British Journal of Pharmacology (1997) 121, 1758–1762 © 1997 Stockton Press All rights reserved 0007–1188/97 $12.00

Comparison of the effects of sibutramine and other monoamine reuptake inhibitors on food intake in the rat

[1]Helen C. Jackson, Andrew M. Needham, Lisa J. Hutchins, Sarah E. Mazurkiewicz & David J. Heal

Knoll Pharmaceuticals Research & Development, Pennyfoot Street, Nottingham, NG1 1GF

1 The effects of the potent 5-hydroxytryptamine (5-HT) and noradrenaline reuptake inhibitor (serotonin-noradrenaline reuptake inhibitor, SNRI), sibutramine, on the cumulative food intake of freely-feeding male Sprague-Dawley rats during an 8 h dark period were investigated and compared to those of the selective 5-HT reuptake inhibitor (selective serotonin reuptake inhibitor, SSRI), fluoxetine; the selective noradrenaline reuptake inhibitor, nisoxetine; the 5-HT and noradrenaline reuptake inhibitors, venlafaxine and duloxetine; and the 5-HT releaser and 5-HT reuptake inhibitor, (+)-fenfluramine.

2 Sibutramine (3 and 10 mg kg^{-1}, p.o.) and (+)-fenfluramine (1 and 3 mg kg^{-1}, p.o.) produced a significant, dose-dependent decrease in food intake over the 8 h dark period. These responses became apparent within the first 2 h following drug administration.

3 Fluoxetine (3, 10 and 30 mg kg^{-1}, p.o.), and nisoxetine (3, 10 and 30 mg kg^{-1}, p.o.) had no significant effect on food intake during the 8 h dark period. However, a combination of fluoxetine and nisoxetine (30 mg kg^{-1}, p.o., of each) significantly decreased food intake 2 and 8 h after drug administration.

4 Venlafaxine (100 and 300 mg kg^{-1}, p.o.) and duloxetine (30 mg kg^{-1}, p.o.) also significantly decreased food intake in the 2 and 8 h following drug administration.

5 The results of this study demonstrate that inhibition of 5-HT and noradrenaline reuptake by sibutramine, venlafaxine, duloxetine, or by a combination of fluoxetine and nisoxetine, markedly reduces food intake in freely-feeding rats and suggest that this may be a novel approach for the treatment of obesity.

Keywords: Sibutramine; monoamine reuptake inhibition; serotonin-noradrenaline reuptake inhibitor (SNRI); 5-hydroxytryptamine; noradrenaline; food intake

Introduction

Sibutramine hydrochloride (BTS 54 524; *N*-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*,*N*-dimethylamine hydrochloride monohydrate; Reductil; Meridia) is a potent 5-hydroxytryptamine (5-HT) and noradrenaline reuptake inhibitor *in vivo* (Buckett *et al*., 1988; Luscombe *et al*., 1989). It therefore belongs to a new class of drugs called the serotonin-noradrenaline reuptake inhibitors or SNRIs. Sibutramine has been demonstrated to produce dose-dependent, long-lasting weight reduction in obese patients (Weintraub *et al*., 1991; Ryan *et al*., 1995) and is currently being developed as a drug for the treatment of obesity. Animal studies have shown that sibutramine reduces body weight by a dual mode of action, viz. it decreases food intake in rats by enhancing satiety (Fantino & Souquet, 1995; Halford *et al*., 1995; Stricker-Krongrad *et al*., 1995) and increases energy expenditure by stimulating thermogenesis (Connoley *et al*., 1995; 1996).

This study explores the relative contribution of 5-HT and noradrenaline reuptake inhibition to the decrease in food intake induced by sibutramine by comparing its hypophagic effects with those of the selective 5-HT reuptake inhibitor (selective serotonin reuptake inhibitor, SSRI), fluoxetine (Wong *et al*., 1995); the selective noradrenaline reuptake inhibitor, nisoxetine (Fuller *et al*., 1975; Wong & Bymaster, 1976); the 5-HT and noradrenaline reuptake inhibitors, venlafaxine (Holliday & Benfield, 1995) and duloxetine (Wong *et al*., 1993) and the 5-HT releaser and 5-HT reuptake inhibitor, (+)-fenfluramine, which is used clinically in the treatment of obesity (Davis & Faulds, 1996).

Some of the results of this study have previously been published in abstract form (Jackson *et al*., 1996b).

[1] Author for correspondence.

Methods

Animals and environment

Experiments were performed on male Sprague-Dawley rats (350–500 g at the start of the experiment) which were obtained from Charles River (Margate). Animals were individually-housed in polypropylene cages with metal grid floors at a temperature of $21 \pm 1^{\circ}C$ and 55% humidity. Polypropylene trays were placed below each cage to detect any food spillage. Animals were maintained on a reverse phase light-dark cycle. Lights were off from 09h 00min to 17h 00min during which time the laboratory was illuminated by a red lamp. Animals had free access to a standard powdered rat diet (Compound Rat and Mouse Diet, Special Diet Services, Witham, Essex) and tap water at all times. The powdered diet was contained in glass feeding jars (10 cm diameter; 8 cm deep; Solmedia Laboratory Supplies, Romford) with aluminium lids. Each lid had a hole (3 cm diameter) cut in it to allow access to the food. Spillage of powdered diet from the feeding jars was negligible. Animals were accustomed to these conditions for at least two weeks before experimentation began.

Experimental procedures

On the test day, animals were randomly allocated to four treatment groups containing 6–8 rats. All procedures began at 09h 00min and food intake was monitored over the dark phase since animals consume most of their food intake during the nocturnal period. Feeding jars were weighed (to the nearest 0.1 g on a Sartorius top-pan balance) at the time of drug administration and after 2 and 8 h. The 8 h reading was taken immediately before the lights came on at 17h 00min. Each experiment included a vehicle-treated control group and 3 drug-treatment groups. The food intake of animals in the four different groups was monitored concurrently. Variations in

body weight were accounted for by expressing the results as g kg^{-1} rat weight (treatment group means ± s.e.mean). Rats in the weight-range used in this study would normally eat 15–20 g over the 8 h dark period, i.e. 30–50 g kg^{-1}. Animals were then divided into groups at random and re-used in the feeding studies after a wash-out period of at least 72 h.

Drugs

Sibutramine hydrochloride (BTS 54 524), fluoxetine hydrochloride, venlafaxine hydrochloride and duloxetine hemioxalate were synthesized at Knoll Pharmaceuticals Research & Development (Nottingham). (+)-Fenfluramine hydrochloride and nisoxetine hydrochloride were purchased from Research Biochemicals International (St Albans, U.K.). Sibutramine, venlafaxine, nisoxetine and (+)-fenfluramine were dissolved in deionized water. Duloxetine was suspended in 0.25% cellosize (hydroxethyl cellulose) and fluoxetine was dissolved in deionized water minimally acidified with glacial acetic acid. All drug doses are expressed as the salt and drugs were administered p.o. in a dose volume of 1 mg kg^{-1}.

Statistical analysis

Statistical comparisons between the food intake of the different treatment groups were made by one-way analysis of variance followed by the Dunnett's multiple comparisons test (two-tailed). ED_{50} values (the dose of drug required to reduce food intake to 50% of control levels) were calculated from a logistic sigmoid curve with maximum at the control mean and minimum at 0. The curve was fitted by least squares (Marquardt's compromise method) by use of the computer programme PROC NLIN in SAS.

Results

Effect of sibutramine and (+)-fenfluramine on food intake

Sibutramine (3 and 10 mg kg^{-1}, p.o.) and (+)-fenfluramine (1 and 3 mg kg^{-1}, p.o.) produced a significant, dose-dependent decrease in food intake over the 8 h dark period (Figure 1a and b, respectively). These responses became evident within the first 2 h following drug administration.

Effect of fluoxetine and nisoxetine, alone and in combination, on food intake

Fluoxetine (3, 10 and 30 mg kg^{-1}, p.o.) and nisoxetine (3, 10 and 30 mg kg^{-1}, p.o.) had no significant effect on cumulative food intake during the dark period (Figure 2a and b, respectively). However, a combination of fluoxetine and nisoxetine (30 mg kg^{-1} of each, p.o.) significantly decreased food intake 2 and 8 h after drug administration (Figure 2c).

Effect of venlafaxine and duloxetine on food intake

Food intake was significantly decreased 2 and 8 h following administration of the SNRIs, venlafaxine (100 and 300 mg kg^{-1}, p.o.; Figure 3a) and duloxetine (30 mg kg^{-1}, p.o.; Figure 3b).

Comparison of the potency of sibutramine, (+)-fenfluramine, venlafaxine and duloxetine to reduce food intake

The doses of sibutramine, (+)-fenfluramine, venlafaxine and duloxetine reducing food intake to 50% of control levels (ED_{50} values) 2 and 8 h after drug administration are shown in Table 1. Sibutramine was 3–6 times less potent than (+)-fenfluramine; 4–5 times more potent than duloxetine and nearly 30 times more potent than venlafaxine.

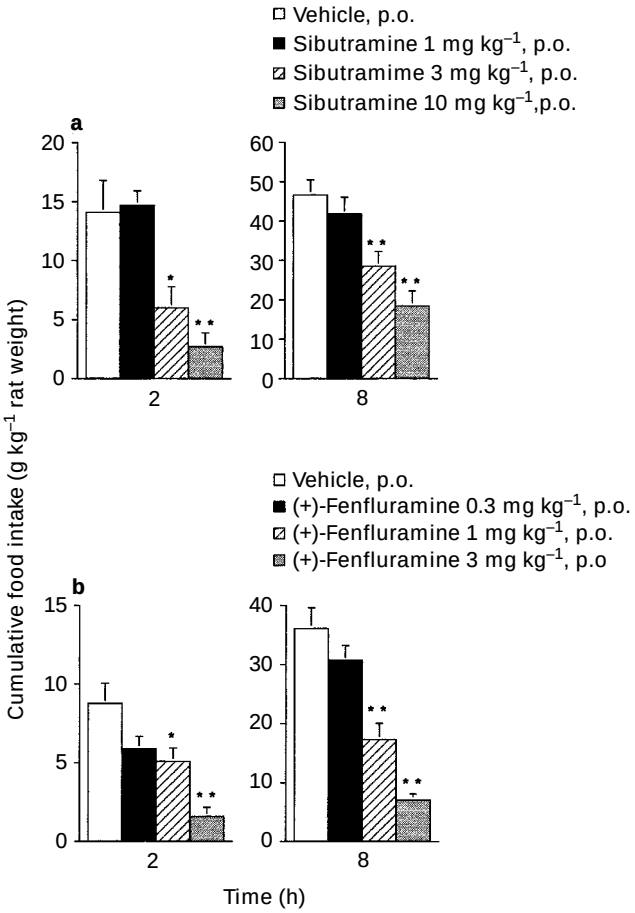

Figure 1 Effect of (a) sibutramine and (b) (+)-fenfluramine on food intake in the rat. Results are expressed as treatment group means for groups of 6–8 animals; vertical lines represent s.e.mean. Significant differences from control values are denoted by $*P<0.05$ and $**P<0.01$.

Discussion

The major finding of this study is that inhibition of both 5-HT and noradrenaline reuptake, either by administration of sibutramine, venlafaxine or duloxetine, or by combined administration of fluoxetine and nisoxetine, produces a marked decrease in food intake in the rat. These findings are in accordance with results showing that both 5-HT and noradrenaline play important roles in the regulation of food intake (for review see Rowland *et al*., 1996).

The dose-related decrease in food intake induced by sibutramine in the present study confirms other data on the hypophagic effects of this compound in normal (Fantino & Souquet, 1995; Halford *et al*., 1995) and genetically-obese (Stricker-Krongrad *et al*., 1995) rats. Sibutramine decreases food intake in rats at doses that inhibit reuptake of noradrenaline and 5-HT, as shown in a variety of behavioural and biochemical tests (Buckett *et al*., 1988; Luscombe *et al*., 1989). Its hypophagic effects would therefore appear to be related to its inhibition of noradrenaline and 5-HT reuptake with the subsequent activation of monoamine receptors. In support of this hypothesis, the hypophagic effects of sibutramine are inhibited by α_1-adrenoceptor, β_1-adrenoceptor and 5-$HT_{2A/2C}$ receptor antagonists (Jackson *et al*., 1996a), although neither sibutramine, nor its two amine metabolites, which are thought to be primarily responsible for its pharmacological effects *in vivo* (Luscombe *et al*., 1989), exhibit any direct affinity for α_1-adrenoceptors, β_1-adrenoceptors or 5-$HT_{2A/2C}$ receptors (S.C. Cheetham, personal communication).

In the present study, sibutramine induced a similar decrease in food intake to (+)-fenfluramine over the 8 h dark period.

However, the effects of sibutramine on the 5-HT system can be clearly differentiated from those of (+)-fenfluramine. Sibutramine inhibits the reuptake of 5-HT into presynaptic nerve terminals (as described above). Microdialysis studies in conscious rats have shown that it produces a small, prolonged increase in 5-HT in the hypothalamus (Gundlah *et al*., 1996; Prow *et al*., 1996) – a brain area known to play an integral part in the control of food intake. In contrast, (+)-fenfluramine is a potent 5-HT releasing agent (Mennini *et al*., 1981; 1985; Fuller *et al*., 1988) and although it also inhibits 5-HT reuptake, this property is unlikely to contribute to its effects on food intake. It is a much weaker 5-HT reuptake inhibitor than fluoxetine *in vitro* (Garattini *et al*., 1989; Cheetham *et al*., 1993) and does not inhibit 5-HT reuptake *in vivo* (Fuller *et al*., 1988). Microdialysis studies have shown that (+)-fenfluramine produces a marked and rapid increase in extracellular 5-HT in rat hypothalamus maximal 40 min after drug administration (Prow *et al*., 1996), although this ability of (+)-fenfluramine to increase 5-HT availability may not necessarily underlie its effects on food intake (see recent review by Curzon *et al*., 1997).

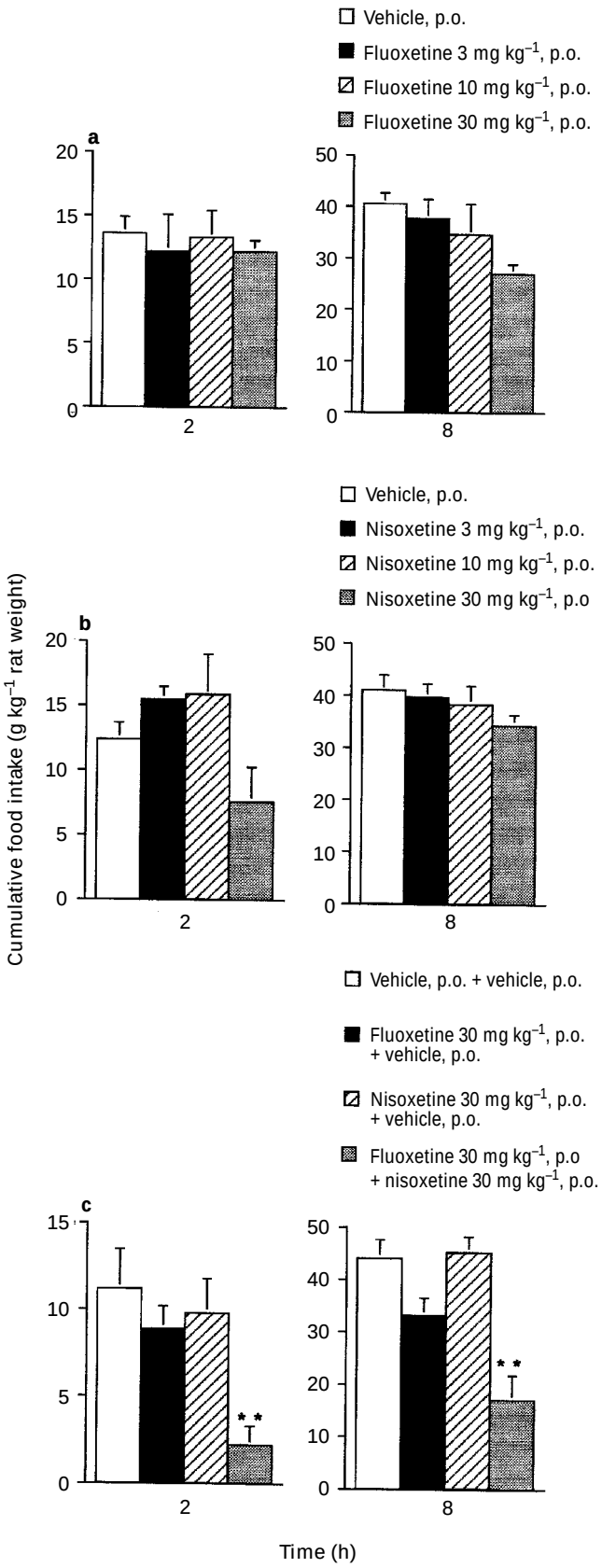

Figure 2 Effect of (a) fluoxetine, (b) nisoxetine and (c) a combination of fluoxetine and nisoxetine on food intake in the rat. Results are expressed as treatment group means for groups of 6–8 animals; vertical lines represent s.e.mean. Significant differences from the vehicle-treated control group are denoted by $^{**}P<0.01$.

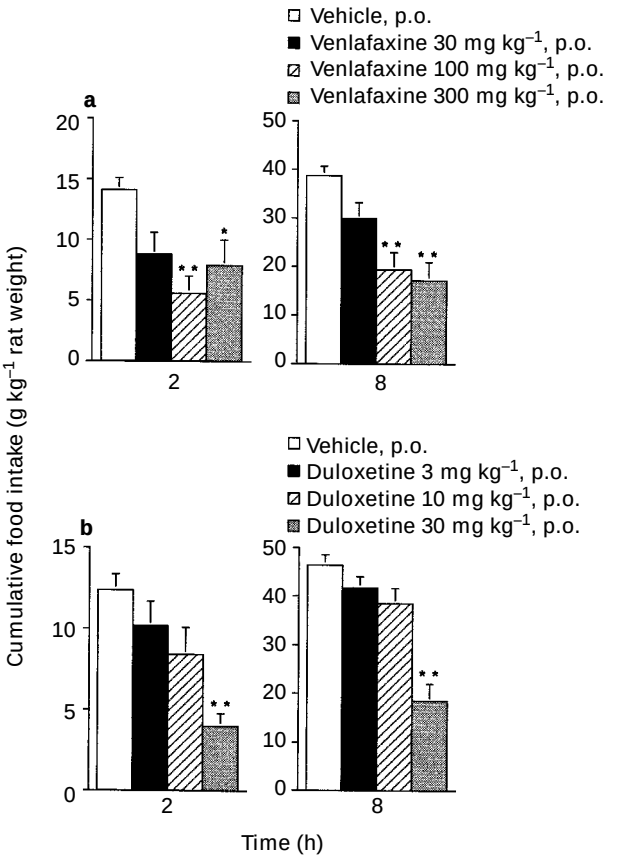

Figure 3 Effect of (a) venlafaxine and (b) duloxetine on food intake in the rat. Results are expressed as treatment group means for groups of 6–8 animals; vertical lines represent s.e.mean. Significant differences from control values are denoted by $^{*}P<0.05$ and $^{**}P<0.01$.

Table 1 Comparison of the hypophagic effects of sibutramine, (+)-fenfluramine, venlafaxine and duloxetine in the rat

	ED_{50} values and 95% confidence intervals (mg kg^{-1}, p.o.) *Time* (h)	
Treatment	*2*	*8*
Sibutramine	2.8 (1.6–5.0)	5.7 (3.0–11.1)
(+)-Fenfluramine	1.0 (0.4–2.2)	1.0 (0.6–1.5)
Venlafaxine	–	158 (62–402)
Duloxetine	15.2 (7.5–30.7)	21.9 (17.0–28.4)

The ED_{50} value for venlafaxine at 2 h could not be determined as the effects of venlafaxine on food intake were not dose-dependent.

The lack of effect of oral administration of fluoxetine, at a dose that inhibits 5-HT reuptake *in vivo* (Jackson *et al*., 1995), on food intake in freely-feeding animals was perhaps not surprising. A large number of other workers have shown hypophagic effects of fluoxetine in animals (e.g. Goudie *et al*., 1976; Dumont *et al*., 1981; Wong *et al*., 1988; Garattini *et al*., 1992; Halford & Blundell, 1996; Lightowler *et al*., 1996). However, in these studies, fluoxetine was administered i.p. in relatively high doses ($\geqslant$10 mg kg^{-1}) and/or the effects of fluoxetine on food intake were examined in animals on food-deprivation schedules – models which do not mirror the clinical situation and which are extremely sensitive to agents which suppress food intake via either direct effects on appetite or non-specific behavioural disruption due to the high levels of food intake of control animals. Data on the effects of fluoxetine on food intake in man are also controversial. It has been shown to produce weight loss in some studies (Ferguson & Feighner, 1987; Levine *et al*., 1987; Pijl *et al*., 1991; Wise, 1992; Goldstein *et al*., 1994; Lawton *et al*., 1995) although, in general, high doses were required to produce this effect, i.e. two–three times greater than those used to treat depression. In other cases, fluoxetine was found to be inactive (Fernández-Soto *et al*., 1995), or paradoxically, to produce hyperphagia and weight gain (Fogelson, 1991; Gualtieri, 1991). It therefore appears that selective 5-HT reuptake inhibition *per se* is not a suitable pharmacological strategy for producing an efficacious anti-obesity agent.

The noradrenaline reuptake inhibitor, nisoxetine, also failed to alter food intake in rats following oral administration. The behavioural effects of this compound *in vivo* have not been extensively studied. However, it is active in the rat Porsolt test, an animal model which can be used to predict antidepressant action and which is sensitive to monoamine reuptake inhibitors such as imipramine (Paul *et al*., 1990). Furthermore, nisoxetine has been shown to produce a small, transient hypophagic response in severely (42 h) food-deprived animals (Wong *et al*., 1993).

In contrast, to their lack of effect on food intake when given alone, a combination of fluoxetine and nisoxetine produced a marked hypophagic response which was similar in magnitude to that produced by the highest dose of sibutramine. The most parasimonious explanation for the decrease in food intake produced by the combination of fluoxetine and nisoxetine is that it is due to inhibition of both 5-HT and noradrenaline reuptake. However, it has recently been suggested that fluoxetine may act independently of 5-HT (Curzon *et al*., 1997), therefore this hypothesis needs to be confirmed with the more selective 5-HT reuptake inhibitor, sertraline, and either monoamine-depleting agents or monoamine receptor antagonists. Further studies are also required to rule out the possibility that pharmacokinetic drug interactions may have resulted in elevated brain levels of fluoxetine or nisoxetine and hence effects on food intake. Little is known about the metabolism of nisoxetine in the liver or its effects on drug-metabolizing enzymes. However, it has a similar structure to fluoxetine, which has been shown to inhibit several members of the cytochrome P450 isoenzyme system (Lane, 1996).

The decrease in food intake induced by venlafaxine and duloxetine supports the concept that inhibition of both 5-HT and noradrenaline reuptake reduces food intake in rats. The effects of these compounds on food intake in animals or man have not been widely studied although duloxetine has been shown to reduce food consumption in food-deprived rats (Katoh *et al*., 1995). Both venlafaxine and duloxetine are described as 5-HT and noradrenaline reuptake inhibitors or SNRIs, although they appear to have a small degree of selectivity for 5-HT, over noradrenaline, reuptake (5 and 3 fold, respectively; Bolden-Watson & Richelson, 1993; Wong *et al*., 1993; Kasamo *et al*., 1996). In contrast, sibutramine is an equipotent 5-HT and noradrenaline reuptake inhibitor *in vivo* (Luscombe *et al*., 1989). The potent hypophagic effects of sibutramine in relation to duloxetine, and particularly venlafaxine, are consistent with the potencies of these compounds in the Porsolt test and in other behavioural models of monoamine reuptake inhibition, including antagonism of reserpine-induced hypothermia and ptosis (Buckett *et al*., 1988; Luscombe *et al*., 1989; Yardley *et al*., 1990; Katoh *et al*., 1995; H.C. Jackson, unpublished observations).

In conclusion, this study demonstrates that inhibition of both 5-HT and noradrenaline reuptake, either by administration of sibutramine, venlafaxine or duloxetine, or by combined administration of fluoxetine and nisoxetine, produces a marked decrease in food intake in the rat. These results suggest that drugs which inhibit the re-uptake of both 5-HT and noradrenaline may be efficacious anti-obesity agents. In this context, clinical trials have shown that sibutramine produces dose-dependent, long-lasting weight reduction in obese patients (Weintraub *et al*., 1991; Ryan *et al*., 1995).

References

BOLDEN-WATSON, C. & RICHELSON, E. (1993). Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. *Life Sci*., **52,** 1023–1029.

BUCKETT, W.R., THOMAS, P.C. & LUSCOMBE, G.P. (1988). The pharmacology of sibutramine hydrochloride (BTS 54 524), a new antidepressant which induces rapid noradrenergic down-regulation. *Prog. Neuro-Psychopharmacol. Biol. Psychiat*., **12,** 575–584.

CHEETHAM, S.C., VIGGERS, J.A., SLATER, N.A., HEAL, D.J. & BUCKETT, W.R. (1993). [^{3}H]paroxetine binding in rat frontal cortex strongly correlates with [^{3}H]5-HT uptake: Effect of administration of various antidepressant treatments. *Neuropharmacology*, **32,** 737–743.

CONNOLEY, I.P., FROST, I., HEAL, D.J. & STOCK, M.J. (1996). Role of β-adrenoceptors in mediating the thermogenic effects of sibutramine. *Br. J. Pharmacol*., **117,** 170P.

CONNOLEY, I.P., HEAL, D.J. & STOCK, M.J. (1995). A study in rats of the effects of sibutramine on food intake and thermogenesis. *Br. J. Pharmacol*., **114,** 388P.

CURZON, G., GIBSON, E.L. & OLUYOMI, A.O. (1997). Appetite suppression by commonly used drugs depends on 5-HT receptors but not on 5-HT availability. *Trends Pharmacol. Sci*., **18,** 21–25.

DAVIS, R. & FAULDS, D. (1996). Dexfenfluramine: An updated review of its therapeutic use in the management of obesity. *Drugs*, **52,** 696–724.

DUMONT, C., LAURENT, J., GRANDADAM, A. & BOISSIER, J.R. (1981). Anorectic properties of a new long acting serotonin uptake inhibitor. *Life Sci*., **28,** 1939–1945.

FANTINO, M. & SOUQUET, A.-M. (1995). Effects of Metabolites 1 and 2 of sibutramine on the short-term control of food intake in the rat. *Int. J. Obesity*, **19,** 145.

FERGUSON, J.M. & FEIGHNER, J.P. (1987). Fluoxetine-induced weight loss in overweight non-depressed humans. *Int. J. Obesity*, **11,** 163–170.

FERNÁNDEZ-SOTO, M.L., GONZÁLEZ-JIMÉNEZ, A., BARREDO-ACEDO, F., LUNA DEL CASTILLO, J.D. & ESCOBAR-JIMÉNEZ, F. (1995). Comparison of fluoxetine and placebo in the treatment of obesity. *Ann. Nutr. Metab*., **39,** 159–163.

FOGELSON, D.L. (1991). Weight gain during fluoxetine treatment. *J. Clin. Psychopharmacol*., **11,** 220–221.

FULLER, R.W., SNODDY, H.D. & MOLLOY, B.B. (1975). Blockade of amine depletion by nisoxetine in comparison to uptake inhibitors. *Psychopharmacol. Commun*., **1,** 455–464.

FULLER, R.W., SNODDY, H.D. & ROBERTSON, D.W. (1988). Mechanisms of effects of d-fenfluramine on brain serotonin metabolism in rats: Uptake inhibition versus release. *Pharmacol. Biochem. Behav*., **30,** 715–721.

GARATTINI, S., BIZZI, A., CODEGONI, A.M., CACCIA, S. & MENNINI, T. (1992). Progress report on the anorexia induced by drugs believed to mimic some of the effects of serotonin on the central nervous system. *Am. J. Clin. Nutr.*, **55,** 160S – 166S.

GARATTINI, S., MENNINI, T. & SAMANIN, R. (1989). Reduction of food intake by manipulation of central serotonin: Current experimental results. *Br. J. Psychiat.*, **155,** 41 – 51.

GOLDSTEIN, D.J., RAMPEY, A.H., ENAS, G.G., POTVIN, J.H., FLUDZINSKI, L.A. & LEVINE, L.R. (1994). Fluoxetine: A randomised clinical trial in the treatment of obesity. *Int. J. Obesity*, **18,** 129 – 135.

GOUDIE, A.J., THORNTON, E.W. & WHEELER, T.J. (1976). Effects of Lilly 110140, a specific inhibitor of 5-hydroxytryptamine uptake, on food intake and on 5-hydroxytryptophan-induced anorexia. Evidence for serotonergic inhibition of feeding. *J. Pharm. Pharmacol.*, **28,** 318 – 320.

GUALTIERI, C.T. (1991). Paradoxical effects of fluoxetine. *J. Clin. Psychopharmacol.*, **11,** 393 – 394.

GUNDLAH, C., MARTIN, K.F., HEAL, D.J., SCHJOTT, J. & AUERBACH, S.B. (1996). In vivo criteria to differentiate monoamine uptake inhibitors (MARIs) from serotonin releasing drugs: sibutramine is a MARI. *Soc. Neurosci. Abs.*, **22,** 612.

HALFORD, J.C.G. & BLUNDELL, J.E. (1996). Metergoline antagonises fluoxetine-induced suppression of food intake but not changes in the behavioural satiety sequence. *Pharmacol. Biochem. Behav.*, **54,** 745 – 751.

HALFORD, J.C.G., HEAL, D.J. & BLUNDELL, J.E. (1995). Effects in the rat of sibutramine on food intake and the behavioural satiety sequence. *Br. J. Pharmacol.*, **114,** 387P.

HOLLIDAY, S.M. & BENFIELD, P. (1995). Venlafaxine: A review of its pharmacology and therapeutical potential in depression. *Drugs*, **49,** 280 – 294.

JACKSON, H.C., BEARHAM, M.C., MAZURKIEWICZ, S.E., HEAL, D.J. & BUCKETT, W.R. (1996a). Investigation of the mechanisms underlying the hypophagic effects of the 5-HT and NA reuptake inhibitor sibutramine in the rat. *Br. J. Pharmacol.*, **117,** 168P.

JACKSON, H.C., CHEETHAM, S.C., LUSCOMBE, G.P., MAZURKIEWICZ, S.E., VIGGERS, J.A. & HEAL, D.J. (1995). The anxiolytic effects of selective 5-HT reuptake inhibitors in the elevated plus-maze are not explained by reuptake inhibition or affinity for 5-$HT_{1A,\ 2A,\ 2C}$ and $_3$ receptor subtypes. *Br. J. Pharmacol.*, **114,** 391P.

JACKSON, H.C., HUTCHINS, L.J., MAZURKIEWICZ, S.E., HEAL, D.J. & BUCKETT, W.R. (1996b). Comparison of the effects of sibutramine and other monoamine reuptake inhibitors on food intake in the rat. *Br. J. Pharmacol.* **117,** 323P.

KASAMO, K., BLIER, P. & DE MONTIGNY, C. (1996). Blockade of the serotonin and norepinephrine uptake processes by duloxetine: In vitro and in vivo studies in the rat brain. *J. Pharmacol. Exp. Ther.*, **277,** 278 – 286.

KATOH, A., EIGYO, M., ISHIBASHI, C., NAITOH, Y., TAKEUCHI, M., IBII, N., IKEDA, M. & MATSUSHITA, A. (1995). Behavioral and electroencephalographic properties of duloxetine (LY248686), a reuptake inhibitor of norepinephrine and serotonin, in mice and rats. *J. Pharmacol. Exp. Ther.*, **272,** 1067 – 1075.

LANE, R.M. (1996). Pharmacokinetic drug interaction potential of selective serotonin reuptake inhibitors. *Int. Clin. Psychopharmacol.*, **11,** 31 – 61.

LAWTON, C.L., WALES, J.K., HILL, A.J. & BLUNDELL, J.E. (1995). Serotoninergic manipulation, meal-induced satiety and eating pattern: effect of fluoxetine in obese female subjects. *Obesity Res.*, **3,** 345 – 356.

LEVINE, L.R., ROSENBLATT, S. & BOSOMWORTH, J. (1987). Use of a serotonin reuptake inhibitor, fluoxetine, in the treatment of obesity. *Int. J. Obesity*, **11,** 185 – 190.

LIGHTOWLER, S., WOOD, M., BROWN, T., GLEN, A., BLACKBURN, T., TULLOCH, I. & KENNETT, G. (1996). An investigation of the mechanism responsible for fluoxetine-induced hypophagia in rats. *Eur. J. Pharmacol.*, **296,** 137 – 143.

LUSCOMBE, G.P., HOPCROFT, R.H., THOMAS, P.C. & BUCKETT, W.R. (1989). The contribution of metabolites to the rapid and potent down-regulation of rat cortical β-adrenoceptors by the putative antidepressant sibutramine hydrochloride. *Neuropharmacology*, **28,** 129 – 134.

MENNINI, T., BORRONI, E., SAMANIN, R. & GARATINNI, S. (1981). Evidence of the existence of two different intraneuronal pools from which pharmacological agents can release serotonin. *Neurochem. Int.*, **3,** 289 – 294.

MENNINI, T., GARATTINI, S. & CACCIA, S. (1985). Anorectic effect of fenfluramine isomers and metabolites: Relationship between brain levels and in vitro potencies on serotonergic mechanisms. *Psychopharmacology*, **85,** 111 – 114.

PAUL, I.A., DUNCAN, G.E., KUHN, C., MUELLER, R.A., HONG, J.-S. & BREESE, G.R. (1990). Neural adaptation in imipramine-treated rats processed in forced swim test: Assessment of time course, handling, rat strain and amine uptake. *J. Pharmacol. Exp. Ther.*, **252,** 997 – 1005.

PIJL, H., KOPPESCHAAR, H.P., WILLEKENS, F.L., OP DE KAMP, I., VELDHUIS, H.D. & MEINDERS, A.E. (1991). Effect of serotonin re-uptake inhibition by fluoxetine on food intake and spontaneous food choice in obesity. *Int. J. Obesity*, **15,** 237 – 242.

PROW, M.R., HANNON, S.D., ASPLEY, S., MARTIN, K.F. & HEAL, D.J. (1996). Comparison of the effects of sibutramine, fluoxetine and d-fenfluramine on extracellular 5-HT in rat anterior hypothalamus: An in vivo microdialysis study. *Br. J. Pharmacol.*, **120,** 351P.

ROWLAND, N.E., MORIEN, A. & LI, B.-H. (1996). The physiology and brain mechanisms of feeding. *Nutrition*, **12,** 626 – 639.

RYAN, D.H., KAISER, P. & BRAY, G.A. (1995). Sibutramine: A novel new agent for obesity treatment. *Obesity Res.*, **3,** 553S – 559S.

STRICKER-KRONGRAD, A., SOUQUET, A.-M. & BURLET, C. (1995). Effects of sibutramine on feeding behaviour in obese and lean Zucker rats. *Int. J. Obesity*, **19,** 145.

WEINTRAUB, M., RUBIO, A., GOLIK, A., BYRNE, L. & SCHEINBAUM, M.L. (1991). Sibutramine in weight control: A dose-ranging, efficacy study. *Clin. Pharmacol. Ther.*, **50,** 330 – 337.

WISE, S.D. (1992). Clinical studies with fluoxetine in obesity. *Am. J. Clin. Nutr.*, **55,** 181S – 184S.

WONG, D.T. & BYMASTER, F.P. (1976). Effect of nisoxetine on uptake of catecholamines in synaptosomes isolated from discrete regions of rat brain. *Biochem. Pharmacol.*, **25,** 1979 – 1983.

WONG, D.T., BYMASTER, F.P. & ENGLEMAN, E.A. (1995). Prozac (fluoxetine, Lilly 110140), the first selective serotonin uptake inhibitor and an antidepressant drug: Twenty years since its first publication. *Life Sci.*, **57,** 411 – 441.

WONG, D.T., BYMASTER, F.P., MAYLE, D.A., REID, L.R., KRUSHINSKI, J.H. & ROBERTSON, D.W. (1993). LY248686, a new inhibitor of serotonin and norepinephrine uptake. *Neuropsychopharmacology*, **8,** 23 – 33.

WONG, D.T., REID, L.R. & THRELKELD, P.G. (1988). Suppression of food intake in rats by fluoxetine: Comparison of enantiomers and effects of serotonin antagonists. *Pharmacol. Biochem. Behav.*, **31,** 475 – 479.

YARDLEY, J.P., HUSBANDS, G.E.M., STACK, G., BUTCH, J., BICKSLER, J., MOYER, J.A., MUTH, E.A., ANDREE, T., FLETCHER III, H., JAMES, M.N.G. & SIELECKI, A.R. (1990). 2-Phenyl-2-(1-hydroxycycloalkyl)ethylamine derivatives: Synthesis and antidepressant activity. *J. Med. Chem.*, **33,** 2899 – 2905.

(Received February 13, 1997
Revised May 9, 1997
Accepted May 14, 1997)