Serotonin (5-HT) Drugs: Effects on Appetite Expression and Use for the Treatment of Obesity

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Abstract: The pivotal role of 5-HT in the control of appetite was formally proposed nearly 30 years ago. In particular endogenous hypothalamic 5-HT has been implicated in the processes of within meal satiation and the end state of post meal satiety. Of the numerous 5-HT receptor subtypes currently identified, 5-HT_{1B} and 5-HT_{2C} receptors are believed to mediate the 5-HT induced satiety. 5-HT drugs such as d-fenfluramine, selective serotoninergic reuptake inhibitor (SSRIs) and 5-HT_{2C} receptor agonists have all been shown to significantly attenuate rodent body weight gain, an effect strongly associated with marked hypophagia. D-Fenfluramine, sibutramine, fluoxetine and the 5-HT_{2C} receptor agonist mCPP have also all been shown to reduce caloric intake by modifying appetite in both lean and obese humans. Specifically, 5-HT drugs reduce appetite prior to and after the consumption of fixed caloric loads, and reduce pre meal appetite and caloric intake at ad libitum meals. Clinically significant weight loss over a year or more can be produced by both d-fenfluramine and sibutramine treatment, but apparently not by the SSRI fluoxetine. Treatment with the preferential 5-HT_{2C} receptor agonist mCPP and the serotonin precursor 5-HTP has also been shown to produce weight loss in the obese. Issues around the actual and possible side effects of these compounds, and in the case of d-fenfluramine toxicity, have led to a search for drugs that act selectively on the CNS 5-HT receptors critical to the satiety response. Currently, a new generation of 5-HT_{2C} selective agonists have been developed (including Ro 60-0175, Org 12962, VER-3323, BVT-933 and YM348) and at least one, ADP356, is currently undergoing clinical trials. Hopefully, such drugs will be as or even more effective at regulating appetite and controlling body weight, and will also be free of their predecessors' side effect.

Key Words: Serotonin, 5-HT, food intake, appetite, satiety, sibutramine, d-fenfluramine, mCPP, ADP356, obesity, weight loss.

INTRODUCTION

Appetite is the expression of the regulatory processes that underpin the initiation and termination of meals, meal length and frequency, the amount and types of foods consumed, and determines the duration of between meal intervals (i.e. episodic). The short-term consequences of food ingestion produce a powerful inhibition on further intake. Signals generated from the very start of consumption act in concert to terminate eating behaviour. These signals provide the brain with an estimation of a meal rather than an accurate analysis of its content. It is worth drawing a distinction between short-term satiety signals generated by the physiological consequences of meal intake (episodic), and the long-term signals generated by the body's constant metabolic need for energy (tonic). The former are critical to the meal-by-meal regulation of energy intake. They underpin both the flux of appetite we experience and the pattern of eating behaviour we engage in across the day. The term episodic refers to the characteristic oscillations of feeding behaviour, which are common to many omnivores, and the flux in appetite we experience. The monoamine neurotransmitter serotonin (5-HT) has been linked with satiety, and thus this episodic meal-by-meal regulation of food intake [1]. In contrast, tonic inhibitory signals are not generated by the meal-by-meal flux of sensory, cognitive, pre-absorption and post absorptive factors so critical to the development of satiety. Instead tonic factors are generated by the storage and metabolism of energy. A key example is the adipose tissue hormone leptin, secreted in response to excess fat deposition and which also acts as an inhibitor of food intake. Previously, we have argued that serotonin and leptin form distinct aspects of appetite regulation, generated by marked differing processes, but both potently inhibiting food intake via the same hypothalamic circuitry [1].

The purpose of this review is to examine the efficacy of 5-HT drugs at inhibiting appetite and food intake, and ultimately inducing weight loss. The review will not be an in depth review of the pharmacology of 5-HT receptor subtypes and their role in feeding. Such material has already been covered in great detail in other recent reviews [2, 3]. Instead this review will focus a little on the research identifying the role of 5-HT in satiety and the functioning of the endogenous 5-HT satiety system. This review will then go on to examine the effects of 5-HT drugs on human feeding behaviour studies and clinical weight loss trials.

The monoamine neurotransmitter, serotonin (5-HT, 5-hydroxytryptamine) was first linked to the control of food intake, and of feeding behaviour, near 30 years ago. Early studies showed that increasing CNS 5-HT levels by using 5-HT precursors such as tryptophan and 5-hydroxytryptophan (5-HTP) produced a significant reduction in the food intake

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of laboratory animals. Increasing 5-HT activity by other mechanisms such as directly administering 5-HT into the CNS, blocking synaptic 5-HT breakdown or directly stimulating (agonising) 5-HT receptors also produced this hypophagic response [4-8]. Moreover, it was noted that neurotoxic lessioning of 5-HT neurons (with 5, 7-dihyroxytryptamine, 5, 7-DHT), or preventing 5-HT synthesis (using parachlorophenylanine, pCPA) which depletes neuronal 5-HT, not only prevented 5-HT induced hypophagia but increased food intake [9]. Even with the relatively non-specific pharmacological tools available to early researchers, it became apparent that CNS 5-HT was involved in controlling food intake. In 1977 Blundell [10] proposed that the 5-HT system not only had an inhibitory role in feeding, but was also a key satiety factor (part of a natural energy intake control mechanism).

Endogenous 5-HT Synthesis and 5-HT Receptors

Neuronal 5-HT is synthesised from the essential amino acid tryptophan. In the cytoplasm of the cell body, dietary l-tryptophan is hydoxylated to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase. At the terminal 5-HTP is rapidly decarboxylated by the enzyme l-amino acid decarboxylase to produce 5-HT. Most of the 5-HT produced is stored in pre-synaptic vesicles (taken up via a vesicle membrane transport). Once released, synaptic 5-HT continues to stimulate pre- and post-synaptic receptors until it is either re-absorbed into the pre-synaptic neuron for re-use (sodium dependent), or is converted to 5-hydoxyindole acetic acid (5-HIAA) by monoamine oxidase (MAO). During the late 1980's and early 1990s advances in the discovery and identification of novel 5-HT receptors took place [11]. At the present time the 5-HT receptors most directly implicated in feeding control are 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2C}. Post-synaptic 5-HT_{1B} and the 5-HT_{2C} receptors are generally believed to be involved in the 5-HT satiety system [12] (see later).

THE 5-HT SATIETY SYSTEM: INTERACTION WITH OTHER NEUROPEPTIDE SIGNALLING PATHWAYS

The regulation of energy balance is controlled by numerous peripherally generated signals many of which converge on the hypothalamic nuclei critical in controlling the expression of feeding behaviour. These contain a variety of neuropeptide systems which either stimulate (orexignic) or inhibit (anorexigenic) food intake. A number of studies have explored the extent to which 5-HT induced hypophagia may involve other neuropeptide signalling systems implicated in the hypothalamic regulation of appetite.

Serotonin and NPY

Neuropeptide Y (NPY) plays a significant role in the control of food intake and energy balance. Early studies have indicated an interaction between NPY and 5-HT with the observation that NPY induced hyperphagia is blocked by the 5-HT drug, d-fenfluramine. Additionally, hypothalamic NPY peptide levels are reported to decrease after treatment with 5-HT agonists and increase following 5-HT antagonist administration [13, 14]. Furthermore, reduced 5-HT availability is also found to decrease the density of NPY neurones [15]. NPY is synthesised in the arcuate nucleus (ARC) and released in a variety of hypothalamic areas, particularly the paraventricular nucleus (PVN) and ventromedial hypothalamic nucleus (VMH). As feeding evoked by NPY injection into the VMH is not altered by administration of 5-HT drugs (Currie, 2003), more recent studies have focused specifically on the potential interactive relationship of PVN NPY and 5-HT and the influences of this interaction on the control of feeding. Interestingly, only administration of 5-HT_{2A} agonists and antagonists into the PVN has been found to modulate NPY induced hyperphagia [16]. Although the nature of the 5-HT receptor expressed by PVN NPY neurones remains to be confirmed, these findings provide continued support for interaction between NPY and 5-HT mechanisms.

Serotonin and the Melanocortin System

The melanocortin system is now well established as a fundamental regulator of food intake and body weight. Using a combination of neuroanatomical, molecular and electrophysiological methods it has been shown that 5-HT drugs require a functional melanocortin system to exert their effects on feeding. Specifically, examining FOS-like immunoreactivity in response to D-Fenfluramine administration, it has been shown that anorectic 5-HT drugs activate pro-opiomelancortin (POMC) neurones in the ARC [17]. Electrophysiological studies, investigating the expression of green fluorescent protein under control of the POMC promoter, confirm that d-fenfluramine directly activates these neurones [17]. Alpha-melanocyte stimulating hormone (MSH) is the main breakdown product of POMC (particularly in terms of feeding). Up to 80% of α-MSH express mRNA for the 5-HT_{2C} receptor [17] and it is likely that these receptors contribute to the 5-HT-mediated activation of POMC neurones. Finally, pharmacological or genetic blockade of melanocortin 3 and 4 receptors is sufficient to attenuate the anorectic effects of 5-HT drugs [18]. These results suggest that 5-HT targets downstream melanocortin pathways, acting via 5-HT_{2C}, to decrease food intake and body weight.

Serotonin and Orexin

Both orexin and 5-HT are implicated in the regulation of feeding behaviour, as well as the sleep-wake cycle. Orexin neurones are located specifically in the lateral hypothalamus (LHA) from where they project to almost all parts of the brain. Interestingly, dense projections are observed in monoaminergic nuclei such as the noradrenergic locus ceruleus, the serotonergic dorsal raphe nucleus (DRN) and the dopaminergic ventral tegmental area. Of these, the serotonergic DRN is one of the densest projection sites [19]. Additionally, the serotonergic neurones in the DRN express both OX_1R and OX_2R [20, 21] and are excited by orexin-A [22, 23]. Furthermore, orexin has been shown to stimulate 5-HT release in the hypothalamus [24]. These anatomical projections and interactions suggest an involvement of a serotoninergic pathway in orexin-induced behaviour. This has also been reported with evidence for a 5-HT-based contribution to orexin-induced stimulation of grooming [25]. However, it remains for studies to be published that focus on the interaction of 5-HT and orexin in the mediation of feeding behaviour. As 5-HT exerts an inhibitory effect on food intake it is likely that orexin projections to DRN form

part of an inhibitory feedback loop to the hypothalamus [26]. This probably occurs via the 5-HT_{1A} and 5-HT_{2C} receptor mechanisms [27, 28]. In support of this, 5-HT_{1A} receptor immunoreactivity has been identified, amongst other places, in the orexin neurones of the LHA [29]. Furthermore, it has been shown that 5-HT hyperpolarises orexin neurones through the 5-HT_{1A} receptor [30]. This inhibitory serotoninergic input is also likely to be important for the physiological regulation of the orexin system.

ENDOGENOUS SEROTONIN AND ALTERED NUTRITIONAL STATUS

Reduced Energy Intake or Body Weight

A variety of models can be employed to introduce perturbations in nutritional status. These provide insight into the nutritional and physiological regulation of neurotransmitter systems that act to control feeding and energy balance. With regard to reduced energy intake, in malnourished animals a significant reduction in CNS 5-HT concentrations is observed in a number of brain areas [31]. Moreover, fasted animals exhibit intense food-seeking behaviour and increased food-intake when food is made available. Such food-deprivation increases the turnover of 5-HT in the hypothalamus [32]. Furthermore, it also significantly reduces the ration of neurones in the Ventromedical Hypothalamus (VMH) that respond to 5-HT [33]. This change in responsiveness to 5-HT, possibly due to alterations in the expression of 5-HT receptor subtypes, may partially explain the increased motivation for feeding following fasting. Interestingly, plasma concentration of the 5-HT precursor tryptophan is reduced in female volunteers placed on a week four hypo-caloric diet [34]. The reductions in tryptophan correlated with the degree of weight loss observed in the women over the 28 day study period. The effect of dieting on tryptophan has been observed a number of times and suggests that dieting in humans may lead to diminished central 5-HT function. In one such study dieting was also shown to increase to prolactin response to the 5-HT_{2C} receptor preferential agonist mCPP [35]. These data suggest that chronic restrictions of food intake increase the sensitivity of 5-HT_{2C} receptor. To summarise, hypo-caloric diets or inadequate nutrition appear to reduce endogenous 5-HT and increase the sensitivity of 5-HT receptors.

Rat cancer models provide chronic anorexic conditions. The hypothalamic 5-HT system, specifically in the VMH, also plays a critical role in this anorexia model [36]. VMH 5-HT concentrations are increased in tumour bearing rats, and in normal rodents following injection of IL-1α into the VMH [37]. Similarly, levels of tryptophan (the 5-HT precursor) are elevated in tumour bearing rats and demonstrate a positive correlation to the degree of anorexia [38]. Strengthening the relationship between tumour, 5-HT and anorexia is the observation that plasma tryptophan levels normalise after tumour resection in patients, resulting in improved food intake [39]. Data from such models of anorexia supports the hypothesis that 5-HT is a critical anorectic agent.

Increased Energy Intake or Body Weight

With regard to increased energy intake, study of obese Zucker rats has provided insights into the effects of chronic hyperphagia and obesity on the regulation of 5-HT. A number of studies have demonstrated that in this leptin-resistant obesity model, abnormal hypothalamic 5-HT activities contribute to hyperphagia and weight gain. Specifically, whilst these animals showed an unaltered pattern of 5-HT release associated with food deprivation and re-feeding, baseline levels of 5-HT are significantly lower in obese than lean animals [40]. These low levels points to an impaired postsynaptic monoaminergic action to produce an adequate metabolic response in obese Zucker rats in response to feeding state. Other laboratories have shown obese Zucker rats have lower hypothalamic levels of the 5-HT metabolite 5-HIAA [41]. This suggests these animals have reduced rates of endogenous 5-HT turnover. Moreover, this inadequacy in the functioning of the endogenous 5-HT system appears to permit weight gain.

Models of genetic obesity, such as the Zucker rat, provide valuable tools in determining the role of neurotransmitters in the regulation of energy balance. However, dietary induced obesity induced by exposure to highly-palatable food, is the rodent model that most closely resembles human obesity. In this model, the severity of obesity varies between individuals, with approximately 50% of a population developing obesity when placed on a palatable diet [42]. These obesity prone rats show abnormalities of diurnal and fasting-induced alterations in brain 5-HT turnover. In contrast to the obesity-resistant animals, obesity-prone rats fail to demonstrate diurnal variation in 5-HT turnover in the Acurate Nucleus (ARC) and Paraventriculatr nucleus (PVN). Additionally, obesity-prone rats show significant reductions in VMH 5-HT turnover compared to their obesity-resistant counterparts [43]. These abnormalities may constitute part of a genetic programming predisposing prone rats to become obese when exposed to palatable food. Furthermore, once obesity develops these abnormalities are normalised and may contribute to the persistence of the obesity, with rats avidly defending their elevated body weight against food-restriction. Interestingly, in obese humans plasma concentrations of tryptophan are reported low. They are also not normalised by substantial weight reduction [44]. In rodents, an unresponsive endogenous 5-HT system or reduced 5-HT turnover is associated with obesity proneness. In humans, reduced levels of CNS 5-HT in the obese may contribute to an inability to adequately control their own daily caloric intake.

THE EFFECTS OF 5-HT DRUGS ON FOOD INTAKE IN RODENTS

5-HT Receptors and Food Intake (Animal Studies)

From the initial identification of 5-HT as a key inhibitor system, a search began for which receptors mediated the 5-HT satiety response. The earliest studies employed 5-HT manipulations (i.e. drugs which promote the release of 5-HT and/or prevent its re-uptake). The resulting suppression in food intake was pharmacologically challenged with selective 5-HT receptor antagonist to reveal the exact 5-HT receptor subtypes underlying drug induced hypophagia.

Most of the studies employing antagonists to identity receptors critical to 5-HT induced hypophagia used fenfluramine / d-fenfluramine induced food suppression as the model. This was no doubt in part because fenfluramine / d-

fenfluramine induced reduction in food intake and reduction of body weight gain were robust models, and partly due to the fact that fenfluramine and later d-fenfluramine had proven to be effective treatments for human obesity at the time. The use of selective 5-HT receptor antagonists of various 5-HT_1 and 5-HT_2 receptor subtypes had indicated d-fenfluramine induced hypophagia is mediated by 5-HT_{1B} receptors [45]. This was based on the evidence of a number of studies which blocked d-fenfluramine actions with ant-agonists of 5-$HT_{1A/1B}$ receptors, but failed to block d-fen-fluramine action with antagonists of 5-$HT_{2A/2C}$ receptors [46-48]. Indeed recently, Simansky and Nicklous [49] blocked d-fenfluramine induced reduction in food intake by infusion of the highly selective 5-HT_{1B} receptor antagonist directly into the paerebrachial nucleus of the rat. However, not all experimental evidence confirms this central role of 5-HT_{1B} receptors. Another recent study by Vickers *et al*. [50] demonstrated that hypophagia induced by d-fenfluramine could be blocked by pre-treatment with the highly selective 5-HT_{2C} receptor antagonist SB-242084, but not by pre-treatment with the highly selective 5-HT_{1B} receptor ant-agonists GR-127935 and SB-224289.

The selective serotoninergic re-uptake inhibitor (SSRI) fluoxetine produces a reliable reduction in food intake that is not easily blocked by 5-HT antagonists [51-53]. However, fluoxetine induced hypophagia has been partially, and fully blocked by the 5-$HT_{1/2}$ antagonist metergoline [54, 55 respectively]. These data suggest that at the doses used, fluoxetine induced hypophagia may be mediated by the 5-HT_{1B} and 5-HT_{2C} receptor subtypes critical to meditating the effects of D-Fenfluramine on food intake. In contrast to fluoxetine, the hypophagia induced by other SSRIs such as sertraline [56] appear to be more reliably blocked by 5-HT antagonists acting on 5-HT_{1B} and 5-HT_{2C} receptors [57].

Along with the development of more selective 5-HT receptor antagonists, selective 5-HT receptors agonists have became available. More recently, scientists have had the opportunity to work with selective 5-HT agonists specifically developed as novel obesity treatments. In rodents, direct agonism of 5-HT receptors reliably produces reductions in food intake. Moreover, agonists of 5-HT_{1B} and/or 5-HT_{2C} receptor subtypes produce the changes in feeding behaviour consistent with the operation of satiety (see later). Such agonist agents include mCPP (preferential 5-$HT_{1B/2C}$ agonist), TFMPP (preferential 5-$HT_{1B/2C}$ agonist), CP-93, 129 (selective 5-HT_{1B} agonist), CP-94 253 (selective 5-HT_{1B} agonist) and Ro 60-0175 (selective 5-HT_{2C} agonist) [58-65, 28 respectively]. These food intake studies appear to confirm the role of both receptor subtypes in mediating the 5-HT hypophagic response. However, was drug induced hypophagia due to enhanced satiety?

5-HT and Feeding Behaviour (Animal Studies)

It is important to distinguish between drugs that reduce food by acting on the natural satiety mechanisms and those that reduce food intake by inducing nausea, sedation, hyperactivity, or malaise. Early pre-clinical studies comparing fenfluramine with amphetamine showed that both drugs produced similar effects of food intake but distinct effects on feeding behaviour [66]. Specifically, fenfluramine appeared to enhance satiety by reducing meal size, whilst amphetamine fragmented normal feeding behaviour. Subsequently, many studies have shown that 5-HT releasing and re-uptake inhibiting drugs produce changes in feeding behaviour, as measured by the Behavioural Satiety Sequence (BSS) or other behavioural assays, which are consistent with the operation of satiety.

In particular, many serotoninergic drugs have been shown to enhance the behavioural satiety sequence (BSS) [67]. The BSS is a stochastic progression of behaviour in which, as satiety develops, initial feeding behaviour is replaced with activity, then grooming and then terminates with a prolonged period of resting/inactivity. If drugs reduce food intake but disrupt or delay this temporal pattern of behaviour, it is likely that drug induced hypophagia is at least in part due to mechanisms other than satiety disturbing normal feeding behaviour (such as hyperactivity, sedation, nausea or malaise). Alternatively, if the drug induces hypophagia but leaves the sequence untouched, then it can be concluded that this drug does not interfere with the natural development of satiety. However, if the drug reduces food intake and enhances the BSS (early termination of feeding behaviour and the earlier onset of each of the other phases of the sequence) then it is likely its primary mechanism of action is satiety [67].

Fenfluramine and d-fenfluramine have been shown to adjust feeding behaviour in a manner consistent with the operation of satiety [68-70]. Fluoxetine, sertraline and other SSRIs have also been shown to produce similar effects as d-fenfluramine on various behavioural indices of appetite in rodents inducing the BSS [55, 67, 71-73]. Moreover, the current globally licenced anti-obesity treatment sibutramine (5-HT and noradrenaline re-uptake inhibitor - SNRI) also enhances the BSS [67]. Of the drugs which are selective agonists of 5-HT receptors, the selective 5-HT_{1B} receptor agonists CP -94, 253, the preferential 5-$HT_{1B/2C}$ receptor agonists mCPP and TFMPP, and the selective 5-HT_{2C} all produce changes in feeding behaviour consistent with the operation of satiety [61, 65, 67, 72]. Notably, drugs which also agonise other 5-HT receptor subtypes such as DOI (5-$HT_{2A/2C}$) or RU-24969 (5-$HT_{1A/1B}$) disrupt the BSS by inducing hyperactivity, a critical side effect induced by some 5-HT drugs indicating unsuitability for further development.

5-HT Receptor Knockouts, Food Intake and Obesity

The final and perhaps most convincing evidence for the critical role of 5-HT_{2C} receptors in mediating the hypophagic effects of endogenous 5-HT comes from 'knock out' mice. Tecott *et al*. [75] successfully produced a breed of mice that possessed no functional 5-HT_{2C} receptors. Interestingly, these 5-HT_{2C} knock out mice demonstrated marked hyperphagia from five weeks after birth. This was accompanied by marked hyperactivity. Obesity developed later in the life of these animals as hypophagia persisted but hyperactivity declined [76]. Interestingly these knock out mice were also resistant to d-fenfluramine induced hypophagia [77]. D-Fenfluramine treatment still produced a significant reduction in food intake in the mutant mice. Moreover, in response to the drug some indication of enhanced satiety in the BSS paradigm was apparent. However, these responses were considerably lesser in magnitude in the knockout mice compared to control wild-type mice. It would thus seem that

obese 5-HT_{2C} knock out mice have a deficient endogenous 5-HT satiety system. Similarly, 5-HT_{1B} receptor knockout mice are also significantly heavier than wild types [78], an effect associated with significantly greater food consumption. However, these animals appear just to be larger rather than fully obese [2].

5-HT DRUGS, FOOD INTAKE AND FEEDING BEHAVIOUR IN HUMANS

Much of the original data on the effects of pharmacological manipulation 5-HT on human food intake came from studies first employing racemic fenfluramine and then D-Fenfluramine. Studies employing the SSRI fluoxetine and then sibutramine were also subsequently published. In addition over the past 12 years a number of studies using 5-HT precursor 5-HTP and preferential 5-HT receptor subtype agonists have also been published. Such studies demonstrate the robust hypophagia produced by increasing neuronal or synaptic levels of 5-HT or directly agonising specific 5-HT receptor subtypes. Moreover, the careful description of the effects of the manipulation of behaviour and subjective of ratings hunger and satiety confirm that these pharmacological inventions have produced hypophagia by modifying the expression of human appetite.

5-Hydoxy-Tryptophan (5-HTP)

The 5-HT precursor, 5-HTP, has been shown to produce potent effects on self reported food intake in the obese. In a twelve week study twenty obese individuals, defined as 'hyperphagics' were treated with either 5-HTP (900 mg) or placebo [79]. During the first six weeks of the study the participants were given no diet regime. During the second six weeks of the study all participants were prescribed a diet. All participants recorded their food intake in a diary at regular intervals before treatment commenced and during the non-diet and diet phases. During the treatment those receiving 5-HTP lost 5.0 kg in body weight from baseline (1.7 kg in the non-diet phase and 3.3 kg in the diet phase) compared to a non-significant reduction in body weight of 1.2 kg seen in those receiving placebo for 12 weeks. Those receiving the drug reported significant decreases in daily energy intake of 41% (5636 kJ) in the non-diet phase and 60% (8202 kJ) in the diet phase from baseline (reductions in self reported food intake in the placebo group were 14% and 24% respectively). In a shorter study the same group replicated their original findings [80]. In a two week study 25 overweight type 2 diabetics were randomly allocated to receive either placebo or 5-HTP (750 mg). Again diet diaries were used. In the 5-HTP treated group weight loss from baseline was 2.1 kg over the two weeks. This was accompanied by significant decreases of self reported energy expenditure of 21% (1700 kJ) on day 7 and of 22% (1760 kJ) on day 14. Examining these figures it is likely there was much underreporting of energy intake by participants in the trial as a whole. However, hypophagia does appear to be associated with weight loss.

Fenfluramine and D-Fenfluramine

The effects of fenfluramine on human food intake were demonstrated in the late 1970s. For instance, a key study by Rogers and Blundell [81] demonstrated that a single dose of fenfluramine (60 mg) given to lean healthy males could reduce the intake of food during a lunchtime meal by 789 KJ (26%). This reduction in caloric intake was accompanied by a significant decrease in eating rate and desire to eat, indicative of a drug induced modulation of normal appetite. The reduction in desire to eat prior to the meal and the low rate of consumption at the start of the meal suggests fenfluramine had enhanced the pre-meal satiety state retarding normal hunger. Similarly, Foltin *et al*. [82] found that fenfluramine (40 mg), given to healthy normal weight males and females, living in a residential laboratory, reduced their total daily caloric intake. This was achieved by a reduction in meal size rather than number, suggesting fenfluramine enhanced processes within meal satiation, without producing any compensatory weakening of the between meal state of satiety.

D-Fenfluramine induced hypophagia in humans has been demonstrated in a number of differing laboratory-based feeding paradigms. Not all are detailed here. It is, however, useful to consider some studies, which indicated the efficacy of both acute and chronic d-fenfluramine doses on food intake, in both lean and in the obese. With regard to the effects of acute doses of d-fenfluramine, Goodall and Silverstone [83] conducted a study in lean healthy males. They found a single 30 mg dose of d-fenfluramine significantly reduced cumulative intake and eating rate over a 2-hour period by approximately 23%. As with fenfluramine, d-fenfluramine produced a significant decrease in pre-meal hunger ratings in this ad libitum feeding paradigm. Blundell and Hill [84] also noted that d-fenfluramine produced significant reductions in hunger in both the lean and the obese prior to a meal. Moreover, the effect on hunger was greater in magnitude in the obese. The drug also reduced prospective consumption in both the obese and lean and enhanced feelings of fullness in the lean alone.

Drent *et al*. [85] gave 30 mg a day of d-fenfluramine to overweight and obese individuals over a 9 week period, in a randomised, placebo controlled, double blind trial. D-Fenfluramine produced a marked reduction in self reported food intake throughout the trial duration. During the 9 week study those receiving d-fenfluramine lost 3.1kg whilst those in the placebo group actually gained 0.2 kg. D-Fenfluramine treatment reduced total self reported daily food intake from baseline by 30%, significantly greater than the reduction in self reported total daily food intake from baseline reported placebo condition (15%). As the placebo group failed to lose weight it is possible there was underreporting of energy consumed by participants in the trial as a whole. However, despite this the effects of d-fenfluramine on body weight and food intake are still impressive. Analysis of the food diaries revealed that the overall reduction in energy intake in the d-fenfluramine condition came from reductions in energy intake both during meals and in snacks. D-Fenfluramine treatment reduced meal and snack size but not number. The Drent *et al*. study demonstrated that d-fenfluramine induced reductions in food intake were associated with the drug's effect on body weight. Secondly, d-fenfluramine induced reductions in food intake appeared to be a robust phenomenon, even when the drug is given chronically to the obese.

Fluoxetine

With regard to fluoxetine, a study by McGuirk and Silverstone [86] examined the effect of 2 week's treatment with fluoxetine (60 mg) on food intake. The study employed lean healthy male participants in a double blind, placebo controlled, crossover design. Food intake and eating behaviour were assessed on three separate probe days (days 1, 8 and 15). Over the 2 weeks treatment significantly more weight was lost in the drug condition (1.07 kg) than the control (0.15 kg). Fluoxetine treatment reduced cumulative intake at the 2 hour buffet meal on day 1 (by 15.7%) and day 8 (by 12.6%), but not day 15. A significant reduction in hunger in the fluoxetine group was reported on day 8. It is not clear from this study whether day 15 was the last day of fluoxetine treatment of the first day of the wash out period. In another study of the effects of 14 days administration fluoxetine on meal patterns were assessed [87]. The fluoxetine (60 mg) treated group lost 3.6 kg compared to a weight gain of 0.3 kg seen in placebo control group. Self-reported meal and snack intake were significantly reduced by fluoxetine treatment compared to placebo control.

Lawton *et al*. [88] carried out a more detailed study of the effects of fluoxetine (60mg) on the food intake and eating behaviour of obese females. As with the McGuirk and Silverstone study [86] volunteers underwent 14 days treatment with both drug and placebo in a double blind randomised crossover design. On days 7 and 14 participants returned to the laboratory to receive fixed test meals to assess if fluoxetine induced hypophagia was intensified or weakened by equi-caloric test meals differing in macronutrient composition. As in the previous fluoxetine studies, over the 2 weeks treatment significantly more weight was lost in the drug condition (1.97 kg) compared with the control (0.04 kg). This was associated with a significant reduction in post-test meal hunger when on drug. Fluoxetine increased the satiety impact of fixed equi-caloric test meals irrespective of their macronutrient composition. Direct measurement of subsequent food intake after the test meal on days 7 and 14 showed that fluoxetine produced a 27% (198 kcal) reduction in energy consumption at the ad libitum evening meal. Additionally, during the study participants were also asked to fill in daily food diaries. These revealed that fluoxetine produced a self-reported reduction in daily energy of 22.4% (421 kcal per day) during the 14 days of treatment.

The data from the McGuirk and Silverstone [86] study would seem to suggest that tolerance appears to develop to fluoxetine induced hypophagia after two weeks chronic dosing. However, in a 16 week out-patient study in the obese, Ward *et al*. [89] invited participants to attend the laboratory at weeks 7 and 16 of the treatment. On these days they found that chronic fluoxetine administration continues to reduce total food intake in participants. Specifically, fluoxetine reduced the mean number of total eating occasions within a study day. Unlike drug induced hypophagia, tolerance did appear to develop to drug induced weight loss in this study. Fluoxetine induced weight loss was significantly greater than placebo at the week 7 time point but not at the week 16 study endpoint.

Sibutramine

As with d-fenfluramine and fluoxetine, acute doses of sibutramine, a 5-HT and nor-adrenaline reuptake inhibitor (SNRI), have been shown to reduce food intake [90] and appetite in lean male participants [90, 91]. Whilst, Hansen *et al*., [91] studied the effect of 30 mg of sibutramine on energy expenditure, they also noted that the drug enhanced the inhibition of appetite produced by the set breakfast (2.1 kJ), given to all participants. Effects on subsequent ad libitum food intake were not measured in this study. However, sibutramine treatment was shown to increase the satiety impact of a fixed load of food. In Chapelot *et al*.'s study, [90] the effect of a single dose of 15 mg sibutramine on all daily energy consumption was examined in a placebo controlled counter balanced design. The drug, taken prior to a fixed load breakfast, reduced the total caloric intake on the study by 1304 kcal (approximately 12%). This was achieved through significant reductions in caloric intake at both lunch (637 kJ) and dinner (393 kJ). The number of food items eaten during the day was significantly reduced by an average of 1.6 items (approximately 10%), an effect which occurred mainly at lunch. Along with pronounced hypophagia and changes in feeding behaviour at lunch, the 15 mg dose of sibutramine significantly reduced hunger 4 hours after dosing, an effect which coincided with the start of the said lunch.

The effects of sibutramine on food intake and appetite in the obese were examined by Rolls *et al*. [92]. Rolls conducted a 14 day study similar in design to previous fluoxetine studies [86, 88]. Participants were invited into the laboratory on days 7 and 14 to have their eating behaviour directly assessed. In this double blind placebo controlled cross over study two doses of the drug were used, the normally prescribed 10 mg, and a higher dose of 30 mg. Participants took the drug before breakfast. On study days participants attended the laboratory for breakfast, lunch and dinner. All the meals consumed within the laboratory were ad libitum. The effect of the 30mg dose of sibutramine on food intake, subject measures of appetite and on body weight were observed earlier in the study and were greater in magnitude. Sibutramine 30 mg reduced caloric intake by 1763 kJ (23%) on day 7 and by 2079 kJ (26%) on day 14 (from placebo). Sibutramine 10 mg significantly reduced total caloric intake only on day 14 (by 1290 kJ or 19%). The significant reductions in total caloric intake (on days 7 & 14 for 30mg, on day 14 only for 10 mg) came from significant reductions in energy intake at both lunch and at dinner, but not at breakfast. Whether drug induced hypophagia was greater at lunch or at dinner is not clear. However, sibutramine-induced hypophagia was accompanied by reduction of pre-meal hunger and prospective consumption at the 30 mg dose. It is notable that in both the Chapelot and Rolls studies [90, 91], significant effects on appetite were observed prior to and not after the ad libitum meal. After an ad libitum meal, drug induced reductions appear to 'normalise' the subsequent post meal appetite ratings, rather than suppressing them, an effect which tends to occur after a fixed load. In both studies, under sibutramine treatment the same post meal satiety was attained, in lean and obese, by significantly less food consumption.

In the Rolls *et al*. study [92] over the 14 days of dosing, tolerance to the hypophagic effects of sibutramine did not appear. Moreover, changes in food intake and in appetite were accompanied by significant drug induced weight loss. At day 7 the sibutramine 10 mg had reduced body weight by 0.7kg, and by day 14 body weight was reduced by 0.8 kg compared to placebo. Sibutramine 30 mg had reduced body weight by 0.6 kg on day 7 and by 1.2 kg on day 14. So it would seem that both hypophagia and associated weight loss are produced by sibutramine treatment in the obese. Hansen *et al*. [93] conducted an eight week randomised placebo controlled double blind study in the obese. The study was devised to examine the effect of 15 mg of sibutramine in energy expenditure and involved two laboratory visits (at the start and at the end of treatment) in which the participants were asked to live for 32 hours in a respiration chamber. During their stay participants were allow to eat freely at set meals and their appetite was assessed. Whilst the authors did not report the effects of sibutramine on food intake at these visits they did report that the drug significantly decreased daily ratings of hunger and prospective food consumption on both the first (day 1) and the last (day 56) day of sibutramine treatment. During the study sibutramine produced a significant decrease in body weight of 2.4 kg compared with a slight rise of 0.3 kg seen in the placebo condition. As the authors reported that sibutramine had little effect on energy expenditure it is likely that weight loss observed was due to the effects of the drug on food intake.

Perhaps the most convincing demonstration of the link between sibutramine induced hypophagia and sibutramine induced weight loss is a recent study by Barkeling *et al*. [94]. Barkeling and colleagues devised a multiphase study to examine the effects of sibutramine on appetite in the obese, to see whether this predicted weight loss on a subsequent long-term trial, and finally to see whether sibutramine still reduced food intake after 10 months of treatment. Obese volunteers were recruited to a 14 day fully randomised, placebo controlled cross over study. After 14 days treatment with 15mg sibutramine or placebo the participants were invited into the laboratory to consume an ad libitum lunch. Sibutramine produced a 16% kcal reduction in energy intake at the test lunch during the initial double blind study. The participants then went on 10 month open label treatment with sibutramine. At the end of the 10 months the participants were invited to return to the laboratory for a final time and given the same ad libitum meal they had received on previous occasions. Compared to their pre weight loss trial placebo intake, the participant lunch intake was reduced by 27%. Sibutramine also significantly increased ratings of fullness and decreased prospective consumption after the fixed breakfast but not after the ad libitum lunch. It is particularly interesting that the appetite response to sibutramine was not diminished after 10 months of treatment. Notably, the initial effect of sibutramine on appetite in the 14 day trial predicted the effect of sibutramine on body weight during a subsequent 10 month open label weight loss trial.

Preferential and Selective 5-HT Receptor Agonists

Direct agonism of 5-HT receptors also potently reduces food intake. mCPP (5-HT $_{1B/2C}$ receptor preferential agonist) has been shown to reduce food intake in the rat via activation of 5-HT_{2C} receptors. In humans a number of studies have shown that mCPP also reliably reduces food intake. The effect of an acute dose of mCPP (0.4 mg/kg) was first examined in a double blind, placebo controlled, crossover design study, conducted with lean healthy female volunteers [95]. The participants were dosed orally with either placebo or mCPP 150 minutes prior to the presentation of a buffet lunch. mCPP treatment produced a 30% (approximately 1000 kJ) reduction in food intake at the ad libitum meal. In this study the effect on mCPP on food intake was significantly associated with reductions in pre-meal hunger ratings. The initial study was replicated in a larger group of lean and healthy male and female volunteers [96]. Again the drug was effective at reducing food intake in women (28% reduction, 1205 kJ) and also in men (20% reduction, 1219 kJ). The drug again significantly reduced ratings of hunger prior to the meal in men and women (150 minutes post dosing), an effect which occurred slightly after peak plasma levels of mCPP (120 minutes post dosing) and just prior to the lunch.

The effects of mCPP on appetite and body weight, but not on food intake, have also been studied in the obese [97]. Participants were treated for 14 days of treatment with mCPP (20 mg twice a day for women, 25 mg twice day for men). During this placebo control, double blinded crossover trial, the obese lost 0.8 kg from baseline, significantly greater weight loss than observed in placebo (0.04 kg). On the penultimate day of dosing participants were invited to the laboratory and blood samples were taken to assess mCPP level and prolactin response. Participants were given hunger rating scales to fill in during this procedure. Drug treatment produced a significant decrease in hunger ratings. Collectively, these three studies demonstrate that mCPP is effective at reducing food intake and appetite in the lean, and body weight and appetite in the obese. However, in the lean participants mCPP also produced transient but significant increases in subjective ratings of nausea, light-headedness and anxiety [95, 96]. Transient increases in blood pressure and heart rate have also been observed in response to acute doses of mCPP [98]. The development of more specific 5-HT_{2C}, agonists could be an important development for the treatment of obesity, particularly if these avoid some of the transient side effects produced by the less specific preferential 5-HT receptor agonist mCPP. It should be noted that the hypophagic affects of mCPP and more selective 5-HT_{2C} receptor agonists in the obese remain to be demonstrated.

Of course, the 5-HT_{2C} receptor is not the only receptor implicated in the mediating the effects of the endogenous 5-HT satiety system. A novel 5-$HT_{1B/1D}$ receptor agonist, sumatriptan has also been found to significantly decrease food intake in healthy women [99]. In a double blinded, placebo controlled crossover design study the effects of an acute dose of sumatriptan 6 mg on a buffet style lunch were assessed. The drug injection produced a 23% reduction in food intake (approximately 850 kJ) from placebo at the lunch. Most notable was the 34% decrease in fat intake observed during the buffet meal after sumatriptan dosing. No significant effects of the drug on ratings of nausea and light headedness were observed in this study. No significant effects were observed on appetite either, suggesting the study may have been statistically underpowered.

5-HT DRUGS AND OBESITY: RODENT STUDIES

D-Fenfluramine and SSRIs

Drugs which promote 5-HT release or re-uptake inhibition have been proven to inhibit body weight gain in various rodent models. For instance, Fisler and colleagues [100] found that daily injections of d-fenfluramine (10 mg/kg) over a 12 day period were particularly effective at abolishing weight gain associated with exposure to high fat diets in Osborne-Mendel rats (a strain particularly susceptible to dietary induced obesity). The reduction in body weight gain was associated with a marked reduction in caloric intake. Similarly, Vickers *et al*. [101] noted that tolerance did not develop to the body weight gain attenuating effects of d-fenfluramine (6 mg/kg/day infused peripherally via a mini-pump) during a 14 day study in Lister hooded rats. The animals treated with d-fenfluramine weighed 5% less than controls at the end of the study. Again, in this study these effects on body weight were associated with drug induced reductions in food intake. However, d-fenfluramine induced hypophagia was less pronounced in the second week of the study.

In a longer study (28 days), d-fenfluramine was administered (2.5 mg/kg) twice daily [102]. Again the drug attenuated body weight gain and reduced food intake. Animals treated with d-fenfluramine for 28 days weighed approximately 50g (12%) less than controls. This time no tolerance developed to the hypophagic effects of d-fenfluramine. The same effects on body weight gain and food intake have been produced by the administration of a number of other serotoninergic drugs. For instance, SSRI's such as fluoxetine [103, 104] sertraline [105], fluvoxamine [106] and paroxetine [107] have also all been shown to attenuate body weight gain in various rodent models, an effect normally associated with significant hypophagia.

5-HT Receptor Agonists

The direct agonism of 5-HT_{2C} receptors also appears to effect weight gain in rodent models. For instance, the inhibitory effects of the preferential 5-HT_{2C} receptor agonist mCPP on rodent body weight gain have been demonstrated by Vickers *et al*. [101, 102]. In their first study the effects of mCPP (12 mg/kg/day delivery by implanted mini-pumps) on body weight were linked, at least in part, with hypophagia. Moreover, during the study period tolerance did not develop to the effects of mCPP on rodent body weight gain. Animals treated with mCPP weighed 8% less than controls by the end of the study. As mCPP also agonises a number of other 5-HT receptors (e.g., 5-HT_{2A} and 5-HT_{2B} receptors) and activation of any of these receptors could account for drug induced attenuation of body weight gain. However, studies with selective antagonists demonstrate mCPP induced hypophagia specifically by activation of the 5-HT_{2C} receptor [108]. It is therefore likely that at least the hypophagic component of mCPP induced weight loss is mediated via activation of the 5-HT_{2C} receptor. In the second study, oral doses of mCPP (10 mg/kg twice daily) were given for 28 days. Again mCPP induced significant attenuation of body weight gain and reductions in daily food intake. Animals treated with mCPP for 28 days weighed approximately 50g (12%) less than controls. In this study no tolerance appears to develop to the hypophagic effects of the 5-HT_{2C} agonist. Pair-feeding to match the food intake of mCPP treated animals produced the same degree of weight gain suggesting that attenuation of body weight gain was attributable to the drug's hypophagic effects.

The effects on rodent body weight of a number of more selective 5-HT_{2C} receptor agonists have recently been studied. In the Vickers *et al* [101] study, the effects of 14 day treatment with Ro 60-0175 (26 mg/kg/day), infused into the animal via implanted mini-pumps were detailed. Ro 60-0175 significantly reduced body weight gain. Animals treated with Ro 60-0175 weighed 10% less than controls at the end of the study. Like mCPP, Ro 60-0175 reduced food intake over the treatment period, however, tolerance did appear to the hypophagic effect of the drug at day 11. Similarly, YM348, another potent and highly selective 5-HT_{2C} receptor agonist also produced an attenuation of body weight gain (at doses of 3 and 20 mg/kg/day) over a two week treatment period [109]. Animals treated with the higher dose of YM348 (30 mg) weighed 21.5% less than controls at the end of the study. Again, tolerance appeared to develop to drug induced hypophagia in the second week of treatment. In data from a recently presented study of the novel selective 5-HT_{2C} receptor agonist APD356, multiple doses (4.5, 9. 18 and 36 mg/kg) of the drug were shown to inhibit the development of dietary induced obesity [110]. APD356 treatment significantly reduced body weight gain in male and female rats, an effect associated with an initial episode of marked hypophagia. During the study tolerance appeared to develop to the hypophagic effects of all doses of APD356.

5-HT DRUGS AND WEIGHT LOSS: CLINICAL DATA

It appears from clinical data, that if hypophagia is the primary mechanism by which 5-HT induces weight loss, then 5-HT drugs must restrain the motivation to eat and maintain lower levels of food consumption for considerable periods of time. Again, much of the early clinical data on weight loss comes from studies employing the now withdrawn fenfluramine and d-fenfluramine. Indeed, clinical data on the effects of fenfluramine on body weight have been collected and published since the late 1960's. Given the amount of studies conducted and given this drug is now withdrawn, these studies will not be detailed. However, an extremely useful meta-analysis of both early drug and more recent drug trials has been produced by Haddock *et al*. [111].

Fenfluramine

For those interested in these numerous early therapeutic trials of fenfluramine, we suggest the reader consults an extensive review of fenfluramine published by Pinder and colleagues [112] in 1975. Examination of the review reveals that most of the early fenfluramine studies were small scale (participant numbers in each condition were often under 30) and compared the effects of fenfluramine either with placebo or other then available anorectic drugs (such as Deithylpropion, Manzindol, Phentermine, d-Amphetamine) generally over periods of less than 12 weeks. In these studies fenfluramine induced weight loss varied between 1.2 kg to11.9 kg depending on the duration of the trial, the dose of fenfluramine given, the additional dietary advice/ regime given to

the participants and the differences between the target population included in each of these trials. Despite this, fenfluramine induced weight loss appeared to be a robust clinical effect. From Haddock *et al*.'s [111] meta-analysis of 14 trials of fenfluramine which met inclusion criteria, the drug produced an average of 5.06 kg weight loss (placebo subtracted = 2.41 kg). The data was gained from studies which varied in duration (average trial length was only 9.7 weeks, the longest trial was only 18 weeks in duration), dosage (from 39 to 120 mg a day), dietary advice, participant numbers (the average number of participants in the fenfluramine groups of these included trials was 20, the maximum was 58) and characteristics.

D-Fenfluramine

One of the key studies of the clinical efficacy of d-fenfluramine was the European INDEX trial (International DEXfenfluramine study) [113]. INDEX was a multi-centre, randomised, placebo controlled, double blind trial conducted in 822 obese patients. 404 of the patients recruited to the trial received 15mg of d-fenfluramine twice daily, the rest received placebo. At 12 months, of the completers, 52% of the patients in s-fenfluramine condition had lost 10% or more of their initial body compared to only 30% in the placebo group. Average weight loss from baseline during the trial on d-fenfluramine was 9.82 kg (10.26%), which was significantly greater than that observed in the placebo condition (7.15 kg; 7.18%). Interestingly, after the 12 month INDEX trial, withdrawal from d-fenfluramine led to an immediate rise in daily energy consumed. This was accompanied by rapid weight regain over a 2 month period [114]. It would seem that d-fenfluramine treatment had maintained a strong influence on food intake for the entire 12 months (although weight loss stopped after 6 months). D-Fenfluramine had reduced weight (and reported hunger) to a point of physiological resistance at which equilibrium between hunger urges and drug anorectic activity had been reached. The rebound in hunger after drug withdrawal (at 12 months) demonstrated a lack of tolerance to the hypophagic effects of d-fenfluramine. D-Fenfluramine, despite the fact that most reduction in food intake was in the first 6 months, maintained an energy intake reduction of 6% to 10% over the course of the year [114].

Similar d-fenfluramine has been shown to inhibit weight regain and human food intake after treatment with a very low calorie diet (VLCD). In a study by Finer *et al*. [115] a VLCD was employed to reduce weight in the obese by 14 kg in eight weeks. Such a rapid reduction in weight, and adherence to a diet, normally creates a strong disposition to resume over eating and gain the weight lost. However, after the termination of the 8 week VLCD, patients given d-fenfluramine (15 mg twice daily for 26 weeks) continued to lose weight. The d-fenfluramine group lost an additional 5.8 kg (bringing total weight loss to 21.3 kg over the full 34 weeks of the study) in comparison to the placebo group who regained on average 2.9 kg. In the Finer *et al*. study [115] d-fenfluramine overcame the physiological and psychological drive to eat following substantial weight reduction.

Haddock *et al*.'s [111] meta-analysis of the published randomised clinical trials reveals that from the 14 trials meeting inclusion criteria d-fenfluramine induced weight loss from baseline averaged 8.9 kg, the largest average effect observed for any anti-obesity drug included within their analysis. This was probably due in part to longer trial lengths (average of 33 weeks) and the successful lifestyle interventions included in nearly all of the d-fenfluramine studies analysed. However, the average placebo-subtracted weight loss produced by d-fenfluramine was still 3.82 kg equal or greater than any other drug including current obesity treatments such as sibutramine and orlistat.

Sibutramine

The STORM (Sibutramine Trial of Obesity Reduction and Maintenance) trial demonstrates the clinical efficacy of 5-HT NA re-uptake inhibitor sibutramine. In this randomised double blind trial, obese patients were prescribed sibutramine (10 mg) with a low caloric diet over 6 months and lost 11.3 kg [116]. At the end of this open label run in period the diet phase ended and patients entered an 18 month randomised, double blind placebo controlled study, randomly allocated to either a sibutramine (10 mg) or placebo treatment. The group maintained on sibutramine for 18 months appeared to show little weight regain. Their body weight at the study end point end was 9.3 kg lower than at pre-run in baseline 24 months earlier. In contrast the placebo group appeared to start to regain weight within two months of entering the trial. Whilst weight loss was not observed after the 6 months, little tolerance developed to sibutramine over the 24 months of treatment. The weight loss inducing efficacy of sibutramine has been observed in a number of other one and two year studies [117-120]. In examining data from studies conducted over a year or more, irrespective of specific protocols or patient populations (diabetic or none diabetic, hypertensives etc.), it is again apparent that the dynamic phase of sibutramine induced weight loss occurs within the first 6 months of treatment. Thereafter sibutramine stabilises body weight at a significantly lower level than at the pre-treatment (i.e. baseline). Two meta-analyses of clinical data shown that sibutramine produces a placebo subtracted weight loss of 4.45 or 4.3 kg [121, 122 respectively].

Selective Serotonin Reuptake Inhibitors (SSRIs)

The most comprehensive studied SSRI for its anti-obesity properties is fluoxetine. Early clinical studies, of 6 to 8 weeks in duration indicated that fluoxetine treatment could produce weight loss of on average 0.5 kg per week [123]. Indeed, in Haddock *et al*.'s [111] meta-analysis of 11 fluoxetine trials, the drug produced an average reduction in body weight from a baseline of 4.1 kg (3.3 kg placebo subtracted). However, the trajectory of fluoxetine induced weight loss after six months demonstrated that the drug's effects could not be sustained [124]. Patients treated with fluoxetine displayed significant weight loss early in the trial (maximum weight loss of approximately 4.9 kg at week 24). At the end of the 60 week trial weight loss was still significantly greater in the fluoxetine group than in the placebo. However, at week 60 those receiving fluoxetine had lost only 2.2 kg compared to 1.5 kg in the placebo control. Both groups had started to regain weight half way through the study, an effect noted previously in smaller scale one year trials and in analysis of subsets of this data [125, 126].

Currently, there is little evidence that any other SSRIs would be any more efficacious. Sertraline for instance, in contrast to Dd-fenfluramine, seems ineffective at preventing weight regain after a brief period of VLCD [127]. Interestingly, an early report on the effects of Zimelidine (100 mg twice daily), another 5-HT reuptake inhibitor, demonstrated that 8 weeks treatment could produce significant placebo subtracted weight loss, an effect associated with a significant reduction in ratings of appetite [128]. A re-examination of the weight loss inducing effects of existing SSRIs or their active metabolites may produce a suitable candidate for a new anti-obesity drug.

5-HT Precursors and Receptor Agonists

There are no large scale clinical trial data on the effects of 5-HT precursors or receptor agonists on weight loss in the obese. Studies by Cangiano *et al*., [79, 80] mentioned previously, demonstrate that 5-HTP can induce weight loss in the obese for up to 12 weeks at least (a 6% reduction of initial body mass). The study by Sargent *et al*., [97] also demonstrates that the preferential 5-HT_{2C} receptor agonist mCPP can also induce weight loss in the obese over a 2 week period. A number of selective 5-HT_{2C} receptor agonists are about to or have already reached phase 2 clinical trials. As yet such data is not widely available although some of it has been presented. For instance, the efficacy of a 5-HT_{2C} receptor agonist Org 12962 had been detailed. In a 12 week study, the effects of Org 12962 (10 mg twice daily), were studied in 40 obese participants [129]. Participants treated with Org 12962 lost 13.7 kg (14%) of their initial body mass. However, those in the placebo condition lost the same proportion of weight during the treatment period (a strikingly large placebo effect). No effects of drug treatment on appetite were detailed. Towards the end of the treatment phase compliance to Org 12962 appeared to increase compared to placebo. Org 12962 treatment helped the participants adhere to the rigorous but effective weight loss measures prescribed to all of the volunteers. This could have been due to the agonists' efficacy at suppressing diet induced increases in hunger. Consequently, if the trial had been extended Org 12962's continued modulation of appetite may have translated into weight loss significantly greater than that observed in placebo.

CURRENT AND FUTURE SEROTONINERGIC ANTI-OBESITY DRUGS.

With the voluntary withdrawal of d-fenfluramine (Redux) in 1997 due to primary pulmonary hypertension, the development of serotoninergic anti-obesity compound was dealt a blow [130]. The nor-adrenergic and 5-HT reuptake inhibitor sibutramine (Reductil, Meridia) was subsequently approved for the treatment of obesity. The drug is supposed to reduce both weight by inducing satiety and thermogenesis, although the latter effect is difficult to observe in humans. If the sibutramine's primary action is on satiety in humans, as studies quoted in this review suggest, it is likely these are mediated by 5-HT activation despite what the limited pre-clinical data suggests. Certainly, the effects of sibutramine on rodent feeding behaviour and human appetite are indistinguishable from those of d-fenfluramine, fluoxetine and preferential and selective 5-HT_{2C} agonists. Sibutramine has itself not been without side effect issues which are still currently under investigation.

Consequently, pharmaceutical companies have focused on developing 5-HT_{2C} receptor agonists. This is in part due to the increasing evidence that these were critical to d-fenfluramine mechanism of action. Secondly, these receptors are apparently not widely distributed outside the CNS, avoiding any issue of primary pulmonary hypertension [2]. A number of selective 5-HT_{2C} agonists (including Ro 60-0175 from Roche and Vernalis, Org 12962 from Organon, VER-3323 from Vernalis, BVT-933 from Biovitrum and Glaxo-SmithKline and YM348 from Yamanouchi Pharmaceuticals) have been developed [2]. Whilst some of the compounds have passed into phase 1 and in the case of BVT-933 (Biovitrum and GlaxoSmithKline) into phase 2 trials, their effects on human food intake, appetite and body weight regrettably remain largely unknown. Drug affinity to 5-HT receptors other than 5-HT_{2C}, causing unwanted side effects during the clinical trial studies may have been an issue. However, ADP356 (Arena Pharmaceuticals), is currently known to be undergoing clinical trials [131]. According to the company, the drug significantly reduced meal size in a phase 1a study. A 10 mg dose produced a statistically significant 10.7% (122.5 kcal) mean reduction in meal size relative to placebo. The drug has also recently completed a phase 1b safety dose-escalation study. No effect on heart values or pulmonary artery pressure was observed. It is likely that phase 2 trials will begin in 2005 [132].

In 2003, Halford *et al*. [133] described the ideal attributes of any appetite suppression anti-obesity drug. An ultimate appetite suppressant anti-obesity drug should ideally:

1) reliably alter feeding behaviour and food choice to produce a reduction in caloric intake sustaining the period of weight loss.
2) enable the establishment of healthier eating patterns.
3) reduce meal size and the number of between meal eating episodes whilst the patient experiences greater and longer lasting satisfaction for those still remaining.
4) selectively reduce the intake of energy dense high fat foods most associated with obesity and ill health (these generally being snack and so called convenience foods).

These will be the criteria, above and beyond those for anti-obesity drugs in general, by which the efficacy of all future serotoninergic drugs will be measured. In addition, any drug will have to produce placebo subtracted weight loss over one year greater than that currently produced by anti-obesity drugs orlistat (less than 4kg) and sibutramine (over 4 kg), and that reported to be produced by novel anti-obesity Rimonabant (approx 5-6 kg) [134]

SUMMARY

The endogenous 5-HT satiety response has been a target for past, present and probably future anti-obesity treatments. Endogenous 5-HT levels respond to both deprivation and energy excess. Reduced caloric intake lowers CNS 5-HT levels and turnover. Low levels of endogenous 5-HT and 5-HT dysfunction may also underpin susceptibility to weight gain in both rodents and humans. The hypothalamic 5-HT

satiety system interacts with orexigenic systems such as Neuropeptide Y (NPY) and Orexin. Blockade of these 'hunger' signals is one means by which 5-HT may inhibit feeding behaviour. Additionally, the anorexogenic melanocortin (MC) system appears to mediate the hypophagic effects of serotoninergic drugs. Thus, 5-HT the episodic satiety transmitter, which like the tonic adiposity signal leptin, influences feeding behaviour through their stimulatory and inhibitory effects on various regulatory hypothalamic neuropeptide systems.

In rodents, drugs which directly or indirectly stimulate hypothalamic 5-HT_{2C} receptors produce reductions in food intake and changes in the structure of feeding behaviour consistent with the operation of satiety. In both lean and obese humans these drugs enhance the post meal satiety potency of fixed caloric loads, and reduce pre-meal appetite and food intake at ad libitum meals. In rodents dietary induced obesity models, and in human clinical trials, reductions in body weight gain / decreases in body weight from baseline are strongly associated with the hypophagic action of these drugs. A new generation of selective 5-HT_{2C} agonists have been developed and some have passed into clinical testing. By means of their selectivity, these compounds should avoid the side effects associated with their predecessors. However, these drugs will need to produce marked effects on appetite and feeding behaviour, inducing substantial and sustained hypophagia sufficient to produce clinically significant weight loss. The effects of these drugs on the expression of human appetite should be assessed not only in terms of kcal or gram reduction in intake but also in terms of feeding behaviour (eating rate, meal size, daily meal and snack number) and appetite (hunger, prospective consumption, fullness etc.). Given that obesity is linked to the consumption of high fat and/or high in sugar, highly palatable, energy dense foods it is also critical to consider how a drug modifies the type of food chosen (in terms of palatability, energy density, and macronutrient composition). A drug which reduced the liking for or the wanting of highly palatable foods that promote over consumption and weight gain would be of particular therapeutic value.

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