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Full Length Research Paper

Comparative effects of imipramine, sertraline, nifedipine, furosemide and bumetanide on ingestive behaviour in mice

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The objective of the study was to evaluate the comparative effects of imipramine, sertraline, nifedipine, furosemide and bumetanide on ingestive behavior in rodents. Twelve groups (with six in each group) of male mice (25 to 35 g) were used in the experiments. They were housed in labelled plastic cages in the departmental laboratory and allowed access to food and water *ad libitum*. Six groups were treated respectively, with 10 mg/kg of furosemide, 5 mg/kg of sertraline, 5 mg/kg of nifedipine, 10 mg/kg of furosemide, 2.5 mg/kg of bumetanide and 0.25 ml of placebo, intraperitoneally daily for 30 days. Another six groups of mice were treated with the combination of furosemide (10 mg/kg) + sertraline (5 mg/kg); bumetanide (2.5 mg/kg) + sertraline (5 mg/kg); furosemide (10 mg/kg) + imipramine (10mg/kg); imipramin (10 mg/kg) + nifedipine (5 mg/kg); furosemide (10 mg/kg) + nifedipine (5 mg/kg) and placebo, respectively. The weights of the mice were recorded weekly for four weeks. Sertraline and imipramine decreased the weights of mice significantly at four weeks when compared to the controls ($p < 0.05$), while nifedipine and furosemide caused weight increases at four weeks, which is significantly different from the control ($p < 0.05$). Bumetanide did not cause significant weight increase when compared with controls ($p > 0.05$). In conclusion, the results suggest that sertraline and imipramine are anorexigenic in mice, while nifedipine and furosemide may be orexigenic.

Key words: Imipramine, sertraline, nifedipine, furosemide, bumetanide, weight of mice.

INTRODUCTION

Body weight is an indicator of appetite (Lin et al., 2008) and coordination of food intake and energy use is necessary for its regulation. The appetite centre of the body is in the arcuate nucleus of the hypothalamus and loss of sensitivity to hormones and metabolites in the arcuate nucleus is the cause of dysregulated energy intake and use.

Neuropeptide Y (NPY) and agouti-related peptide (AgRP) are related to appetite stimulation, while pro-opiomelanocortin (POMC) is related to appetite suppression. Agents that inhibit NPY/AgRP release include leptin, insulin, cholecystokinin, peptide YY (PYY) and acylated long-chain fatty acids, while orexin-A, ghrelin and glucose in the fasted state induce NPY/AgRP release (Winsberg et al., 2007; Ueta et al., 2003). Leptin and ghrelin have opposing effects on appetite and weight control, acting on different receptors in the arcuate nucleus of the hypothalamus, while orexin-A and leptin levels are inversely correlated (Komaki et al., 2001).

Moreover, it has been shown that leptin increases serotonin turnover by inhibition of brain nitric oxide synthesis (Calapai et al., 1999) and several experiments have shown that serotonin decreases food intake (Blundell, 1984; Morley et al., 1981) and the mechanism may be by facilitation of leptin secretion (Yamada et al., 2006).

Serotonin, the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants (TCAs) target distinct serotonin receptor signaling to mediate their effects and may regulate serotonin outputs independently

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Table 1. Effect of nifedipine, sertraline, imipramine, bumetanide and furosemide on weights of mice.

Drug	Average weight (initial) (mg)	Average weight of 1st week (mg)	Average weight of 2nd week (mg)	Average weight of 3rd week (mg)	Average weight of 4th week (mg)	Percentage change in weight
Control	30.00	30.50	31.00	31.50	32.00	+ 6.6%
Nifedipine	30.00	30.60	31.20	31.80	32.40	+ 8.0%
Sertraline	30.00	29.00	28.00	27.00	27.00	- 10.0%
Imipramine	30.00	29.00	30.00	30.00	27.00	- 10.0%
Bumetanide	30.00	30.40	30.80	31.20	31.60	+ 5.32%
Furosemide	30.00	30.40	30.00	31.20	32.20	+ 7.30%

of synaptic levels of serotonin (Dempsey et al., 2005), and this may explain sertraline (SSRI)- and imipramine (TCA)-induced hypophagia in mice.

Nifedipine has been shown to inhibit leptin (Glavaski-Joksimovic et al., 2004) but an interaction between leptin and the loop diuretics has not been demonstrated though furosemide may increase salt-appetite through orexin-induced release of adrenocorticoids (Nanmoku et al., 2002). Additionally, furosemide activation of the endogenous enkephalin/mμ-opioid receptor system (Grondin et al., 2011) may increase ingestive behavior (Nathan et al., 2011); an attribute nifedipine and bumetanide have not been reported to share. The aim of this study was to investigate the effects of sertraline, imipramine, nifedipine, furosemide and bumetanide on the weights of mice, a parallel study to the investigation of furosemide, bumetanide and nifedipine as agents with antidepressant-like effects. Nifedipine, furosemide and bumetanide have recently been shown to affect some neural circuits and signalling pathways.

MATERIALS AND METHODS

Male albino mice (25 to 35 g) in 12 groups were used. They were housed in the departmental laboratory in labelled plastic cages and cared for. They were allowed access to food and water *ad libitum* for the period of the \test and weighed weekly. All drugs were supplied by Sigma-Aldrich through Rovet Chemicals, Benin-City. All the drugs were dissolved in 10% Tween 80 in distilled water because of furosemide solubility. The mice were injected intra- peritoneally (i.p.) and 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).

Effect of sertraline, imipramine, nifedipine, bumetanide and furosemide on appetite in mice

Six groups (six mice in each group) of male mice weighing 25 to 35 g were observed in the laboratory for one month. They were fed freely and given treatment i.p. of sertraline 5 mg/kg, imipramine 10 mg/kg, nifedipine 5 mg/kg, bumetanide 2.5 mg/kg and furosemide 10 mg/kg daily for 30 days. The weights of the mice were recorded weekly.

Effect of drug combinations on appetite in mice

Six groups of mice were used as earlier mentioned. Treatment given were as follows: a) Furosemide (10 mg/kg) and sertraline (5 mg/kg); b) bumetanide (2.5 mg/kg) and sertraline (5 mg/kg); c) furosemide (10 mg/kg) and imipramine (10 mg/kg); d) imipramine (10 mg/kg) and nifedipine (5 mg/kg); e) furosemide (10 mg/kg) and nifedipine (5 mg/kg); f) 0.25 ml of Tween 80 to control group.Injections were given daily to the mice i.p. for a period of 30 days and their weights were recorded weekly.

Statistical analysis

Paired t-test was used when comparing the means of the two groups. The difference was considered to be significant at $p < 0.05$.

RESULTS

Sertraline (5 mg/kg) and imipramine (10 mg/kg) given to mice for 30 days decreased the weights of mice by 10%, respectively, and this decrease was significant when compared with control values ($p < 0.05$). Nifedipine (5 mg/kg) and furosemide (10 mg/kg) given to mice for 30 days increased the weights of mice by 8.00 and 7.33%, respectively and this increase was significant when compared with the control values ($p < 0.05$). Bumetanide (2.5 mg/kg) given to mice for 30 days did not increase the weights significantly as compared to control values ($p > 0.05$) (Table 1).

Nifedipine and furosemide increased the weights of mice after 30 days significantly as compared to controls ($p < 0.05$), while sertraline and imipramine decreased the weights of mice significantly as compared to controls ($p <0.05$). Bumetanide did not increase the weights of mice significantly ($p > 0.05$) after 30 days administration.

Table 2. Effect of the drug combinations furosemide + sertraline, furosemide + imipramine, bumetanide + sertraline, nifedipine + imipramine and nifedipine + furosemide on weights of mice.

Drug	Average weight (initial) (mg)	Average weight of 1st week (mg)	Average weight of 2nd week (mg)	Average weight of 3rd week (mg)	Average weight of 4th week (mg)	Percentage change in weight
Control	30.00	30.00	31.00	31.50	32.00	+ 6.6%
Furosemide + sertraline	30.00	28.50	27.00	26.50	27.20	- 9.60%
Bumetanide + sertraline	30.00	28.50	27.00	26.50	27.30	- 9.00%
Furosemide + imipramine	30.00	28.50	27.00	25.80	27.30	- 9.00%
Imipramine + nifedipine	30.00	30.00	30.80	31.20	31.60	+ 5.30%
Furosemide + nifedipine	30.00	31.50	32.50	33.50	33.80	+ 12.60%

Effect of (furosemide + sertraline), (bumetanide + sertraline), (furosemide + imipramine), (imipramine + nifedipine) and (furosemide + nifedipine) on weights of mice

The combinations of furosemide (10 mg/kg) + sertraline (5 mg/kg), furosemide (10 mg/kg) + imipramine (10 mg/kg) and bumetanide (2.5 mg/kg) + sertraline (5 mg/kg) decreased the weights of mice by 9.6, 9.00 and 9.00%, respectively, after 30 days and the results were significant as compared to controls ($p < 0.05$). The combination of imipramine + nifedipine did not increase the weights significantly at 30 days ($p > 0.05$), while the combination of furosemide and nifedipine increased the weights significantly at 30 days ($p < 0.05$) (Table 2). The combinations of furosemide + sertraline, furosemide + imipramine and bumetanide + sertraline decreased the weights of mice significantly as compared to controls ($p < 0.05$) at 30 days. The combination of furosemide and nifedipine increased the weights of mice significantly as compared to controls ($p < 0.05$). The combination of nifedipine and imipramine had no significant effect on weight of mice as compared to controls ($p > 0.05$).

DISCUSSION

The present results suggest that furosemide induces hyperphagia in rodents, confirming the reported observation that salt appetite and ingestive behaviour are increased after furosemide treatment (Houpt et al., 1991; Na et al., 2007). Enhanced sodium appetite also occurs after angiotensin administration (Fitzsimons, 1998) and furosemide enhances angiotensin release (Charron et al., 2002). Data suggested that the need for sodium induces neural plasticity at central sites associated not only with body fluid balance, but also with motivation, reward and mood (Na et al., 2007). Recent evidence points out that the induction of salt appetite by furosemide may affect the physiological behaviour of rodents by activating the endogenous enkephalin/mμ-opioid receptor system (Grondin et al., 2011) and cross-sensitize with amphetamine (Clark and Bernstein, 2004); effects which may partially explain the increase in ingestive behaviour (Nathan et al., 2011) and anti-depressant-like effects of furosemide (Oriaifo and Omogbai, 2010). In this study, we found that furosemide and bumetanide increased mice weight after 30 days by 7.33 and 5.3%, respectively, and this may reflect their influence on salt appetite and ingestive behaviour. Brain serotonin depletion exaggerates this sodium appetite (Lima et al., 2004). Serotonergic drugs reduce appetite (Badaue-Passos Jr. et al., 2003) and cause weight loss (Fernstrom et al., 1987; Halford et al., 2007) and in this study, attenuate furosemide-induced salt appetite. This furosemide-induced enhancement of hyperphagia may be orexin-A dependent (Nanmoku et al., 2002). We found in this study that combination of furosemide + sertraline, bumetanide + sertraline, furosemide + imipramine was able to reduce mice weight after 30 days by 9.60, 9.00 and 9.00%, respectively. This may imply that decreased salt intake and food intake can be caused by sertraline and imipramine which are both serotonergic agents. Imipramine has previously been reported to decrease preference for sweets in depressed patients (Fernstrom et al, 1987) and sertraline has

been shown to be able to reduce salt appetite (Lima et al., 2004) and serotonergic agents are known to be able to reduce food intake and weight (Boschmann et al., 2001).

Nifedipine and appetite

Nifedipine as sole agent increased the weight of mice (8.0%) after 30 days more than the control value of 6.6% (Table 1). Also, nifedipine + imipramine, nifedipine + furosemide combinations increased mice weight after 30 days by 5.33 and 12.66%, respectively. This corroborates present evidence that nifedipine could interact with leptin to block the stimulatory effect of leptin on intracellular calcium, thereby antagonising leptin (Glavaski-Joksimovic et al., 2004) to cause weight gain as noted in our experiments or could also interact with orexin-A (Xia et al., 2009) in the body system. The effects of high-calcium diet in reduction of obesity (Zemel, 2002) and inhibition of obesity-induced pro-inflammatory cytokines are blocked by nifedipine (Sun and Zemel, 2007). The present results suggest that the hyperphagia induced by nifedipine is potentiated by furosemide and attenuated by imipramine (Table 2).

Sertraline, imipramine and salt appetite

Sertraline (SSRI) reduces salt appetite (de Magalhaes-Nunes et al., 2007) and imipramine (TCA) reduces carbohydrate intake (Fernstrom et al., 1987). Brain serotonin depletion enhances sodium appetite (Lima et al., 2004) and serotonergic drugs are able to significantly attenuate or reduce rodent body weight gain (Halford et al., 2007). In this study, sertraline and imipramine were found to reduce mice weight gain by 10%, respectively (Table 1). The anorexigenic agent, leptin, has been reported to increase brain serotonin turn-over (Calapai et al., 1999) and the hypophagia induced by serotonin involves leptin (Yamada et al., 2006) which facilitates the anorexia induced by serotonin agonists. The TCAs and the SSRIs may mediate their effects through serotonergic signalling to cause hypophagia (Dempsey et al., 2005).

A combination of furosemide and imipramine, furosemide and sertraline and bumetanide + sertraline have been found in this study to reduce weight gain in mice significantly when compared with control values (Table 2) showing that furosemide-induced hyperphagia is overridden by sertraline- and imipramine-induced hypophagia.

Conclusion

The results show that furosemide and nifedipine are orexigenic in mice in contrast to sertraline and imipramine which are anorexigenic. This investigation further shows that the anorexigenic effect of sertraline and imipramine is able to override the orexigenic effect of furosemide and nifedipine.

REFERENCES

Badaue-Passos Jr D, Ventura RR, Silva LFS, Olivares LE, Reis LC (2003). Effect of brain serotonergic stimulation on sodium appetite of euthyroid and hypothyroid rats. Exp. Physiol. 88: 251-260

Boschmann M, Adams F, Klaus S (2001). *In situ* metabolic and hemodynamic response to dexfenfluramine in white adipose tissue of rats. Ann. Nutr. Metabolism, 45: 24-29

Blundell JE (1984). Serotonin and appetite. Neuropharmacol. 23: 1537-1551

Calapai G, Corica F, Corsonello A, Sautebin L, Di Rosa M, Buemi M, Mauro V, Caputi A (1999). Leptin increases serotonin turnover by inhibition of brain nitric oxide synthesis. J. Clin. Invest. 104(7): 975-982

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

Clark JJ, Bernstein IL (2004). Reciprocal cross-sensitization between amphetamine and salt appetite. Pharmacol. Biochem. Behaviour. 78(4): 691-698.

Cryan J, O'Leary O, Jin S, Friedland J (2004). Norepinephrine-deficient mice lack responses to antidepressant drugs including selective serotonin reuptake inhibitors. PNAS, 101(21): 8186-8191.

Dempsey CM, Mackenzie SM, Gargus A, Blanco G, Sze JY (2005). Serotonin (5HT), Fluoxetine, Imipramine and Dopamine target distinct 5HT receptor signalling to modulate Caenorhabditis elegans egg-laying behaviour. Genet. 169(3): 1425-1436

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 OAT knock-out mice. Biol. Chem. 281: 5072-5082.

Fernstrom MH, Krowinski RL, Kupfer DJ (1987). Appetite and food preference in depression: Effects of imipramine treatment. Biol. Psychiatry, 22(5): 529-539.

Fitzsimons JT (1998). Angiotensin, thirst and sodium appetite. Physiol. Reviews, 78(3): 583-686

Glavaski-Joksimovic A, Rowe EW, Jeftinija K, Scanes CG, Anderson LL, Jeftinija S (2004). Effect of leptin on intracellular calcium concentration in isolated porcine somatotropes. Neuroendocrinology, 80(2): 73-82

Grondin M-E, Gobeil-Simard A, Drolet G, Mouginot D (2011). Na^+ appetite induced by depleting extracellular fluid volume activates the enkephalin/mμ-opioid receptor system in rat forebrain. J. Neuroscience. In Press, doi: 10.1016/j.neuroscience. 2011.66.054

Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE (2007). Serotonergic drugs: Effect on appetite expression and use for the treatment of obesity. Drugs, 67(1): 27-55

Hesdorffer D, Stables JP, Hauser H, Annegers J, Cascino G, Sergievsky GH (2001). Are certain diuretics also anticonvulsants? Ann. Neurol. 50(4): 458-462

Houpt KA, Northrup N, Wheatley T, Houpt TR (1991). Thirst and salt appetite in horses treated with furosemide. J. Appl. Physiol. 71(6): 2380-2386

Komaki G, Matsumoto Y, Nishikata H, Kawaki K, Nozaki T, Taki M, Sogava H (2001). Orexin-A and leptin change inversely in fasting non-obese subjects. Eur. J. Endocrinol. 144(6): 645-651

Kosuda S, Fisher S, Wahl R (1997). Animal studies on the reduction and/or dilution of 2-deoxy-2(18F) fluoro-D-glucos (FDG) activity in the urinary system. Ann. Nuclear Med. 11(3): 213-218

Lima HRC, Cavalcante-Lima H, Cedraz-Mercez PL, Costa-E-Souza RH, Olivares EL, Badaue'-Passos D Jr, Medeiros MA, Cortes WS, Reis LC (2004). Brain serotonin depletion enhances the sodium appetite induced by sodium depletion or beta-adrenergic stimulation. Anais da Academia Brazileira de Gencias. 76(1): doi: 10:1590/s0001-37652004000100008.

Lin JC, Tsao D, Barras P, Bastarrachea RA, Boyd B, Chou J, Rosete R, Long H, Fergie A, Abdiche Y, Dilley J, Stratton J, Garcia C, Sloane DL, Comuzzie AG, Rosenthal A (2007). Appetite enhancement and weight gain by peripheral administration of TrkB agonists in non-human primates. PLos ONE 3(4): e1900 doi:10.137. l/journal.pone-0001900.

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

De Magalhaes-Nunes AP, Badaue'-Passos D Jr, Ventura RR, da Silva Guedes D Jr, Araujo JP, Granadeiro PC, Milanez-Barbosa HT, da Costa-E-Souza RH, de Medeiros MA, Antunes-Rodriguez J, Reis LC (2009). Sertraline, a selective serotonin reuptake inhibitor, affects thirst, salt appetite and plasma levels of oxytocin and vasopressin in rats. Exp. Physiol. 92(5): 913-922.

Morley JE, Flood JF (1991). Evidence that nitric oxide modulates food intake in mice. Life Sci. 49: 707-711.

Na ES, Morris MJ, Johnson RF, Beltz TG, Johnson AK (2007). The neural substrates of enhanced salt appetite after repeated sodium depletions. Brain Res. 1171: 104-110.

Nanmoku T, Isobe K, Sakurai T, Yamanaka A, Takeoshi K, Kawakami Y, Goto K, Nakai T (2002). Effects of orexin on cultured porcine adrenal medullary and cortex cells. Regulatory Peptides, 104(1-3): 125-130.

Nathan PJ, O'Neill BV, Mogg K, Bradley BP, Beaver J, Bani M, Merio-Pich E, Fletcher PC, Swirski B, Koch A, Dodds CM, Bullmore ET (2011). Opioid receptor modulation of hedonic taste preference and food intake: A single-dose safety, pharmacokinetic, and pharmacodynamic investigation with GSK1521498, a novel μ-opioid receptor inverse agonist. J. Clin. Pharmacol. doi: 10.1177/0091270011399577.

Oriaifo SEO, Omogbai EKI (2010). The antidepressant-like actions of furosemide, bumetanide and nifedipine in the forced swim test in mice. West Afr. J. Pharmacol. Drug Res. 26: 43-47.

Sun X, Zemel MB (2007). Calcium and 1, 25-dihydroxyvitamin D3 regulation of adipokine expression. Obesity, 15: 340-348.

Ueta Y, Ozaki Y, Saito Y, Onaka T (2003). Involvement of novel feeding-related peptides in neuroendocrine response to stress. Exp. Biol. Med. 228: 1168-1174.

Winsberg B, Usubiaga H, Cooper T (2007). Ghrelin and leptin response to oral glucose challenge among anti-psychotic drug-treated children. J. Clin. Psychopharmacol. 27(6): 590-594.

Xia JX, Fan SY, Yan J, Chen F, Li Y, Yu ZP, Hu ZA (2009). Orexin A-induced extracellular calcium influx in prefrontal cortex neurons involves L-type calcium channels. J. Physiol. Biochem. 65(2): 125-136.

Yamada J, Sugimoto Y, Ujikawa M (2006). Involvement of leptin in hypophagia induced by the serotonin precursor 5-hydroxytryptophan (5-HTP) in mice. Biol. Pharm. Bull. 29(3): 557-559.

Zemel MB (2002). Regulation of adiposity and obesity risk by dietary calcium: mechanisms and implications. J. Am. College Nutr. 21(2): 1465-1518.