (10mg/kg) i.p. daily for 30 days. The third group received nifedipine (5mg/kg) + sertraline (5mg/kg) i.p. daily for 30 days and the fourth group received nifedipine (5mg/kg) + furosemide (10mg/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 100mg/kg.

Statistical analysis

One-way ANOVA was applied followed by DMR as post-hoc test. Mann-Whitney non-parametric test was used when comparing the means of two samples. The difference was considered to be significant at $P < 0.05$, < 0.01 .

RESULTS

Acutely in the FST (Figure 1), the nifedipine (5mg/kg) + (imipramine (10mg/kg) combination prolonged the period of onset of immobility in the FST to 92.80 ± 1.00 seconds,

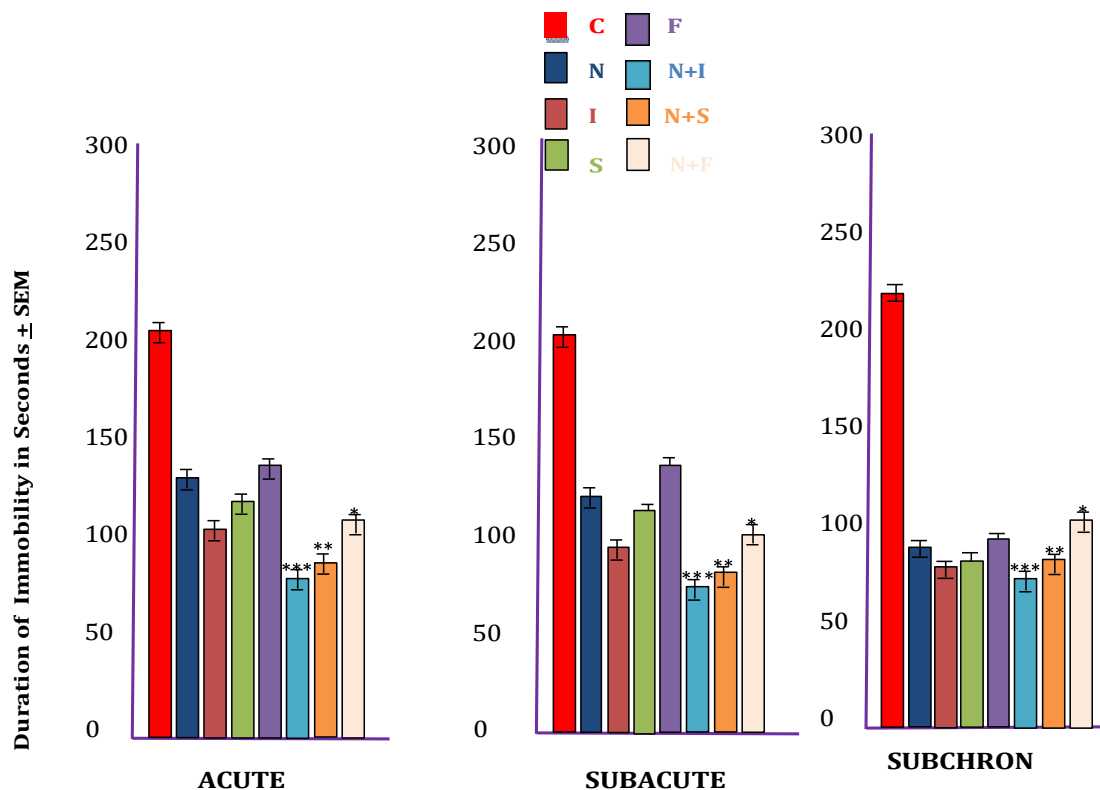


Figure 2. Effect of acute, subacute and subchronic administration of Nifedipine + Imipramine, Nifedipine + Sertraline, Nifedipine + Furosemide on duration of immobility in the TST.

and this became 136.13 ± 1.61 seconds and 171.45 ± 2.41 seconds at 15 and 31 days respectively. The nifedipine (5mg/kg) + (sertraline (5mg/kg) combination gave 90.20 ± 0.90 seconds acutely, 105.00 ± 0.50 seconds at Day 15 and 119.85 ± 1.47 seconds at Day 31. The nifedipine (5mg/kg) + (furosemide (100mg/kg) combination gave 79.04 ± 1.02 seconds acutely, 101.14 ± 3.68 seconds at Day 15 and 114.10 ± 0.63 seconds at Day 31. The drug combinations significantly enhanced responses when the subacute values are compared to the acute values ($F(3,20) = 15.47$, $P < 0.05$, < 0.01) and to the values obtained with the individual drugs, and when subchronic values are compared to subacute values ($F(3, 20) = 10.53$, $P < 0.05$, < 0.01). Post-hoc DMR test showed the nifedipine + imipramine combination gave the most significant response. This combination displayed synergy because the value at 31 days was more than the sum of the individual acute values. Acutely in the TST (Figure 2), the nifedipine (5mg/kg) + imipramine (10mg/kg) combination reduced the duration of immobility in the TST to 87.50 ± 4.60 seconds, and this became 79.31 ± 3.70 seconds and 74.62 ± 1.04 seconds at 15 and 31 days respectively. The nifedipine (5mg/kg) + sertraline (5mg/kg) combination gave 93.17 ± 0.50 seconds acutely, 85.10 ± 0.50 seconds at Day 15 and 78.16 ± 2.48 seconds at Day 31. The nifedipine (5mg/kg) + furosemide (100mg/kg)

combination gave 108.62 ± 5.40 seconds acutely, 101.10 ± 5.79 seconds at Day 15 and 100.10 ± 0.42 seconds at Day 31. The drug combinations significantly enhanced responses when the subacute values are compared to the acute values ($F(3, 20) = 18.08$, $P < 0.05$, < 0.01) and to the values obtained with the individual drugs, and when subchronic values are compared to subacute values ($F(3, 20) = 26.28$, $P < 0.05$, < 0.01). Post-hoc DMR test showed the nifedipine + imipramine combination gave the most significant response. The order of magnitude of response was nifedipine + imipramine > nifedipine + sertraline > nifedipine + furosemide.

DISCUSSION

The results show that the drug combinations, nifedipine + imipramine, nifedipine + sertraline and nifedipine + furosemide reduced immobility significantly in the FST and TST models of depression in mice, and their effects were enhanced after 15 days and after 31 days ($P < 0.05$, < 0.01). The DMR post-hoc test showed that the nifedipine + imipramine combination gave the most significant response; and the nifedipine + imipramine combination demonstrated synergy while the nifedipine + sertraline and nifedipine + furosemide combinations dem-

onstrated enhancement after 30 days of treatment. Both in the FST and TST, the order of potency was nifedipine + imipramine > nifedipine + sertraline > nifedipine + furosemide.

Calcium channel blockers (CCBs) have antidepressant-like properties (Biala, 1998; Mogilnicka et al., 1987) and its combination with imipramine, sertraline or with furosemide may affect more than one signalling pathway or affect sequential steps in a pathway to produce synergistic effects. We have shown in a separate report that while nifedipine mediates serotonergic signalling as previously reported (Tazi et al., 1992), furosemide mediates noradrenergic signalling and these two signalling pathways could synergise as happened in our experiments.

Why nifedipine + imipramine combination is more efficacious than nifedipine + sertraline combination is not readily explainable but it may involve interaction at the reuptake sites and relative effect on calcium currents. Nifedipine acts on the cell membrane to block the movements of calcium through the voltage-dependent and receptor-operated calcium channels involved in glutamate-mediated excitotoxicity (Griffiths et al., 1998; Lerea et al., 1992; Nakatsu et al., 2006; Orallo et al., 1991) while imipramine also has the same effect by inhibiting the influx of calcium through both the receptor-operated and voltage-gated calcium channels (Shim et al., 1999). Griffiths et al. (1998) had shown that, following exposure to excitotoxic doses of glutamate, calcium influx via L-type voltage sensitive calcium channels (VSCC) specifically maintain the excitotoxicity. So it is not surprising if nifedipine + imipramine combination synergises as happened in our experiments. Other investigators (Geoffrey et al., 1988; Rehavi et al., 1988; Joshi et al., 1999) have shown evidence for a likely nifedipine + imipramine potentiation. Joshi et al. (1999) showed evidence that low concentrations of CCBs inhibit calcium signalling paradoxically. Our experiments still showed some potentiation of sertraline by nifedipine and this may further be explained by the fact that 5HT_{1A} agonists such as sertraline act through 5HT_{1A} receptors to reduce voltage-activated Ca²⁺ signals (Ladewig et al., 2004) or blockade of reuptake of serotonin by nifedipine could further result in enhancement (Wendling et al., 1987). Also, the other down-stream effects of imipramine and sertraline to enhance neurotrophic signalling cascades may also lead to synergism with nifedipine. The fact that furosemide inhibits GABA-induced Ca²⁺ accumulation (Ikeda et al., 1977; Takebayashi et al., 1996) and glutamate-mediated Ca²⁺ accumulation (Sanchez-Gomez et al., 2011) may account for its potentiation by nifedipine as shown by the experimental results. Chronic application of furosemide may lead to hyperphosphorylation of the L-type calcium channel resulting in inefficient calcium cycling (McCurley et al., 2004).

Nifedipine may act independent of calcium channels to

inhibit PKC (Hempel et al., 1999). Nifedipine's PKC inhibitory effect may antagonise the apoptotic effects of protein kinase C δ (PKC delta) and protein kinase C ζ (PKC zeta) (Gonzalez-Guerrico et al., 2005; Peng et al., 2011). PKC delta is activated in various cell types by oxidative stress (Talior et al., 2003). Desipramine, the metabolite of imipramine, which inhibits PKC (Mann et al., 1995) may enhance this anti-apoptotic effect of nifedipine; and this may also help explain present results.

Further avenues for interaction between nifedipine and furosemide exist. Chronic application of furosemide also affect the monoamine transporters (Habecker et al., 2003; Lucas et al., 2007) and both furosemide and nifedipine antagonise oxidants, adenosine and phosphodiesterase which may help explain our experimental results.

In conclusion, the drug combinations nifedipine + imipramine, nifedipine + sertraline and nifedipine + furosemide show enhanced actions on chronic administration in the FST and TST models of depression in mice.

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