Full Length Research Paper

Differential effect of furosemide on the antidepressant actions of imipramine and atropine in the TST in mice

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The objective of the study was to investigate the possible effect of furosemide on the antidepressant effects of imipramine and atropine in the tail suspension test model of depression using mice. Groups of mice (25-40g), after acclimatisation in the animal house, were treated with imipramine (10mg/kg), atropine (2.5mg/kg), and furosemide (10mg/kg) ; and with the drug combinations furosemide (10mg/kg) + imipramine (10mg/kg); atropine (2.5mg/kg) + imipramine (10mg/kg); and furosemide (10mg/kg) + atropine (2.5mg/kg) for 14 days respectively. Experiments were done on Day 1 and Day 15 using the tail suspension test. Results showed that the three agents reduced immobility in the tail suspension test significantly compared to controls ($P < 0.05$, < 0.01) on acute administration. On chronic administration, atropine did not reduce immobility significantly compared to controls ($P > 0.05$). The combination of furosemide + imipramine did not reduce immobility significantly on acute administration ($P > 0.05$); and the effect of the combination furosemide + atropine demonstrated attenuation of the anti-immobility effect of atropine by furosemide. Results further showed that atropine enhanced the antidepressant effect of imipramine in the tail suspension test. In conclusion, furosemide antagonised the antidepressant effects of imipramine and atropine in the tail suspension test in mice but with greater antagonism of the effect of imipramine.

Keywords: Imipramine, Atropine, Furosemide, TST, Antidepressant

INTRODUCTION

Cholinergic excess (Renshaw et al., 1997) has been implicated as a mechanism for the causation of depressive disorder with increased muscarinic receptor density in the brain of depressive-suicide victims and central cholinomimetics such as physostigmine have been found to exhibit depressogenic effects (Janowsky and Overstreet, 2000). Though Vaillant in 1969 noted that discrete cholinergic mechanisms do not play an important role in endogenous depression, cholinergic overdrive has been demonstrated to produce increased immobility, increased β-endorphins, ACTH and growth hormone and increased REM sleep and shortening of REM sleep latency which are features of major depression (Dilsaver, 1986), and depressives exhibit state-independent supersensitivity to cholinergic drive (such as administering the centrally-acting physostigmine to Flinders rat lines sensitive to

diisopropylfluorophosphate). Stress increases central acetylcholine release (Janowsky and Overstreet, 1986, 2000) and the antidepressant, fluoxetine, may decrease acetylcholine availability, probably by shifting acetylcholine-serotonin balance to a serotonergic predominance.

According to the noradrenergic-cholinergic interaction hypothesis, antidepressant-treatment should lead to a decrease in cholinergic neurotransmission, which has not been demonstrated consistently, for after repeated electro-convulsive shock (ECS) treatment, there was no change in the acetylcholinesterase (ACHase) activity in the pons (site of the locus coeruleus) and other brain regions assayed (Camarini et al., 1997).

It was reported recently (Huang et al., 2010) that activation of M_1 mACHRs can induce long-term depression through the activation of post-synaptic PLC/PKC/IP3 receptor-and subsequently presynaptic No-sGC-PKG-dependent signalling processes and it has been shown that local calcium influx through NMDARs (Szabadits et al., 2011) and mACHRs

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(Rodriguez-Pascual et al., 1995; Brack et al., 2009) can trigger the production of nitric oxide, which induces cGMG production in the hippocampus and then PKG to affect different messenger systems. So, a synergy between cholinergic signalling and glutamate signalling cannot be ruled out with these lines of evidence, especially, when it is known that acetylcholine acting on M_2 receptors can increase the firing-rate of locus coeruleus neurons (Egan and North, 1985).

Also, atropine was shown recently to potentiate the antidepressant activity of sildenafil, a PD5 inhibitor, through a cholinergic-cGMP-PKG interaction (Liebenberg et al., 2010), underlining a prominent central muscarinic influence; while the major effect of neuronal nicotinic acetylcholine receptors (nACHR), as of now, is the modulation rather than processing of fast synaptic transmission (Vizi and Lendvai, 1999), an effect which could be targets for future therapeutic antidepressants (Shytle et al., 2002; Fryer et al., 1999).

Anticholinergic mechanisms alone may not offer sufficient explanation for atropine's effect in reducing immobility and increasing climbing behaviour in the forced swim test (Mancinelli et al., 1988; Wright et al., 2010), with high doses producing an effect which was not antagonised by physostigmine suggesting that the cholinergic system may only control the neural circuit upon which atropine acts to reduce immobility subject to other influences.

Also, there is up-regulation of muscarinic receptors after long-term atropine administration (Herman and Slominska-Zurek, 1979), an up-regulation that causes enhancement of acetylcholine-induced responses which is opposite to the antagonism after acute atropine administration.

There might be reconciliation amongst the above lines of evidence, firstly, with the report that acetylcholine can induce the synthesis of neuronal nitric oxide (Rodriguez-Pascual et al., 1995; Brack et al., 2009) which can stimulate increase in serotonin uptake, through nitric oxide-cGMP-PKG signaling, a signal transduction regulated by adenosine A3 receptor (Miller et al., 1994), and whose blockade at any point can lead to antidepressant effects. In the same vein, Yura et al (1996) reported that calmodulin-dependent protein kinases regulate in vivo serotonin uptake. Taken together, muscarinic receptor blockade could at some point disrupt acetylcholine-nitric oxide-cGMP-PKG signalling to reduce 5-HT uptake, and cause antidepressant effects, and this may also explain the enhancement of the antidepressant effect of the serotonin agonist, 8-OH-DPAT, by atropine apart from atropine's role in attenuation of effect of 5-HT1A autoreceptors (Haddjeri et al., 2004).

Recent evidence indicates that the loop diuretics, furosemide and bumetanide, possess neuroprotective (Malek et al., 2003; Nabekura et al., 2002) and neurotrophic effects (Wardle and Poo, 2003; Szekeres

et al., 2010); and, in particular, that furosemide may enhance long-term potentiation (Wang et al., 2006).

Stress and antidepressants have reciprocal actions on neuronal growth, neuronal vulnerability and synaptic plasticity in the hippocampus and other brain structures (Normann et al., 2007) with antidepressants enhancing long-term potentiation (Zaman and Zaman, 2001). Angiotensin peptides (Wright et al., 2002) are intimately related to neurotransmitter release mechanisms at the nerve endings (Yamada et al., 2002) and furosemide by its effects on brain renin-angiotensin could enhance CREB-BDNF signaling.

Also, the antioxidant (Hamelink et al., 2005), phosphodiesterase inhibiting (Marcus et al., 1978), anti-apoptotic effects (Wang et al., 2007), anti-glutamatergic-excitotoxic effects (Beck et el., 2003; Sanchez-Gomez et al., 2011) and dopamine transporter blocking (Lucas et al., 2007) actions of furosemide could contribute to enhancing cAMP-CREB- BDNF-ERK 1/2-Bcl-2 signalling.

The tricyclic antidepressant, imipramine, has been in use for treatment of depression since 1957 and it enhances neurotrophic signaling cascades.

The aim of the study was to investigate the differential effect of furosemide on the antidepressant actions of atropine and imipramine using the tail suspension test (TST) model of depression in mice.

MATERIALS AND METHODS

Male albino mice (25-35g) were used. Groups of mice were housed in the University's departmental laboratory in separate plastic cages for two weeks prior to acute testing. Animals were housed at room temperature of 25º-27ºC in a 12-hour light/dark cycle. Those for chronic experiments were given pretreatments of intraperitoneal injections, allowed food and water *ad libitum*, and on the day of the test 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 (Liebenberg et al., 2010; Eraly et al., 2006; Luszczki et al., 2003; Cryan et al, 2004; Kosuda et al., 1997; Hesdorfffer et al., 2001; Aburawi et al., 2007).

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 only two samples. The difference was considered to be significant at $P < 0.05, < 0.01$).
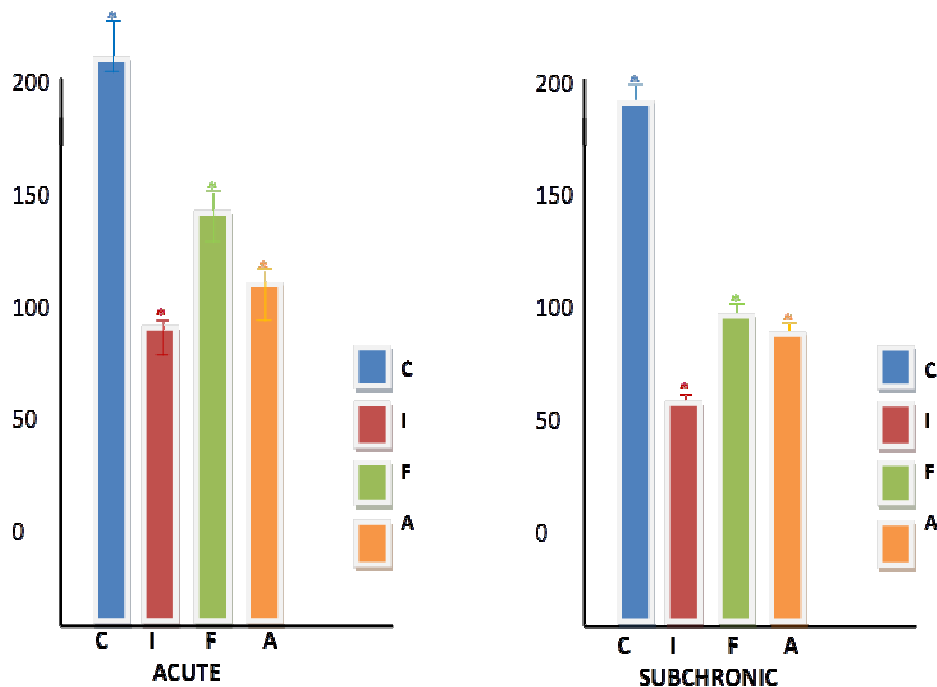
Figure I. Effect of Imipramine (I) Furosemide (F) and Atropine (A) on immobility in the TST. Values are expressed in seconds $\pm$ SD. The three agents significantly reduced immobility compared to controls (P < 0.05; < 0.01)

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 15 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.

In this experiment, the mice were pre-treated i.p. according to the following protocol:

Single-drug experiment

4 groups of mice were used
Group 1 received 0.25 ml of placebo daily for 14 days
Group 2 received 10mg/kg of imipramine daily for 14 days
Group 3 received 10mg/kg of furosemide daily for 14 days but had 50mg/kg of furosemide on test day
Group 4 received 2.5mg/kg of atropine daily for 14 days

but had 5mg/kg of atropine on test day
Tests were done on Day 1 (acute) and Day 15 (subchronic)

Drug-interaction experiment

4 groups of mice were used
Group 1 received 0.25 ml of placebo daily for 14 days
Group 2 received 10mg/kg of imipramine + 10mg/kg of furosemide daily for 14 days but had 10mg/kg of imipramine + 50mg/kg of furosemide on test day
Group 3 received 10mg/kg of imipramine + 2.5mg/kg of atropine daily for 14 days but had 10mg/kg of imipramine + 5mg/kg of atropine on test day
Group 4 received 10mg/kg of furosemide + 2.5mg/kg of atropine daily for 14 days but had 50mg/kg of furosemide + 5mg/kg of atropine on test day
Tests were done on Day 1 (acute) and Day 15 (subchronic)

RESULTS

The results are expressed in seconds $\pm$ SD. In the acute single drug experiments (Figure I), control mice had immobility score of 211.72 $\pm$ 4.39 seconds; mice placed on imipramine gave 101.12 $\pm$ 4.89 seconds; mice placed on furosemide gave 132.65 $\pm$ 2 .38 seconds while mice placed on atropine gave 112.50 $\pm$ 3.60 seconds (F(2,15) = 12.20, P < 0.05, < 0.01) and
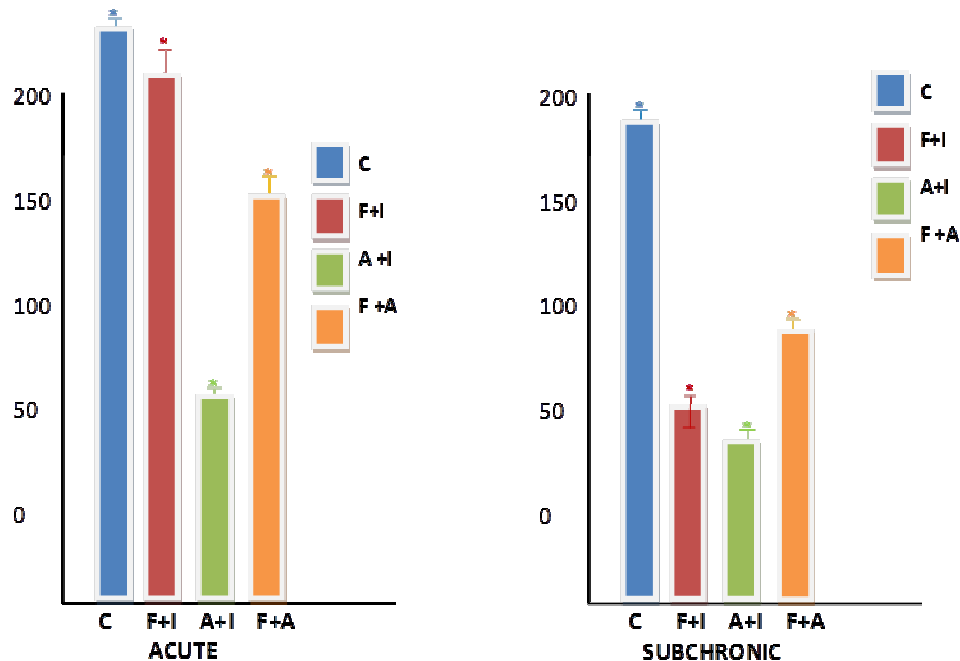
Figure 2. Effect of the Drug Combination Furosemide + Imipramine (F+1), Atropine + Imipramine (A+1), Furosemide + Atropine (F+A) on immobility in the TST. Furosemide + Imipramine combination did   not significantly reduce immobility acutely. The three combinations reduced immobility significantly sub chronically. The Atropine + Imipramine combination demonstrated significant synergy acutely.

the DMR post-hoc test showed the imipramine group gave the most significant result. In the chronic single drug experiments (Figure I), control mice had immobility score of 196.46 ± 3.44 seconds; mice placed on imipramine gave 88.25 ± 4.34 seconds; mice placed on furosemide gave 117.18 ± 2.45 seconds while mice placed on atropine gave 114.45 ± 2.60 seconds $(F_{(2,15)} = 14.60, P < 0.05, < 0.01)$ and DMR post-hoc test showed imipramine gave the most significant response. There was no statistical significant difference $(P > 0.05)$ in values between the acute and chronic atropine groups of mice.

In the acute drug-interaction experiments (Figure II), control mice had immobility score of 220.25 ± 2.55 seconds; mice placed on furosemide + imipramine gave 207.62 ± 4.20 seconds (statistical difference from control was not significant: $P > 0.05$); mice placed on atropine + imipramine gave 78.40 ± 5.40 seconds $(P < 0.05, < 0.01)$ while mice placed on furosemide + atropine gave 160.60 ± 3.00 seconds $(P < 0.05, < 0.01)$. From the values, furosemide antagonised imipramine more than atropine.

In the chronic drug-interaction experiments (Figure II), control mice had immobility score of 196.46 ± 3.44 seconds; mice placed on furosemide + imipramine gave 83.42 ± 2.01 seconds; mice placed on atropine + imipramine gave 75.32 ± 4.10 seconds while mice placed on furosemide + atropine gave 114.20 ± 4.30 seconds $(F_{(2, 15)} = 17.60, P < 0.05, < 0.01)$ and DMR post-hoc test showed the group of mice that received

atropine and imipramine gave the most significant response.

DISCUSSION

Antidepressant effects of atropine has been reported in the forced swim (Mancinelli et al., 1988; Haddjeri et al., 2004) and in the tail suspension (Steru et al., 1985) test models of depression in mice. Present results confirm the previous observation that atropine demonstrates antidepressant properties in the tail suspension test model of depression and results show the antidepressant effect was not significantly enhanced on chronic administration.

We have reported that the antidepressant effects of imipramine and furosemide are enhanced on chronic administration reflecting effects on down-stream neurotrophic signaling cascades (Oriaifo and Omogbai, 2010).

The antidepressant-like effects of atropine may be explained by its acute effect in decreasing cholinergic tone (Janowsky and Overstreet, 2000; Dilsaver, 1986) but anticholinergic mechanisms perse have been reported not sufficient to influence immobility time (Mancinelli et al., 1988) who have suggested that other signaling pathways are involved.

Acetylcholine-nitric oxide-cyclic guanosine monophosphate (ACH-NO-cGMP) signaling has been reported in bovine chromaffin cells (Rodriguez-Pascual,

1995) and this signaling pathway (Miller et al., 1994) and calmodulin-dependent protein kinases (Yura et al, 1996) enhance serotonin reuptake. Atropine could perturb this system to cause its antidepressant effects confirming the report by Liebenberg et al (2010) that atropine enhanced sildenafil's antidepressant effects by its effects on ACH-cGMP-PKG signaling. The prevention of acetylcholine-mediated activation of nitric oxide-cGMP induced enhancement of 5-HT uptake may be the basis of atropine's antidepressant-like actions.

Atropine could also modulate central 5-HT receptor-mediated responses by attenuating somatodendritic 5-HT1A autoreceptor responsiveness, a mechanism that may underlie its enhancement of the antidepressant responses of the serotonin agonist, 8-OH-DPAT (Haddjeri et al., 2004). Since the antidepressant effect of atropine was not enhanced on chronic administration from our results, it may mean that this mechanism may not contribute significantly to atropine's chronic antidepressant activity and supports the finding of Herman and Slominska-Zurek (1979) that atropine induced central cholinergic supersensitivity which enhanced the depressive behavior of acetylcholine thereby obtunding the antidepressant effects of atropine on chronic administration.

In the acute drug-interaction studies between furosemide and imipramine; and between furosemide and atropine, furosemide was able to attenuate the antidepressant response of imipramine and atropine probably by competitive binding to a muscarinic receptor site thereby preventing acetylcholine from activating the NO-cGMP-PKG-ERK signal transduction pathway that enhances 5-HT reuptake. Furosemide has some muscarinic receptor antagonist activity and binds albeit with low affinity to a site on the muscarinic receptor (Hootman and Ernst, 1981), as does imipramine, Hunt et al (1975), which too has low affinity for the muscarinic receptor. The anticholinergic, atropine, has high affinity for mACHR (Hootman and Ernst, 1981). Acute furosemide administration antagonized the acute antidepressant response of imipramine in this experiment most probably due to competitive muscarinic receptor binding. On chronic administration, both atropine and imipramine were not antagonized by furosemide probably due to the fact that both drugs were able to displace furosemide.

mipramine and atropine combination demonstrated significant potentiation acutely whereas attenuation of response would have been expected since they both possess antimuscarinic properties. Golds et al (1980) showed that, at low concentrations imipramine was not significantly displaced by atropine so that atropine's potentiation of imipramine in this experiment may be due to atropine's role in attenuation of effect of 5-HT1A autoreceptors (Haddjeri et al., 2004). Antidepressants may non-competitively inhibit nicotinic acetylcholine receptor function (Fryer et al., 1997) and atropine (Zwart and Vijverberg, 1997) as well as imipramine (Lopez-Valdes and Garcia-Colunga, 2001)

may also inhibit some subsets of nicotinic acetylcholine receptors probably providing another avenue for a synergistic relationship between them.

In conclusion, atropine demonstrated significant acute antidepressant activity in the tail suspension test which was not enhanced significantly on chronic administration. The acute antidepressant effect of atropine and imipramine was antagonized by furosemide, while imipramine potentiated atropine on acute administration in mice.

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