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 (Yuengsrigul 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 Ca2+ increase generates reactive oxygen species (ROS) and the formation of ROS causes the disruption of Ca2+ 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; Luszczyk et al., 2003; Cryan et al., 2004; Kosuda et al., 1997; Hesdorffer et al., 2001; Moglinicka et al., 1987).

Drug studies with the forced swimming 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, 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, 5 mg/kg of nifedipine, 10 mg/kg of imipramine and 5 mg/kg of sertraline i.p. before experimentation in the TST.

Statistical analysis

In the results, data were presented as mean ± 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
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 ± 1.08, 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 responses 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

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**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.
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 ± 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 (Yuengsrigul et al., 1999). Its effect in down-regulating
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 ½; MAP, mitogen activated protein kinase; FST, forced swim test; TST, tail suspension test.

REFERENCES

Abel EL (1994). A further analysis of physiological changes in rats in the forced swim test. Physiol.Behav. 5(4): 795-800.
Charron G, Laforest S, Gagnon C, Drolet G, Mouginet D. (2002). Acute sodium deficit triggers plasticity of the brain angiotensin type 1 receptors. FASEB J.16: 610-612.
Cryan J, O’Leary O, Jin S, Friedland J (2004). Norepinephrine-deficient mice lack responses to antidepressant drugs, including selective serotonin reuptake inhibitors. Proc. Natl. Acad. Sci. USA. 101(21): 8186-8191.
Deltheil T, Tanaka K, Reperton C, Hen R, David DT, Gardier AM (2009). Synergistic neurochemical and behavioural effects of acute intrahippocampal injection of brain-derived neurotrophic factor and antidepressants in adult mice. Int. J. Neropsychopharmacol. CINP 2009 doi: 10.1017/S1461145709000017.
Eraly SA, Valon V, Vaughn DA, Gangoiti JA, Richter K, Nagle M, Monte JC, Rieg T, Truong DM, Long JM, Barshop BA, Kaler G, Nigam SK (2006). Decreased renal organic anion secretion and plasma accumulation of endogenous organic anions in OAT1-/-knockout mice. Biol. Chem. 281: 5072-5082.
Grondin ME, Gobeil-Simard A, Drolet G, Mouginot D (2011). Na appetite induced by depleting extracellular fluid volume activates the enkephalin/m&-opioid receptor system in rat forebrain. J.
Bax and calpain mediate excitotoxic oligodendrocyte death in vivo. In vivo blocking of Bax and calpain activities prevents excitotoxic oligodendrocyte death in mouse and rat brain slices. J Neurosci. 31(8): 2996-3006.

Kreydiyyeh SI (2000). Cyclic AMP and furosemide stimulate the Na-K-ATPase in isolated rat jejunum. Pharmcol. Res. 41: 159-175.

Lahet JJ, Lenfant F, Courderot-Masuyer C, Escarnot-Laubriet E (2003). In vivo studies on the coexistence of anticholinergic effects of antihistamines and furosemide. Life Sci. 73(8): 1075-1082.

Lin C-H, Lu Y-Z, Cheng F-C, Chu L-F, Hsieh C-M (2005). Bax-regulated mitochondrial translocation is responsible for the in vitro ischaemia-induced neuronal cell death of Sprague-Dawley rats. Neurosci. Lett. 387(1): 22-27.

Lucas LR, Grillo CA, McEwen BS (2007). Salt appetite in sodium-depleted or sodium-replete conditions: Possible role of opioid receptors. Neuroendocrinology, 85: 139-149.

Luszczyk J, Sawicka K, Kozinska J, Borowiewiczka K, Czuczwara S (2003). Furosemide potentiates the anticonvulsant action of valproate in the mouse maximal electroshock seizure model. Epilepsia Res. 76(1): 66-72.

Mantovani M, Mesor A, Haas C, Zentner J, Feuerstein T (2011). GABA_A autoreceptors enhance GABA release from human neocortex: a mechanism for high-frequency stimulation (HFS) in brain? Naunyn-Schmiedeberg's Arch. Pharmacol. 380(1): 45-58.

Manzl C, Enrich J, Ebner H, Dallinger R, Krumschnabel G (2004). Copper-induced formation of ROS causes cell death and disruption of calcium homeostasis in trout hepatocytes. Toxicol. 196(1-2): 57-64.

Marcus R, Orner F, Arvessén G, Lundquist C (1978). Thiadizide diuretics do not potentiate cAMP response to parathyroid hormone. Metabolism, 27(6): 701-10.

Mogilnicka E, Czyrak A, Maj J (1987). Dihydropyridine calcium channel antagonists reduce immobility in the mouse behavioural despair tests; antidepressants facilitate nifedipine action. Eur. J. Pharmacol. 138: 413-416.

Moore JB, Fuller BL, Falotico R, Tolman EL (1985). Inhibition of rabbit platelet phosphodiesterase activity and aggregation by calcium channel blockers. Thrombosis Res. 40(2): 401-411.

O'Connor BJ, Chung KF, Chen-Worsdell YM, Fuller RW, Barnes PJ (1991). Effect of inhaled furosemide and bumetanide on adenosine 5’monophosphate and sodium metabolisulfate-induced bronchoconstriction in asthmatic subjects. Am. Rev. Resp. Dis. 143(6): 1329-1333.

Padmanabhan S, Lambert NA, Prasad BM (2008). Activity-dependent regulation of the dopamine transporter is mediated by Ca2+/-calmodulin-dependent protein kinase signaling. Eur. J. Neurosci. 28(10): 2017-2027.

Paul IA (2001). Antidepressant activity and calcium signaling cascades. Human Psychopharmacol.: Clin. Exp. 16(1): 71-80.

Peizhong M (2011). Review Article: Potential antidepressant role of neurotransmitter CART: Implications for mental disorders. Hindawi Publishing Corporation Depression Research and Treatment. 2011, Article ID 762139, doi: 10.1155/2011/762139: 1-11.

Pittenger C, Duman RS (2008). Stress, depression and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology, 33: 88-109.

Porots LD, Berlin A, Jalfre M (1977b). Behavioural despair in mice: a primary screening test for antidepressants. Arch. Int. Pharmacodyn. Ther. 229: 327-336.

Racagni G, Popoli M (2008). Remission-in-Depression. Cellular and molecular mechanisms in the long-term action of antidepressants. Dialogues Clin. Neurosci. 10(4): 385-400.

Rothe MF, Na ES, Anderson G, Jones TA, Bernstein I (2002). Induction of a salt appetite alters dendritic morphology in nucleus accumbens and sensitizes rats to amphetamine. J. Neurosci. 22:RC225 (1-5).

Sanchez-Gomez MV, Alberdi E, Perez-Navarro E, Alberch J, Matute C (2011). Bax and calpain mediate excitotoxic oligodendrocyte death induced by activation of both AMPA and Kainate receptors. J. Neurosci. 31(8): 2996-3006.

Sasaki T, Kitayawa K, Omura-Matsuoka E, Todo K, Terasaki Y (2007). Activation of cAMP-CREB signaling by phosphodiesterase inhibitors. Stroke, 38: 1597-1605.

Steru L, Chermat R, Thierry B, Simon P (1985). The tail suspension test: A new method for screening antidepressants in mice. Psychopharmacology (Berl.), 85(3): 367-370.

Szekeres M, Nadasz GL, Turu G, Supeki K, Svidonya L, Buday L, Chaplin T, Clark A, Hunyady L (2010). Angiotensin 11-induced expression of BDNF in human and rat adrenocortical cells. Endocrinology, 151(4): 1695-1703.

Trentani A, Kuipers SD, Ter Horst GJ, den Boer JA (2002). Chronic stress –induced in vivo ERK1/2 hyperphosphorylation in medial prefronto-cortical dentrites: implication for stress-related cortical pathology. Eur. J. Eur. 15: 1681-1691.

Vaillant GE (1969). Clinical significance of anticholinergic effects of imipramine-like drugs. Am. J. Psychiatry, 125: 1600-1602.

Wang Q-F, Chiang C-W, Wu C-C (2007). Gypenosides induce apoptosis in human hepatoma Huh-7 cells through a calcium/reactive oxygen species-dependent mitochondrial pathway. Planta Medica, 73(6): 535-544.

Wang W, Gong N, Xu T-L (2006). Down-regulation of KCC2 following LTP contributes to EPSP-spine potentiation in rat hippocampus. Biochem. and Biophy. Res. Commun. 343(4): 1209-1215.

Wardie RA, Poo MM (2003). Brain-derived neurotrophic factor modulation of Gabaergic synapses by post-synaptic regulation of chloride transport J. Neurosci. 23(25): 8722-8727.

Warner DS, Sheng H, Bartini-Haberle I (2004). Oxidants, antioxidants and the ischaemic brain. J. Exp. Biol. 207: 3221-3231.

Wright JW, Reichert JR, Davis CJ, Harding J (2002). Neural plasticity and the brain rennin-angiotensin system. Neurosci. Behav. Rev. 26(5): 529-552.

Yuengsrigul A, Chin TW, Nussbaum E (1999). Immunosuppressive and cytotoxic effects of furosemide on human peripheral blood mononuclear cells. Ann. Allergy Asthma Immunol. 83: 559-566.