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Serotonergic Drugs

Effects on Appetite Expression and Use for the Treatment of Obesity

Jason C.G. Halford,[1,2] *Joanne A. Harrold*,[1,3] *Emma J. Boyland*,[1] *Clare L. Lawton*[2] and *John E. Blundell*[2]

1 Kissileff Laboratory for the Study of Human Ingestive Behaviour, School of Psychology, University of Liverpool, Liverpool, UK
2 Institute of Psychology, University of Leeds, Leeds, UK
3 Department of Medicine, Diabetes and Endocrinology Research Group, University of Liverpool, Liverpool, UK

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Abstract

Over 35 years of research suggests that endogenous hypothalamic serotonin (5-hydroxytryptamine) plays an important part in within-meal satiation and post-meal satiety processes. Thus, the serotonin system has provided a viable target for weight control, critical to the action of at least two effective anti-obesity treatments, both producing clinically significant weight loss over a year or more. Numerous serotonin receptor subtypes have been identified; of these, serotonin 5-HT_{1B} and 5-HT_{2C} receptors have been specifically recognised as mediators of serotonin-induced satiety.

A number of serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs), dexfenfluramine and 5-HT_{2C} receptor agonists, have been shown to significantly attenuate rodent bodyweight gain. This effect is strongly associated with marked hypophagia and is probably mediated by the hypothalamic melanocortin system. Additionally, sibutramine, dexfenfluramine, fluoxetine and the 5-HT_{2C} receptor agonist chlorophenylpiperazine (mCPP) have all been shown to modify appetite in both lean and obese humans, resulting in reduced caloric intake. Clinical studies demonstrate serotonergic drugs specifically reduce appetite prior to and following the consumption of fixed caloric loads, and cause a reduction in pre-meal appetite and caloric intake at *ad libitum* meals. Weight loss in the obese has also been produced by treatment with both the serotonin precursor 5-hydroxytryptophan and the preferential 5-HT_{2C} receptor agonist mCPP.

A new generation of 5-HT_{2C} receptor selective agonists have been developed and at least one, lorcaserin (APD356), is currently undergoing clinical trials. In addition, 5-HT_6 receptor antagonists such as PRX-07034 and BVT74316 have been shown to potently reduce food intake and bodyweight gain in rodent models and have recently entered clinical trials. However, the role of the 5-HT_6 receptor in the expression of appetite remains to be determined. The hope is that these drugs will not only be free of their predecessors' adverse effect profiles, but will also be equally or more effective at regulating appetite and controlling bodyweight.

To understand the potential for serotonin (5-hydroxytryptamine)-targeted treatment for obesity it is necessary to consider the nature of appetite regulation and the role of serotonin within it. Appetite is an expression of numerous regulatory processes that determine the initiation and termination of meals, the amount and types of foods consumed, and meal length and frequency, and govern the duration of between-meal intervals. Signals are generated from the very commencement of consumption, the short-term consequences of which serve to terminate eating behaviour and act as powerful inhibitors of further intake. This process signals to the brain an estimation of a meal as opposed to an accurate

analysis of content. There is an important distinction between the short-term satiety signals produced by the physiological consequences of meal intake (episodic) and the longer-term signals created by the body's constant metabolic need for energy (tonic). Episodic signals are a crucial factor in the meal-by-meal regulation of energy intake, and are critical to both the appetite fluctuations and patterns of eating behaviour we undertake throughout the day. The monoamine neurotransmitter serotonin influences this episodic, meal-by-meal, regulation of food intake through its role in satiety.[1] Tonic inhibitory signals, by contrast, are not a result of this flux of sensory, cognitive, pre-absorption and post-absorptive factors that are crucial to the satiety development process. Tonic factors are generated instead by the storage and metabolism of energy. The adipose tissue hormone leptin is a key example of this. Leptin is secreted in response to excess fat deposition and also acts as a potent inhibitor of food intake. We have argued previously that serotonin and leptin constitute separate aspects of appetite regulation and are both generated by markedly distinct processes, but both ultimately act to inhibit food intake via the same hypothalamic circuitry.[1]

Ultimately, for any anti-obesity drug that acts on reducing food intake to be successful it must influence subjective feelings of appetite experiences before, during and after food intake, enabling the individual to consume less food. With regard to serotonin, there is a greater wealth of data on the effects on human appetite and rodent eating behaviour than for any other peripheral or central target. Therefore, the purpose of this review is to explore the efficacy of serotonergic drugs at inhibiting appetite and consequently food intake. These are the effects which should ultimately induce the clinically significant weight loss required to treat obesity. This is not an in-depth review of the serotonin receptor subtype pharmacology or their role in feeding. These topics have been covered comprehensively in other recent reviews and are best discussed by those more qualified.[2,3] This review instead emphasises the research identifying both the role of serotonin and the functioning of the endogenous serotonin satiety system as a whole. The review then focuses on the effects of serotonergic drugs in human feeding behaviour studies as well as clinical weight loss trials.

The monoamine neurotransmitter serotonin was linked to the control of food intake and of feeding behaviour for the first time 30 years ago. Early studies on this subject used serotonin precursors (such as tryptophan and 5-hydroxytryptophan [5-HTP]) to increase CNS serotonin levels and demonstrated a significant reduction in the food intake of laboratory animals in response to this manipulation. This hypophagic response could also be generated via other mechanisms to increase serotonin activity, such as the direct administration of serotonin into the CNS, directly stimulating (agonising) serotonin receptors or blocking synaptic serotonin breakdown.[4-8] Additionally, it was shown that preventing serotonin synthesis (using parachlorophenlyanine [pCPA]), which depletes neuronal serotonin, or the neurotoxic lesioning of serotonin neurons (with 5,7-dihyroxytryptamine [5,7-DHT]), resulted in not only a prevention of serotonin-induced hypophagia but an increase in food intake.[9] Relative to now, the pharmacological tools available to these early researchers were nonspecific; nevertheless, it became evident that CNS serotonin was implicated in the control of food intake. Blundell[10] proposed in 1977 that the serotonin system had not only an inhibitory role in feeding but was also a key satiety factor (i.e. a factor in the natural energy intake control mechanism).

1. Endogenous Serotonin and Serotonin Receptors

Neuronal serotonin is synthesised from the essential amino acid tryptophan. In the cell body cyto-

plasm, the enzyme tryptophan hydroxylase hydroxylates dietary I-tryptophan to 5-HTP. 5-HTP is then rapidly decarboxylated at the terminal, by the enzyme I-amino acid decarboxylase, to produce serotonin. The majority of serotonin produced is taken up via a vesicle membrane transport mechanism and stored in presynaptic vesicles. After release, synaptic serotonin continues to stimulate pre- and postsynaptic receptors until it is either converted to 5-hydroxyindole acetic acid (5-HIAA) by monoamine oxidase (MAO) or reabsorbed into the presynaptic neuron for reuse (a sodium-dependent process) [figure 1]. The late 1980s and early 1990s were a time for significant advances in the discovery and identification of novel serotonin receptors.[11] The serotonin receptors currently thought to be most directly implicated in the feeding control mechanisms are

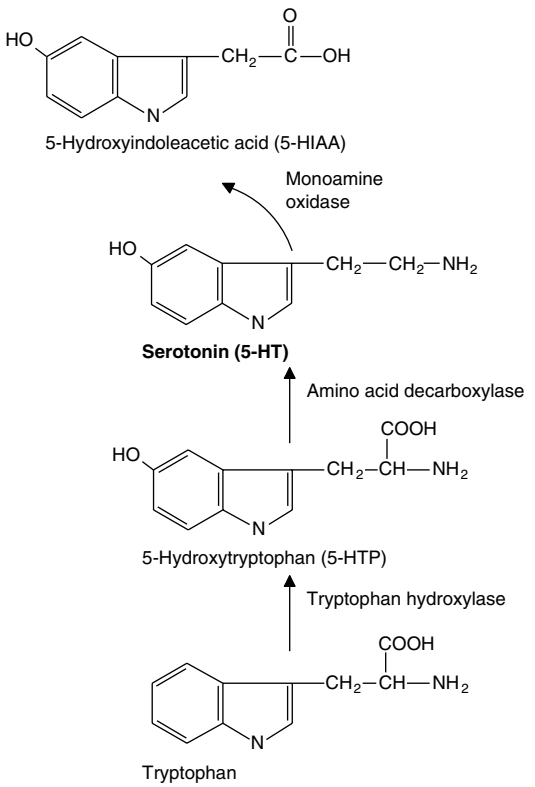

Fig. 1. The synthesis and metabolism of serotonin (reproduced from Blundell and Halford,[12] with permission).

the serotonin 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2C} receptors. The postsynaptic 5-HT_{1B} and 5-HT_{2C} receptors are generally thought to be involved in the serotonin satiety system.[12] However, recent attention has focused on 5-HT_6 receptors with data from a number of sources demonstrating 5-HT_6 receptor antagonism reduces food intake and bodyweight gain (see section 9). Whether these effects are consistent with satiety remains to be determined.

2. The Serotonin Satiety System: Interaction with Other Neuropeptide Signalling Pathways

Energy balance is regulated by a number of peripherally generated signals. Many of these signals converge on the hypothalamic nuclei known to be critical to the control of feeding behaviour expression. These nuclei contain a diverse selection of neuropeptide systems which either inhibit (anorexigenic) or stimulate (orexigenic) food intake. The extent to which serotonin-induced hypophagia involves other neuropeptide signalling systems linked to the hypothalamic regulation of appetite is not yet fully understood and has been explored by a number of studies. Of particular interest is the antagonistic relationship between serotonin and the food intake stimulating neuropeptide neuropeptide Y (NPY). Similarly, links between the serotonergic neurons and another orexigenic system, orexin, may also be critical to the expression of appetite. It seems that the interaction between these orexigenic neuropeptides and serotonin may be critical in determining the expression of appetite, i.e. whether to eat or not. However, perhaps the more critical neuropeptide is the anorexigenic melanocortin system. It seems that a functioning hypothalamic melanocortin system is required for serotonergic drugs to alter feeding behaviour, and presumably for feeding-induced changes in endogenous serotonin to influence appetite. Interestingly, these systems are critical in mediating the effects of tonic peripheral signals such as

leptin and insulin. The serotonin system itself appears to be more sensitive to peripheral episodic signals such as those produced by a number of gut peptides released in response to the ingestion of food.[12] Thus, it has been proposed that the serotonin system is a key link in the integration of episodic signals into the hypothalamic energy regulatory system.[1]

2.1 Serotonin and Neuropeptide Y

NPY plays a significant role in the control of food intake and energy balance. An interaction between NPY and serotonin was suggested by early studies in which NPY-induced hyperphagia was shown to be blocked by the serotonin receptor agonist fenfluramine. In addition to this, hypothalamic NPY levels have been reported to decrease after treatment with serotonin receptor agonists, and to increase after administration of serotonin receptor antagonists.[13,14] Reduced serotonin availability has also been found to decrease the density of NPY neurons.[15] NPY is synthesised in the arcuate nucleus (ARC) and released in a number of hypothalamic areas, predominantly the paraventricular nucleus (PVN) and ventromedial hypothalamic nucleus (VMH). Subsequent studies have narrowed their focus to specifically examine the potential interactive relationship of PVN NPY and serotonin, and the manner in which this interaction exerts influence over the control of feeding. It is worth mentioning that only administration of 5-HT_{2A} receptor agonists and antagonists into the PVN has been shown to modulate NPY-induced hyperphagia.[16] Despite a lack of confirmation over the nature of the serotonin receptor expressed by PVN NPY neurons, the findings highlighted do provide continued support for the interaction of NPY and serotonin mechanisms.

2.2 Serotonin and the Melanocortin System

The melanocortin system is well known to be a key system involved in the regulation of food intake and bodyweight. It appears to be a critical site for the integration of afferent episodic and tonic signals of intake and energy status. Neuroanatomical, molecular and electrophysiological methods have been used in combination to show that serotonergic drugs are dependent on a functioning melanocortin system to exert their effects on feeding. It has been shown that anorectic serotonin drugs activate pro-opiomelanocortin (POMC) neurons in the ARC. This effect was demonstrated by specifically examining FOS-like immunoreactivity in response to dexfenfluramine administration.[17] Confirmation that dexfenfluramine directly activates these neurons comes from electrophysiological studies that investigated the expression of green fluorescent protein under control of the POMC promoter.[17] POMC is the peptide precursor of a variety of molecules, including adrenocorticotrophic hormone (ACTH), endorphins and enkephalins, all of which play important roles in metabolic processes. Many of these products can generate pronounced effects on feeding behaviour. However, α-melanocyte-stimulating hormone (α-MSH) appears to be the major POMC product in terms of an interaction with serotonin. Moreover, α-MSH is the main breakdown product of POMC. Up to 80% of α-MSH-containing neurons express mRNA for the 5-HT_{2C} receptor[17] and it is probable that these receptors play a part in the serotonin-mediated activation of POMC neurons. Furthermore, previous reports indicate that serotonergic compounds cause the release of α-MSH from superfused hypothalamic slices. As a final point, it is worth noting that a blockade of melanocortin 3 and 4 receptors, either by pharmacological or genetic means, is sufficient to attenuate the anorectic effects of serotonergic drugs.[18] These findings indicate that serotonin targets downstream melanocortin pathways and acts via the 5-HT_{2C} receptor to reduce food intake and bodyweight.

In a recent paper, Heisler et al.[19] have further demonstrated the role of downstream melanocortin

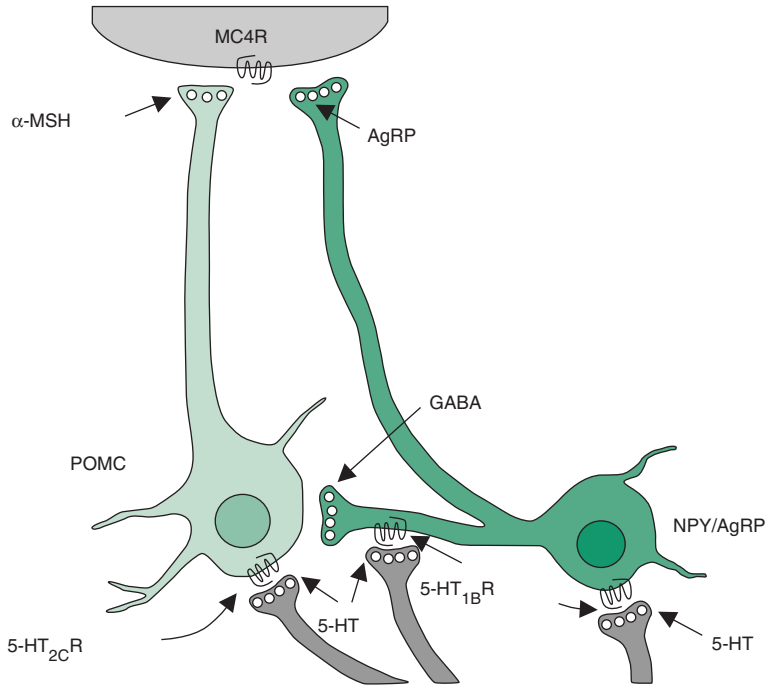

Fig. 2. Schematic diagram of proposed serotonin sites of action on melanocortin pathways. This shows the inhibition of agouti-related peptide (AgRP) neuron and the inhibition of the AgRP axonal projection by serotonin through serotonin 5-HT_{1B} receptor (5-HT_{1B}R) action, and the activation of the pro-opiomelanocortin (POMC) neuron through the 5-HT_{2C} receptor (5-HT_{2C}R) [reproduced from Heisler et al.,[19] with permission]. **MC4R** = melanocortin 4 receptor; **MSH** = melanocyte-stimulating hormone; **NPY** = neuropeptide Y

4 receptors (MC4R) in mediating serotonin-induced hypophagia. It seems that activation of both 5-HT_{2C} and 5-HT_{1B} receptors produce hypophagia by promoting the release of the endogenous agonist and inhibiting the release of the endogenous antagonist of the MC4R. This is achieved through three mechanisms (see figure 2). Firstly, Heisler et al., postulate that serotonin inhibits orexigenic agouti-related peptide (AgRP) neurons in the ARC via 5-HT_{1B} receptor activation. This inhibits the releases of the MC4R antagonist AgRP. Secondly, activation of axonal 5HT_{1B} receptors on AgRP neuronal projections also decreases their inhibitory effect on adjacent anorexigneic POMC neurons. This promotes the release of the MC4R agonist α-MSH. Finally, as previous studies have shown, serotonin also activates these anorexignic POMC neurons via activation of 5-HT_{2C} receptors, again promoting the release of α-MSH. It would be interesting to determine whether blockade of MC4R reverses the effect of 5-HT_{2C} and 5-HT_{1B} receptor agonism on behaviour indicators of satiety such as the behavioural satiety sequence. Certainly, the effects of dexfenfluramine, a drug that reduces food intake through the activation of 5-HT_{2C} and 5-HT_{1B} receptors, is ineffective at reducing food intake at normal anorectic doses in mice with ectopic expression of endogenous AgRP.[19] Reductions in food intake are only observed at doses previously shown to produce sedation.

2.3 Serotonin and Orexin

Serotonin and orexin are both involved in feeding behaviour regulation, in addition to their roles in the sleep-wake cycle. Orexin neurons project to a vast majority of areas in the brain from their specific

location in the lateral hypothalamus. Notably, in monoaminergic nuclei (such as the noradrenergic locus ceruleus, the serotonergic dorsal raphe nucleus and the dopaminergic ventral tegmental area) there are dense projections of orexin neurons. Of these, the serotonergic dorsal raphe nucleus is one of the densest projection sites.[20] In addition to this, within the dorsal raphe nucleus, serotonergic neurons express both orexin OX_1R and OX_2R receptors[21,22] and are excited by orexin-A neuropeptide.[23,24] Moreover, orexin has also been shown to alter serotonin release in the hypothalamus.[25] An involvement of a serotonergic pathway in orexin-induced behaviour is indicated by these anatomical projections and interactions.[26] However, there is to date, a lack of published studies focusing on this interaction between orexin and serotonin that influences feeding behaviour. As it is known that serotonin inhibits food intake, it is probable that orexin projection to the dorsal raphe nucleus establishes part of an inhibitory feedback loop which ultimately connects to the hypothalamus, damping down hypophagic signalling.[27] This is likely to occur via the $5\text{-}HT_{1A}$ and $5\text{-}HT_{2C}$ receptor mechanisms.[28,29] Support for this argument is provided by $5\text{-}HT_{1A}$ receptor immunoreactivity results showing that orexin neurons in the lateral hypothalamus contain $5\text{-}HT_{1A}$ receptors.[30] Additionally, serotonin has been shown to hyperpolarise orexin neurons via the $5\text{-}HT_{1A}$ receptor.[31] It is worth noting that agonism of the presynaptic $5\text{-}HT_{1A}$ autoreceptor could potentially stimulate rather than inhibit food intake. It is likely that this inhibitory serotonergic contribution is important for the physiological regulation of the orexin system.

3. Endogenous Serotonin and Altered Nutritional Status

If a system is critical to the control of energy balance, it should fluctuate in response to nutritional status. There are a variety of models that can be used to cause perturbations in nutritional status. This allows an insight into the regulation (both nutritional and physiological) of neurotransmitter systems that function to control feeding and energy balance. Therefore, if endogenous serotonin is a key appetite regulation factor, its levels and functioning should reflect the organism's nutritional status, fed or fasted.

3.1 Reduced Energy Intake or Bodyweight

It would be logical to assume that a system that inhibits food intake would be inactivated in situations of energy need, allowing the organism to address this with feeding behaviour. It has been shown that malnourished animals demonstrate a significant reduction in CNS serotonin levels in several areas of the brain.[32] Furthermore, intense food-seeking behaviour and increased food intake (when food is made available) has been noted in fasting animals. Food deprivation is thought to increase turnover of serotonin within the hypothalamus.[33] Additionally, it is linked to a significant reduction in the ratio of neurons in the VMH that respond to serotonin,[34] an effect that may be due to alterations in the expression of serotonin receptor subtypes. This reduction in responsiveness to serotonin seen in these rodent models may provide a partial explanation for the increased motivation for feeding after a period of fasting. For instance, fasting-induced reductions in serotonin would allow increased NPY activity and a potent feeding response.

With regard to human studies, when female volunteers were placed on a 4-week hypocaloric diet, plasma levels of tryptophan, the serotonin precursor, were reduced.[35] These reductions in tryptophan correlated with the degree of weight loss observed in the women over the 28-day study period. Several studies have noted the effect of dieting on tryptophan, which suggests that dieting in humans may result in central serotonin function being diminished. In one study, prolactin response to the 5-

HT_{2C} receptor preferential agonist chlorophenylpiperazine (mCPP) was increased following dieting.[36] The data provided by these studies suggest that the sensitivity of the 5-HT_{2C} receptor is increased in response to chronic restrictions of food intake, an effect that results from the decline in the actual transmitter. In summary, it has been shown that inadequate nutrition or hypocaloric diets seem to both reduce endogenous serotonin levels and increase serotonin receptor sensitivity.

3.2 Cachexic and Endogenous Serotonin

Not only do enforced reductions in food availability cause changes in bodyweight; weight loss also results from malaise-induced reductions of food intake. An obvious question is whether endogenous serotonin activation contributes to the suppression of appetite produced by illness. Rat cancer models are useful for providing chronic anorexic conditions. Particularly in the VMH, the hypothalamic serotonin system plays a crucial role in the anorexia.[37] After injection of interleukin (IL)-1α into the VMH, serotonin levels within the VMH are increased in both normal and tumour-bearing rats.[38] Correspondingly, elevations of tryptophan (the serotonin precursor) in tumour-bearing rats positively correlate with the degree of anorexia.[39] In humans there is evidence that plasma tryptophan levels normalise following tumour resection in patients, resulting in improved food intake, which strengthens the relationship between serotonin, tumour and anorexia.[40] These studies again strongly support the notion that serotonin is a key anorectic agent. Interestingly, another system heavily implicated in cachexia is the melanocortins. Therefore, it is possible to hypothesise that the effects of serotonin on food intake in these models are mediated by the hypothalamic melanocortin system.

3.3 Increased Energy Intake or Bodyweight

It is also logical to assume that a system that inhibits food intake would be activated in situations of energy excess, allowing the organism to address other needs by inhibiting feeding behaviour. Thus, intake should promote increases in serotonin which normally prevent weight gain. Numerous studies have demonstrated the effects of dietary carbohydrate on serotonin precursor entry into the CNS. Moreover, central serotonergic systems appear to mediate the effects of episodic satiety signalling hormones such as cholecystokinin (CCK).[1] Furthermore, it is possible to hypothesise that animals unable to control their bodyweight show deficiencies in their endogenous serotonin system. Studies using obese Zucker rats have been instrumental in providing insights into the effects of obesity and chronic hypophagia on the regulation of serotonin. In this leptin-resistant obesity model, numerous studies have shown that abnormal hypothalamic serotonin activity contributes to both hyperphagia and weight gain. These animals demonstrate an unaltered pattern of serotonin release associated with food deprivation and re-feeding. Moreover, baseline levels of serotonin, specifically, are significantly lower in obese than lean animals.[41] It has been shown that such rats have lower hypothalamic levels of 5-HIAA, the serotonin metabolite.[42] These data indicate that obese Zucker rats have reduced rates of endogenous serotonin turnover. Furthermore, this defect in the endogenous serotonin system's functioning appears to permit weight gain.

Dietary-induced obesity following exposure to highly palatable food is the rodent model that resembles human obesity the most closely. The severity of obesity varies between individual animals in this model; approximately 50% of a population develop obesity when provided with a palatable diet.[43] Such rats, demonstrably obesity-prone, exhibit abnormalities of diurnal and fasting-induced alterations in brain serotonin turnover. Specifically, the obesity-

prone rats, in contrast to obesity-resistant animals, fail to show diurnal variation in serotonin turnover in the PVN and ARC. Also, these rats demonstrate significant reductions in VMH nucleus serotonin turnover in comparison to their obesity-resistant equivalents.[44] It is possible that these abnormalities constitute a component of a genetic programming, predisposing prone rats to become obese when exposed to palatable food. Moreover, these abnormalities have been shown to normalise after obesity has developed. This could account for the persistence of the obesity in these rats, whereby the animals avidly defend their increased bodyweight against the food restriction. Therefore, in rodents, reduced serotonin turnover or an unresponsive endogenous serotonin system is associated with proneness to obesity.

Given the rodent data, it seems logical to ask if an impaired serotonin system contributes to human obesity. In obese humans, plasma tryptophan levels are also reported to be low. This could contribute to a reduction in satiety response to food and consequent overconsumption. Moreover, low tryptophan levels are not normalised by considerable weight reductions.[45] Therefore, in humans, a reduction in CNS serotonin levels in the obese could contribute to an inability to exert sufficient control over their own daily caloric intake. Although it is difficult to prove any role for serotonin deficiency in the development of obesity, it seems appropriate to assume it may be critical in preventing the obese individual successfully losing weight.

4. Effects of Serotonergic Drugs on Food Intake in Rodents

4.1 Serotonin Receptors and Food Intake

Following the initial identification of serotonin as a key inhibitor system, the next step was to reveal the receptors responsible for mediating the serotonin satiety response. In the beginning, studies used serotonin manipulations (i.e. drugs promoting the release of serotonin and/or preventing its reuptake). The resulting suppression of food intake was then challenged pharmacologically, using selective serotonin receptor antagonists to identify the specific serotonin receptor subtypes fundamental to drug-induced hypophagia. Fenfluramine or dexfenfluramine-induced food suppression models were used in a majority of the studies to have employed antagonists to identify these receptors. This is likely to be at least partially as a result of the robustness of the models of fenfluramine or dexfenfluramine-induced reduction in food intake and bodyweight, but also partly a reflection of the known effectiveness, at that time, of their treatment for human obesity. The use of selective serotonin receptor antagonists of various 5-HT_1 and 5-HT_2 receptor subtypes had indicated that dexfenfluramine-induced hypophagia is mediated by 5-HT_{1B} receptors.[46] The foundation for this was evidence gathered from numerous studies showing that the actions of dexfenfluramine were blocked with 5-$HT_{1A/1B}$ receptor antagonists, but that the actions of dexfenfluramine were not blocked by 5-$HT_{2A/2C}$ receptor antagonists.[47-49] In 2002, Simansky and Nicklous[50] infused the highly selective 5-HT_{1B} receptor antagonist directly into the parabrachial nucleus of the rat and blocked dexfenfluramine-induced reduction in food intake. Nevertheless, the central role of 5-HT_{1B} receptors is not confirmed by all experimental evidence. Vickers et al.[51] showed that dexfenfluramine-induced hypophagia could be blocked by pretreatment with the highly selective 5-HT_{2C} receptor antagonist SB-242084, whereas this effect was not seen following pretreatment with the highly selective 5-HT_{1B} receptor antagonists GR-127935 and SB-224289.

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) produces a consistent food intake reduction that cannot be blocked easily by serotonin antagonists.[52-54] Nevertheless, the non-selective 5-$HT_{1/2}$ receptor antagonist metergoline has been successful in both partially and fully blocking fluoxe-

tine-induced hypophagia.[55,56] 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 that are critical to the mediation of the effects of dexfenfluramine on food intake. The hypophagia induced by other SSRIs such as sertraline,[57] in contrast to fluoxetine, seems to be blocked more reliably by antagonists of the 5-HT_{1B} and 5-HT_{2C} receptors.[58]

Alongside the development of more selective serotonin receptor antagonists, further serotonin receptor agonists have also become available. More recently, scientists have been able to work with selective serotonin receptor agonists that have been developed specifically as novel obesity treatments. Direct agonism of serotonin receptors in rodents produces consistent reductions in food intake. Furthermore, agonists of the 5-HT_{1B} and 5-HT_{2C} receptor subtypes generate changes in feeding behaviour that are consistent with the operation of satiety (see section 4.2). These agonist agents include mCPP (preferential 5-$HT_{1B/2C}$ receptor agonist), TFMPP (*N*-[3-trifloromethyl)phenyl]piperazine) [preferential 5-$HT_{1B/2C}$ receptor agonist], CP-93129 (selective 5-HT_{1B} receptor agonist), CP-94 253 (selective 5-HT_{1B} receptor agonist), and Ro 60-0175 (selective 5-HT_{2C} receptor agonist).[29,59-66] While these food intake studies seem to have confirmed the role of both receptor subtypes in mediating the serotonin hypophagic response, the question remains; was drug-induced hypophagia due to enhanced satiety?

4.2 Serotonin and Feeding Behaviour

It is important to clarify a key distinction between drugs that reduce food intake by exerting an effect on natural satiety mechanisms and those that cause a reduction in food intake by inducing nausea, sedation, hyperactivity or malaise. For example, when fenfluramine and amfetamine (amphetamine) were compared in early clinical studies it became clear that the two drugs produced similar effects on food intake but distinct effects on feeding behaviour.[67] More specifically, amfetamine seemed to fragment normal feeding behaviour (the duration of feeding is decreased but its frequency is increased and the decline in eating behaviour indicative of satiety disappears), whereas fenfluramine appeared to enhance satiety by reducing meal size. Subsequent studies have shown drugs that either stimulate serotonin release or inhibit serotonin reuptake 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. Specifically, numerous serotonergic drugs have been shown to enhance the BSS.[68]

The BSS is a stochastic progression of behaviour whereby as satiety develops, the initial feeding behaviour is replaced with activity, followed by grooming, and then terminated with a prolonged period of resting/inactivity. If the effects of a drug cause a reduction in food intake but also cause a disruption or delay in this temporal behavioural pattern, it is probable that drug-induced hypophagia is at least partially due to disturbance of this normal feeding behaviour by mechanisms other than satiety, for example, hyperactivity, malaise, sedation or nausea. However, if a drug is shown to induce hypophagia but does not disrupt this sequence of behaviour, it is reasonable to assume that this drug does not interfere with the natural development of satiety. Alternatively, if a drug causes a reduction in food intake and appears to enhance the BSS (i.e. feeding behaviour is terminated early and there is an earlier onset of each of the other phases of the sequence), it can be concluded that satiety is the primary mechanism of action.[68]

Previous studies have shown that both fenfluramine and dexfenfluramine adjust feeding behaviour in a manner consistent with the operation of satiety.[69-71] Sertraline, fluoxetine and other SSRIs have produced similar effects to dexfenfluramine on a number of behavioural indices of appetite in ro-

Table I. Effect of various serotonergic drugs on rodent energy intake and expression of the behavioural satiety sequence (BSS)

Drug	Mechanism (and receptors mediating effect if known)	Effect	
		on intake	on BSS
Dexfenfluramine	Serotonin releaser and reuptake inhibitor (5-HT_{1B} and 5-HT_{2C})	↓	↑
Fluoxetine	Serotonin reuptake inhibitor (5-HT_1 and 5-HT_2)	↓	↑
Sertraline	Serotonin reuptake inhibitor (5-HT_{1B} and 5-HT_{2C})	↓	↑
Paroxetine	Serotonin reuptake inhibitor (receptor involvement unknown)	↓	↑
Femoxitine	Serotonin reuptake inhibitor (receptor involvement unknown)	↓	↑
DOI	5-HT_2 agonist	↓	Disrupts (hyperactivity)
MK-212	5-HT_2 agonist	↓	Disrupts (sedation)
mCPP	5-$HT_{1B/2C}$ agonist	↓	↑
TFMPP	5-$HT_{1B/2C}$ agonist	↓	↑
RU-24969	5-$HT_{1A/1B}$ agonist	↓	Disrupts (hyperactivity)
CP-93,129	Selective 5-HT_{1B} agonist	↓	↑
CP-94,253	Selective 5-HT_{1B} agonist	↓	↑
Ro 60-0175	Selective 5-HT_{2C} agonist	↓	↑
Org 12962	Selective 5-HT_{2C} agonist	Unknown	Unknown
VER-3323	Selective 5-HT_{2C} agonist	Unknown	Unknown
BTV-933	Selective 5-HT_{2C} agonist	Unknown	Unknown
YM348	Selective 5-HT_{2C} agonist	Unknown	Unknown
Lorcaserin (APD356)	Selective 5-HT_{2C} agonist	Unknown	Unknown
Sibutramine	Serotonin and noradrenaline reuptake inhibitor ($NA_{\alpha 1/\beta 2}$ and 5-$HT_{2A/2C}$)	↓	↑

DOI = 2,5-dimethoxy-4-iodoamphetamine; **mCPP** = m-chlorophenylpiperazine; **TFMPP** = *N*-[3-trifloromethylphenyl]piperazine; ↑ indicates increases; ↓ indicated decreases.

dents, i.e. inducing the BSS.[56,68,72-75] Additionally, the current globally licensed anti-obesity treatment sibutramine (serotonin and noradrenaline reuptake inhibitor [SNRI]) has also been shown to enhance the BSS.[68] Several selective agonists of serotonin receptors produce changes in feeding behaviour consistent with the operation of satiety, notably the 5-HT_{1B} receptor agonist CP-94 253, the preferential 5-$HT_{1B/2C}$ receptor agonists mCPP and TFMPP, and the selective 5-HT_{2C} receptor agonists.[62,66,68,73] Importantly, drugs that have also been shown to agonise other serotonin receptor subtypes, for example DOI (2,5-dimethoxy-4-iodoamphetamine) [5-$HT_{2A/2C}$] or RU-24 969 (5-$HT_{1A/1B}$), are unsuitable for further development because they disrupt the BSS by inducing hyperactivity, a critical side effect. For a summary of the effects of serotonergic drugs on rodent food intake and the BSS see table I.

4.3 Serotonin Receptor Knockouts, Food Intake and Obesity

'Knockout' mice provide the final and possibly strongest argument for the vital role of 5-HT_{2C} receptors in mediating the hypophagic effects of endogenous serotonin. A breed of mice was successfully produced by Tecott et al.[76] that did not possess a single functional 5-HT_{2C} receptor. In these 5-HT_{2C} knockout mice, marked hyperphagia was demonstrated from 5 weeks after birth, an effect accompanied by marked hyperactivity. Hyperactivity declined later in the life of these mice, whereas hyperphagia persisted, leading to the development of obesity.[77] Interestingly, these mice were also partly resistant to dexfenfluramine-induced hypophagia.[78] However, reductions in food intake could still be produced in the mutant mice by the use of dexfenfluramine. There was also some evidence

of enhanced satiety in the BSS paradigm in response to this drug. These responses were distinctly lesser in magnitude in the knockout mice than in the control wild-type mice. Therefore, it seems that there is a deficiency in the endogenous serotonin satiety system of obese 5-HT_{2C} receptor knockout mice. Additionally, 5-HT_{1B} receptor knockout mice are significantly heavier than wild types,[79] an effect associated with significantly greater food consumption. However, these animals merely appear to be larger rather than fully obese.[2]

5. Serotonergic Drugs, Food Intake and Feeding Behaviour in Humans

Studies first employing racemic fenfluramine and then dexfenfluramine provided a majority of the original data on the effects of pharmacological manipulation of serotonin on food intake in humans. Subsequently, studies employing the SSRI fluoxetine and then sibutramine were also published. Over the past 13 years, numerous other studies have been published, using the serotonin precursor 5-HTP and preferential serotonin receptor subtype agonists. These studies have shown that by increasing synaptic or neuronal levels of serotonin or directly agonising specific serotonin receptor subtypes, robust hypophagia can be produced. Furthermore, is it clear from the meticulous description of the effects of the manipulation on behaviour and subjective ratings of hunger and satiety that these pharmacological interventions have produced hypophagia by modifying human appetite expression. The effects of serotonergic drugs on appetite are shown in table II.

5.1 5-Hydroxytryptophan

The serotonin precursor 5-HTP has been shown to produce potent effects on self-reported food intake in obese individuals. In one study, 20 obese individuals (defined as 'hyperphagics') were treated with either 5-HTP (900 mg/day) or placebo over 12 weeks.[81] The participants were not prescribed a diet to follow for the first 6 weeks of the study, but during the second 6-week period the participants were given a diet regimen. Each participant recorded their food intake at regular intervals in a diary, both before treatment commenced and during both the initial (non-diet) and latter (diet) phases. From baseline, those receiving 5-HTP lost 5.0kg in bodyweight (1.7kg in the non-diet phase and 3.3kg in the diet phase) in comparison to 1.2kg, a non-significant reduction in bodyweight, seen in those who had received placebo for 12 weeks. Those receiving the drug reported significant decreases in daily energy intake of 41% (5636kJ) in the non-diet phase and 60% (8202kJ) in the diet phase from baseline. Conversely, reductions in self-reported food intake in the placebo group were 14% and 24%, respectively. The same research group then replicated their original findings in a shorter study.[96] In this study, 25 overweight individuals with type 2 diabetes mellitus were randomly allocated to receive either placebo or 5-HTP (750 mg/day) for 2 weeks. Diet diaries were also utilised in this study. In the group treated with 5-HTP, weight loss from baseline over the 2-week study period was 2.1kg. Significant decreases in self-reported energy expenditure accompanied this weight loss effect, with a 21% (1700kJ) reduction reported on day 7 and 22% (1760kJ) on day 14. It is likely, from an examination of these data, that participants in this trial underreported energy intake on a number of occasions. Nevertheless, it does appear that hypophagia is associated with weight loss.

5.2 Fenfluramine and Dexfenfluramine

In the late 1970s, the effects of fenfluramine on human food intake were demonstrated. For example, in 1979 Rogers and Blundell[82] published a key study showing that a single dose of fenfluramine (60mg), when given to lean healthy males, could reduce food intake at a lunchtime meal by 789kJ (26%). The effect of reduced caloric intake was also

Table II. Summary of studies that have investigated the effects of serotonergic drugs on food intake in humans

Drug	Study design	No. of study participants (status)	Duration of treatment	Hunger and food preference	Caloric intake	Reference
Tryptophan	Laboratory study	16 (healthy)	1d	NR	↓Intake	80
5-HTP	Laboratory study	20 (obese)	6wk	↓Carbohydrate intake, early post-meal satiety	↓Intake and bodyweight of 6wk period	81
Fenfluramine	Laboratory study	12 (normal bodyweight)	1d	NR	↓Test meal intake and eating rate	82
Dexfenfluramine	Laboratory study	8 (obese)	3d	↓Hunger, ↑fullness after first meal	↓Intake after second meal (11–19%)	83
Dexfenfluramine	Laboratory study	24 (obese)	2wk	↓Carbohydrate snack intake	NR	84
Dexfenfluramine	Laboratory study	20 (obese)	8d	↓Carbohydrate intake at meal, ↓snack intake	↓Intake	85
Dexfenfluramine	Laboratory study	13 (healthy men)	1d	↓Hunger	↓Intake	86
Dexfenfluramine	Laboratory study	10 (lean women), 11 obese women	1d	↓Hunger	↓Intake	87
Dexfenfluramine	Laboratory study	12 (healthy men)	1d	↓Fat intake	No overall effect	88
Fluoxetine	Laboratory study	11 (healthy men)	2wk	↓Hunger on days 8 and 15, but not on day 1	↓Intake on days 1 and 8, but not on day 15	89
Fluoxetine	Laboratory study	12 (obese women)	14d	No macronutrient preference, ↓hunger	↓Intake (22.4%)	90
Sertraline	Relapse prevention trial	53 (obese women)	6wk	↓Hunger, ↓food preoccupation	NR	91
mCPP	Laboratory study	12 (healthy women)	1d	NR	↓Test meal intake	92
mCPP	Laboratory study	18 (obese)	2wk	↓Hunger, ↓bodyweight	NR	93
Sumatriptan	Laboratory study	15 (healthy women)	1d	No change in hunger, ↓fat intake	↓Intake	94
Sibutramine	Laboratory study	12 (obese women)	14d	↓Hunger	↓Daily intake	95

5-HTP = 5-hydroxytryptophan; **mCPP** = m-chlorophenylpiperazine; **NR** = not reported; ↑ indicates increase; ↓ indicates decrease.

accompanied by significant decreases in eating rate and desire to eat, both indicative of a drug-induced modulation of normal appetite. The desire to eat being significantly lower prior to the meal and the low rate of consumption at the start of the meal signify that fenfluramine had retarded normal hunger by enhancing the pre-meal satiety state. Similarly, Foltin et al.[97] found that both male and female, healthy, normal weight individuals reduced their total daily caloric intake when given fenfluramine 40 mg/day. Specifically, the participants reduced their meal size rather than the number of meals, indicating that fenfluramine had enhanced within-meal satiation processes but had not produced any compensatory weakening of satiety states between meals.

A number of differing laboratory-based feeding paradigms have successfully shown dexfenfluramine-induced hypophagia in humans. Not all can be detailed here but it is useful to consider some of these studies, which have indicated the efficacy of both short- and long-term dexfenfluramine on food intake, in both lean and obese individuals. Acute doses of dexfenfluramine were administered to lean healthy males in a study by Goodall and Silverstone.[86] The results of this study showed that a single 30mg dose of dexfenfluramine produced a significant reduction in cumulative intake and eating rate of approximately 23% over a 2-hour period.

Dexfenfluramine, as with fenfluramine, in this ad libitum feeding paradigm produced a significant decrease in pre-meal hunger ratings. In another study, Blundell and Hill[83] also noted that dexfenfluramine produced significant reductions in hunger prior to a meal in both the lean and the obese. Additionally, the effect on hunger was greater in magnitude in the obese than the lean. In this study, the drug also reduced prospective consumption in the obese and the lean, and solely in the lean enhanced feelings of fullness were reported.

Subsequently, Drent et al.[98] administered dexfenfluramine (30 mg/day) to overweight and obese individuals for 9 weeks, in a randomised, placebo-controlled, double-blind trial. Throughout the trial, dexfenfluramine produced a marked reduction in self-reported food intake. The placebo group actually gained 0.2kg over the study period despite self-reporting a 15% reduction in daily food intake from baseline. Conversely, the group treated with dexfenfluramine lost 3.1kg and reduced self-reported daily food intake by a significant 30% from baseline. It is possible that, as the placebo group failed to lose weight, there may have been an under-reporting of energy consumed by participants in this trial. Despite this, the effects shown on bodyweight and food intake are still impressive. Analysis of the food diaries indicated that dexfenfluramine treatment reduced energy intake by reducing meal and snack size but not number. This study also demonstrated that the dexfenfluramine reductions in food intake were associated with the effect of the drug on bodyweight. Moreover, even when the drug is given long term to obese individuals, dexfenfluramine-induced reductions in food intake appear to be a robust phenomenon.

5.3 Fluoxetine

A study by McGuirk and Silverstone[89] investigated the effect of 2 weeks' fluoxetine (60 mg/day) treatment on food intake. Healthy male participants were employed in a double-blind, placebo-controlled, crossover design. Food intake and eating behaviour were assessed on three distinct probe days (days 1, 8 and 15). Over the 2-week treatment period, participants in the drug treatment group lost significantly more weight than those in the control group (1.07 vs 0.15kg). 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. Again in the fluoxetine group, a significant reduction in hunger was reported on day 8 only. From this study, it is not possible to ascertain whether day 15 was the last day of fluoxetine treatment or the first day of the washout period.

Another study examined the effects of 14 days' administration of fluoxetine (60 mg/day) on meal patterns.[99] The group treated with fluoxetine lost 3.6kg in comparison to a weight gain of 0.3kg seen in the placebo control group. When compared with the placebo control, fluoxetine treatment also significantly reduced reported meal and snack intake. A more detailed study of the effects of fluoxetine (60 mg/day) on the eating behaviour and food intake of obese females was carried out by Lawton et al.[90] Volunteers in this study, as with the McGuirk and Silverstone study,[89] were treated for 14 days with both drug and placebo in a randomised, double-blind, crossover design. Patients returned to the laboratory on days 7 and 14 to receive fixed test meals. This was designed to investigate whether fluoxetine-induced hypophagia was intensified or weakened by equi-caloric test meals that differed in macronutrient composition. The results of this study were similar to those of previous studies, as over the 2-week treatment period significantly more weight was lost in the drug group than the controls (1.97 vs 0.04kg). There was also a significant associated reduction in post-test meal hunger in the drug group. Irrespective of their macronutrient composition, it was shown that fluoxetine increased the satiety impact of the fixed equi-caloric test meals. Direct

measurement of subsequent food intake at the ad libitum evening meal that followed the test meal on days 7 and 14 showed that fluoxetine produced a 27% (198kcal) reduction in energy consumption. During this study participants were also asked to complete daily food diaries. Analysis of these diaries showed that during the 14 days of treatment, fluoxetine produced a self-reported reduction in daily energy intake of 22.4% (421 kcal/day).

It appears that a tolerance to fluoxetine-induced hypophagia develops after 2 weeks of administration, as suggested by the data from McGuirk and Silverstone.[89] However, Ward et al.,[100] carried out a 16-week outpatient study in the obese, in which participants attended the laboratory at weeks 7 and 16 of treatment. On these days, long-term fluoxetine administration was shown to reduce participants' total food intake. Specifically, the mean number of total eating occasions within a study day was reduced by fluoxetine. Unlike drug-induced hypophagia, tolerance did appear to develop to drug-induced weight loss in this study. At the week 7 timepoint, fluoxetine-induced weight loss was significantly greater than with placebo, but this was not the case at the week 16 study endpoint.

5.4 Sibutramine

In addition to fluoxetine and dexfenfluramine, acute doses of sibutramine, an SNRI, have been shown to reduce food intake[101] and appetite in lean male volunteers.[101,102] Hansen et al.,[102] initially studied the effect of sibutramine (30 mg/day) on energy expenditure but also noted that the drug produced an enhancement of the inhibition of appetite resulting from the set breakfast (2.1kJ) given to all participants. Although this study did not measure the effects on subsequent ad libitum food intake, sibutramine treatment was shown to increase the satiety impact of a fixed load of food.

In a subsequent study by Chapelot et al.,[101] a placebo-controlled counterbalanced design was used to investigate the effect of a single 15mg dose of sibutramine on total daily energy consumption. The drug was taken prior to a fixed load breakfast. It was shown to reduce total caloric intake on the study by 1304 kcal, approximately 12%. This figure is achieved through significant reductions in caloric intake at both lunch and dinner (637 and 393kJ, respectively). The number of food items eaten per day was reduced by an average of 1.6 items (approximately 10%). This effect occurred mainly at lunch. In addition to the pronounced hypophagia and changes in feeding behaviour seen at lunch, the 15mg dose of sibutramine significantly reduced hunger 4 hours after administration, an effect that coincided with the start of the lunch.

Rolls et al.[95] examined the effects of sibutramine on food intake and appetite in obese individuals. In this study, the double-blind, placebo-controlled, crossover design used was similar to that of previous fluoxetine studies.[89,90] It was conducted over 14 days, with participants invited into the laboratory to have their eating behaviour assessed directly on days 7 and 14. Two daily dosages of the drug were used, 10mg as is normally prescribed, and a higher 30mg dose. Participants were instructed to take the drug before breakfast. On study days, participants attended the laboratory for breakfast, lunch and dinner, all of which were ad libitum meals. The 30mg dose of sibutramine showed effects on food intake, subjective measures of appetite and bodyweight that were observed earlier in the study and were greater in magnitude than the effects of the lower dose. Specifically, the 30mg dose reduced caloric intake by 1763kJ (23%) by day 7 and by 2079kJ (26%) on day 14 (vs placebo). The 10mg dose also significantly reduced total caloric intake by 1290kJ (19%), but only on day 14. The significant reductions shown in total caloric intake (on days 7 and 14 for the 30mg dose, on day 14 only for 10mg) resulted from significant reductions in energy intake at both lunch and dinner, but not at break-

fast. It is not clear whether sibutramine-induced hypophagia was greater at lunch or at dinner, but the effect does appear to have been accompanied by reductions in pre-meal hunger and prospective consumption ratings at the 30mg dose. Interestingly, both the Chapelot and Rolls studies[2,9,101] demonstrate that sibutramine-induced significant effects on appetite were observed before the ad libitum meal, but not after. Following the ad libitum meal, drug-induced reductions appear to 'normalise' the subsequent post-meal appetite ratings, whereas after a fixed load these ratings are suppressed. Importantly, in both studies the use of sibutramine treatment in the lean and the obese resulted in the same post-meal satiety being attained by significantly less food consumption.

Tolerance to the hypophagic effects of sibutramine did not appear in the 14 days' treatment of the Rolls et al.[95] study. Moreover, it was observed that changes in appetite and food intake were accompanied by significant drug-induced weight loss in this study. The 10mg dose of sibutramine had caused a reduction in bodyweight by 0.7kg at day 7, and by day 14 weight was reduced by 0.8kg compared with placebo. The higher 30mg dose of sibutramine had reduced bodyweight by 0.6kg on day 7 and by 1.2kg on day 14. The results of this study appear to suggest that in the obese, sibutramine treatment produces both hypophagia and associated weight loss.

Hansen et al.[103] conducted an 8-week randomised, double-blind, placebo-controlled study in the obese to examine the effects of sibutramine 15 mg/day on energy expenditure. The study design involved two laboratory visits, one at the start of treatment and one at the end, in which the participants were required to live in a respiration chamber for 32 hours. Participants ate freely at set meals during this time and their appetite was assessed. Disappointingly, the authors did not report the effects of sibutramine on food intake at these visits. However, it was noted that both daily hunger ratings and prospective food consumption were significantly decreased on the first (day 1) and the last (day 56) days of sibutramine treatment. The results of this study also showed that sibutramine produced a significant decrease in bodyweight of 2.4kg compared with a slight rise of 0.3kg seen in the placebo group over the course of the study. Sibutramine was shown to have little effect on energy expenditure; therefore, the weight loss observed is likely to have resulted from the effect the drug had on food intake.

Barkeling et al.[104] recently provided perhaps the most persuasive argument to demonstrate the link between sibutramine-induced hypophagia and sibutramine-induced weight loss. This multiphase study was devised to examine the effects of sibutramine on appetite in the obese, particularly to see whether sibutramine still reduced food intake after 10 months of treatment and how predicted weight loss progressed on a long-term trial. Obese volunteers were recruited to a 14-day fully randomised, placebo-controlled, crossover study. Following 14 days of treatment with sibutramine 15 mg/day or placebo, the participants were invited into the laboratory to consume an ad libitum lunch. During the initial double-blind study, a 16% kcal reduction in energy intake at the test lunch was observed. Subsequently, the participants were placed on a 10-month open-label treatment with sibutramine. At the end of this period, the participants returned to the laboratory for a final visit at which they were provided with the same ad libitum meal they had received on previous occasions. Intake at this lunch was reduced by 27% when compared with their pre-weight loss trial placebo intake. Sibutramine also significantly increased ratings of fullness and decreased prospective consumption after the fixed breakfast but not after the ad libitum lunch. Interestingly, this study demonstrated that the appetite response to sibutramine was undiminished after 10 months of treatment. It is particularly important to note that the

initial effect of sibutramine on appetite in the 14-day trial was predictive of the effect of sibutramine on bodyweight during the subsequent 10-month open-label weight loss trial.

5.5 Preferential and Selective Serotonin Receptor Agonists

Direct agonism of serotonin receptors also potently reduces food intake. In the rat, mCPP (a 5-$HT_{1B/2C}$ receptor preferential agonist) has been shown to reduce food intake via activation of 5-HT_{2C} receptors. A number of studies have also shown that mCPP reliably reduces food intake in humans. The effect of an acute dose of mCPP (0.4 mg/kg) was initially investigated in a double-blind, placebo-controlled, crossover design study, conducted with lean, healthy female volunteers.[92] Each participant was given either mCPP or placebo orally 150 minutes prior to the presentation of a buffet lunch. At this ad libitum meal, food intake in those receiving mCPP was reduced by 30% (approximately 1000kJ). This study also showed that the effect of mCPP on food intake was significantly associated with pre-meal hunger ratings being reduced. Subsequently, this study was replicated in a larger group of both male and female lean, healthy volunteers.[105] The drug was again effective at reducing food intake in women (28%, 1205kJ) and also in men (20% reduction, 1219kJ). Again, the drug produced significantly reduced hunger ratings prior to the meal in both men and women (150 minutes after administration). This effect occurred marginally after peak plasma mCPP concentrations (120 minutes after administration) and just prior to the lunch.

A study in obese individuals examined the effects of mCPP on appetite and bodyweight but not food intake.[93] In this double-blind, placebo-controlled, crossover trial, participants were treated for 14 days with mCPP (20mg twice daily for women, 25mg twice daily for men). Significantly more weight (0.8kg) was lost from baseline with mCPP compared with placebo (0.04kg). Participants were invited to the laboratory on the penultimate day of treatment and blood samples were taken to assess mCPP concentrations and prolactin response. During this procedure, hunger rating scales were also completed by the participants. Analysis of the scales subsequently showed that drug treatment produced a significant decrease in hunger ratings.

Collectively, the three studies discussed make it evident that mCPP can effectively reduce food intake and appetite in lean individuals, and bodyweight and appetite in obese individuals. However, it is important to note that in lean participants, mCPP also produced transient but significant increases in the self-reported subjective ratings of light-headedness, anxiety and nausea.[92,105] It has also been observed that transient increases in blood pressure and heart rate can occur in response to acute doses of mCPP.[106] If more specific 5-HT_{2C} receptor agonists could be developed (particularly if they avoid some of the aforementioned transient adverse effects produced by the less specific mCPP), this could be an important advancement in obesity treatment. However, it still remains to be demonstrated whether the hypophagic effects of mCPP and more selective 5-HT_{2C} receptor agonists occur in obese individuals.

The 5-HT_{2C} receptor is, of course, not the only receptor that has been implicated in mediating the effects of the endogenous serotonin satiety system. Sumatriptan, a novel 5-$HT_{1B/1D}$ receptor agonist, has also been found to produce a significant reduction in food intake in healthy women.[94] This study used a double-blind, placebo-controlled, crossover design to examine the effects of an acute 6mg dose of sumatriptan on food intake at a buffet style lunch. A 23% reduction in food intake (approximately 850kJ) was produced by the sumatriptan injection compared with placebo. Importantly, a 34% decrease in fat intake was also observed at the lunch following drug treatment. In this study, no signifi-

cant effects on ratings of nausea and light headedness were observed. However, as there were no significant effects on appetite reported, it is probable that this study was statistically underpowered.

6. Serotonergic Drugs and Obesity: Rodent Studies

6.1 Dexfenfluramine and Selective Serotonin Reuptake Inhibitors

It has been proven in a number of rodent models that drugs which promote serotonin release or inhibit reuptake do inhibit bodyweight gain. In one study, daily injections of dexfenfluramine (10 mg/kg) over a 12-day period were shown to be 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).[107] This reduction in bodyweight gain was associated with a marked reduction in caloric intake.

It has also been noted in a separate study that no tolerance developed to the bodyweight gain attenuating effects of dexfenfluramine (6 mg/kg/day infused peripherally via a mini-pump) during a 14-day study in Lister hooded rats.[108] At the end of the study, the animals treated with dexfenfluramine weighed 5% less than controls. As with the previously mentioned study,[107] these effects on bodyweight were associated with drug-induced reductions in food intake. However, it was observed that in the second week of this study dexfenfluramine-induced hypophagia was less pronounced.

In a longer 28-day study, dexfenfluramine was administered twice daily (2.5 mg/kg).[109] Again, the drug reduced food intake and attenuated bodyweight gain. Animals treated with dexfenfluramine for 28 days weighed approximately 50g (12%) less than controls, and no tolerance developed to the hypophagic effects of dexfenfluramine in this study. The administration of a number of other serotonergic drugs has also produced these effects on bodyweight gain and food intake. For example, SSRIs such as fluoxetine,[110,111] sertraline,[112] fluvoxamine[113] and paroxetine[114] have also all been shown to attenuate bodyweight gain in various rodent models, an effect normally associated with significant hypophagia.

6.2 Serotonin Receptor Agonists

In rodent models it also appears that direct agonism of 5-HT_{2C} receptors affects weight gain. In their first study, for example, Vickers et al.[108,109] have shown the inhibitory effects of the preferential 5-HT_{2C} receptor agonist mCPP on rodent bodyweight gain. mCPP 12 mg/kg/day was delivered by implanted mini-pumps during the initial study, the results of which demonstrated that the effects of mCPP on bodyweight were associated, at least partly, with hypophagia. Furthermore, tolerance to the effects of mCPP on rodent bodyweight gain did not develop during this study and animals treated with mCPP weighed 8% less than controls by the end of the study.

It is known that mCPP also agonises several other serotonin receptors (e.g. 5-HT_{2A} and 5-HT_{2B} receptors); therefore, it is theoretically possible that the drug-induced attenuation of bodyweight gain could be due to activation of any of these receptors. However, using selective antagonists, it has been demonstrated that mCPP-induced hypophagia is a result of activation of the 5-HT_{2C} receptor specifically.[115] Consequently, it is probable that the hypophagic component of mCPP-induced weight loss, at least, is due to activation of the 5-HT_{2C} receptor. In a second study,[109] mCPP (10 mg/kg/day) was given orally for 28 days. Again, mCPP induced significant attenuation of bodyweight gain and reductions in daily food intake. Animals treated with mCPP over the 28-day period subsequently weighed approximately 50g (12%) less than controls. No tolerance appears to develop to the hypophagic effects of the 5-HT_{2C}

receptor agonist. Pair-feeding was carried out in order to match the food intake of mCPP-treated animals, which produced the same degree of weight gain, suggesting that the drug's hypophagic effects are responsible for the attenuation of bodyweight gain.

The effects of several more selective 5-HT_{2C} receptor agonists on rodent bodyweight have recently been studied. In the study by Vickers et al.,[108] Ro 60-0175 (26 mg/kg/day) was infused into the animals via implanted mini-pumps for 14 days. The results demonstrate that Ro 60-0175 produced a significant reduction in bodyweight gain; the animals treated with Ro 60-0175 weighed 10% less than controls at the end of the study. As with mCPP, Ro 60-0175 reduced food intake over the treatment period; however, by day 11 tolerance to the hypophagic effect was evident. Similarly, YM348, another potent and highly selective 5-HT_{2C} receptor agonist, also produced an attenuation of bodyweight gain over a 2-week treatment period (at dosages of 3 and 20 mg/kg/day).[116] Animals treated with the higher dose of YM348 weighed 21.5% less than controls at the end of the study. Tolerance to drug-induced hypophagia appeared in the second week of this treatment also.

Multiple doses of the novel selective 5-HT_{2C} receptor agonist lorcaserin (APD356 [4.5, 9, 18 and 36 mg/kg]) have recently been shown to inhibit the development of dietary-induced obesity.[117] Lorcaserin significantly reduced bodyweight gain in both male and female rats. This effect was associated with an initial episode of marked hypophagia. Tolerance appeared to develop to the hypophagic effects of all dosages of lorcarserin during this study.

7. Serotonergic Drugs and Weight Loss: Clinical Data

Examination of the clinical data available appears to suggest that hypophagia is the primary mechanism by which serotonin induces weight loss. Correspondingly, serotonergic drugs must restrain the motivation to eat and maintain lower levels of food consumption for substantial periods of time. A majority of the early clinical data on weight loss originates from studies that employed fenfluramine and dexfenfluramine, drugs that have since been withdrawn from the market. Clinical data on the effects of fenfluramine on bodyweight have been collected and published since the late 1960s, but given that this drug is now withdrawn, these studies need not be detailed. However, Haddock et al.[118] have produced an extremely useful meta-analysis of both early and more recent drug trials.

7.1 Fenfluramine

There are numerous early therapeutic trials of fenfluramine, and for those interested in this area, we recommend the extensive review published in 1975 by Pinder and colleagues.[119] Closer examination of the review demonstrates that the majority of the early fenfluramine studies were a comparison of the effects of fenfluramine with either placebo or other anorectic drugs available at the time (for example, phentermine, dexamfetamine, mazindol and amfepramone [diethylpropion]). Moreover, the studies involved treatment over periods of 12 weeks or less and were small scale (participant numbers in each condition were frequently <30). The level of fenfluramine-induced weight loss reported in these studies depended on the dose of fenfluramine given, the duration of the trial, the additional dietary advice/regimen given to the participants and the differences between the target population included in each of these trials, and inevitably varied between 1.2 and 11.9kg. Despite this variation, fenfluramine-induced weight loss was shown to be a robust clinical effect.

Of the 14 trials of fenfluramine to meet inclusion criteria from Haddock and colleagues'[118] meta-analysis, an average of 5.06kg weight loss (placebo subtracted = 2.41kg) was produced by the drug. The

data were obtained from studies which varied in dosage (from 39 to 120 mg/day), duration (the longest trial was just 18 weeks, average trial length was only 9.7 weeks), dietary advice, participant numbers (the maximum number of participants in the fenfluramine groups of the included trials was 58, with an average of just 20) and other characteristics.

7.2 Dexfenfluramine

The European INDEX (INternational DEXfenfluramine) trial was a key study of the clinical efficacy of dexfenfluramine.[120] INDEX was a multicentre, randomised, double-blind, placebo-controlled trial carried out with 822 obese volunteers. Of these, 404 individuals received dexfenfluramine 15mg twice daily and the remaining participants received placebo. After 12 months, of the participants to complete the study, 52% of those receiving dexfenfluramine had lost 10% or more of their initial bodyweight compared with only 30% of those receiving placebo. Average weight loss from baseline with dexfenfluramine during this trial was 9.82kg (10.26%), a figure significantly greater than that achieved with placebo (7.15kg; 7.18%).

Interestingly, withdrawal from dexfenfluramine following completion of the 12-month INDEX trial led to an immediate rise in daily energy consumption which was accompanied by rapid weight gain over a 2-month period.[121] This appears to suggest that despite weight loss stopping after 6 months, dexfenfluramine had maintained a strong influence over food intake for the entire 12-month period. The drug had reduced both self-reported hunger and bodyweight to a point of physiological resistance at which equilibrium had been reached between hunger urges and drug anorectic activity. After the drug withdrawal at 12 months, the rebound in hunger demonstrated a lack of tolerance to the hypophagic effects of dexfenfluramine. Despite the reduction in food intake being predominantly in the first 6 months, dexfenfluramine maintained an energy intake reduction of 6–10% over the year-long study period.[121]

Dexfenfluramine has also been shown to inhibit human food intake and weight regain after treatment with a very low calorie diet (VLCD). A VLCD was used in a study by Finer et al.[122] to reduce weight in the obese by 14kg in 8 weeks. After adherence to a diet and such rapid weight loss, there is often a strong disposition to resume overeating and regain the weight lost. In this study, following termination of the 8-week VLCD, patients given dexfenfluramine 15mg twice daily for 26 weeks continued to lose weight. Compared with the placebo group, who regained an average of 2.9kg, the dexfenfluramine group lost an additional 5.8kg, bringing total weight loss to 21.3kg over the entire 34 weeks of the study. Therefore, in this study,[122] dexfenfluramine overcame the physiological and psychological drive to eat following rapid, substantial weight loss.

Returning to Haddock and colleagues'[118] meta-analysis, of the 14 trials to meet inclusion criteria, average dexfenfluramine-induced weight loss from baseline was 8.9kg. For any anti-obesity drug included within their analysis, this is the largest average effect observed. In part, this could be attributable to the longer trial length (an average of 33 weeks) in a majority of the dexfenfluramine studies analysed and also the successful lifestyle interventions. Despite these factors, the average placebo-subtracted weight loss produced by dexfenfluramine was equal to or greater than that with any other drug, including current obesity treatments such as orlistat and sibutramine. These meta-analyses did not include dexfenfluramine, but Haddock et al.[118] did find exfenfluramine-induced weight loss to be in line with that from sibutramine and orlistat.

7.3 Sibutramine

The STORM (Sibutramine Trial of Obesity Reduction and Maintenance) trial demonstrated the

clinical efficacy of the SNRI sibutramine. Obese patients were prescribed sibutramine 10 mg/day in addition to a low calorie diet over 6 months and lost 11.3kg in this randomised, double-blind trial.[123] Following this open-label run-in period, the diet phase ended and patients were entered into an 18-month randomised, double-blind, placebo-controlled study. Within this study, participants were randomly allocated to either placebo or sibutramine (10 mg/day). Of the group to be maintained on sibutramine for 18 months, there was little weight regain observed (bodyweight gain at study end was 9.3kg lower than at pre-run-in baseline 24 months previously). In contrast, those in the placebo group appeared to begin regaining weight within 2 months of entering the trial phase. Although weight loss was not observed after the first 6 months, there was little indication of any tolerance developing to sibutramine over the 24 months of treatment. A number of other 1- and 2-year studies have demonstrated the weight loss-inducing efficacy of sibutramine.[124-127] Irrespective of variation in specific protocol or patient populations (for example, diabetic or non-diabetic, hypertensive, etc.), when examining data from these studies conducted over a year or more, it is again evident that the dynamic phase of sibutramine-induced weight loss occurs within the first 6 months of treatment. Following this period, sibutramine stabilises bodyweight at a level significantly lower than at the pretreatment point (i.e. baseline). Sibutramine has produced a placebo-subtracted weight loss of 4.45 or 4.3kg, as shown by two meta-analyses of clinical data.[128,129]

7.4 Selective Serotonin Reuptake Inhibitors

In terms of anti-obesity properties, the most comprehensively studied SSRI is fluoxetine. Early clinical studies, of 6–8 weeks in duration, suggested that treatment with fluoxetine was able to produce weight loss of 0.5kg (on average) per week.[130] Accordingly, Haddock and colleagues'[118] meta-analysis of 11 fluoxetine trials demonstrates that an average bodyweight reduction from baseline of 4.1kg (3.3kg placebo subtracted) was achieved by this drug.

However, following the trajectory of fluoxetine-induced weight loss after a 6-month period shows that the drug's effects are not sustained.[131] Early in the trial, participants treated with fluoxetine displayed significant weight loss (at week 24, maximum weight loss of approximately 4.9kg) and even by the end of the 60-week trial weight loss was still significantly greater in the fluoxetine group than in the placebo group. However, at week 60 those receiving placebo had lost 1.5kg and those receiving fluoxetine just 2.2kg. As had been noted in previous, smaller-scale, 1-year trials and in analysis of subsets of these data, both groups were seen to begin regaining weight halfway through the study.[132,133] There is little evidence to date that any other SSRI would be any more efficacious. For example, sertraline, in contrast to dexfenfluramine, appears to be ineffective at preventing weight regain after a brief period of VLCD.[91] However, early reports on the effects of another serotonin reuptake inhibitor, zimeldine have been interesting. One study has demonstrated that 8 weeks' treatment with zimelidine (100mg twice daily) can produce significant placebo-subtracted weight loss, an effect associated with a significant reduction in appetite ratings.[134] It should be noted that while most psychiatric medications produce pronounced weight gain (including lithium, tricyclic antidepressants and antipsychotic medication) and, moreover, that many of the untreated psychiatric population are also liable to gain weight, the evidence for SSRI-induced weight gain in the SSRI-treated psychiatric population is inconsistent. This appears consistent with the reported weight loss-inducing effects of SSRIs in non-psychiatric populations. It is necessary to fully re-examine the weight loss-inducing effects of currently known SS-

RIs and their active metabolites, as this may produce suitable candidates for a new anti-obesity drug.

7.5 Serotonin Precursors and Receptor Agonists

Currently, no large-scale clinical trial data exist on the effects of serotonin precursors or receptor agonists on weight loss in the obese. The previously mentioned studies by Cangiano et al.[81,96] have shown that 5-HTP can induce weight loss for up to 12 weeks in the obese (6% reduction in initial body mass). In addition, the preferential 5-HT_{2C} receptor agonist mCPP has been shown to induce weight loss over a 2-week period in the obese.[93] Several selective 5-HT_{2C} receptor agonists have reached or are about to reach phase II clinical trials, the data from which have not been made widely available, although some have been presented. For example, details have been provided on the efficacy of Org 12962, a 5-HT_{2C} receptor agonist. The effects of Org 12962 (10mg twice daily) were studied in 40 obese participants over a 12-week study.[135] Participants treated with Org 12962 lost 13.7kg (14%) of their initial body mass. However, this study presented a strikingly large placebo effect, as those in the placebo group lost the same proportion of weight during the treatment period. There was no detailing of the effects of drug treatment on appetite. Interestingly, compliance to Org 12962 appeared to increase towards the end of the treatment phase compared with placebo. Org 12962 treatment seemed to help the participants adhere to the rigorous but effective weight loss measures that had been prescribed to all participants in this study, which could be attributable to the agonist's efficacy at suppressing the hunger increases caused by dieting. As a consequence, it would have been interesting to examine if extending the trial would have shown the continued appetite modulation of Org 12962 to translate into a significantly greater weight loss than that seen in the placebo group.[136]

8. Current and Future Serotonergic Anti-Obesity Drugs

Dexfenfluramine was voluntarily withdrawn in 1997 because of the risk of primary pulmonary hypertension, a move which dealt a blow to the development of serotonergic anti-obesity compounds.[137] The heart valve abnormalities discovered in a few patients in the postmarketing period led to the very rapid withdrawal of this drug.[138,139] Subsequently, the SNRI sibutramine was approved for the treatment of obesity. It has been suggested that sibutramine reduces weight by inducing both satiety and thermogenesis. It has been difficult to demonstrate the latter effect in humans. Studies quoted in this review suggest that the primary action of sibutramine is on satiety in humans; therefore, it is likely that despite what the limited preclinical data suggest, this effect is mediated by serotonin activation. Without doubt, the effects of sibutramine on rodent feeding behaviour and human appetite are indistinguishable from those of dexfenfluramine, fluoxetine and the preferential and selective 5-HT_{2C} agonists. There have been adverse effect issues associated with sibutramine itself, which are currently under investigation.

As a consequence, the focus from pharmaceutical companies has been on developing 5-HT_{2C} receptor agonists. This is partially because of the increasing evidence that this receptor subtype was critical to the dexfenfluramine mechanism of action but also because these receptors are not thought to be widely distributed outside the CNS so any issue of primary pulmonary hypertension is avoided.[2] Numerous selective 5-HT_{2C} receptor agonists have been developed including Org 12962 from Organon, Ro 60-0175 from Roche and Vernalis, VER-3323 from Vernalis, BVT-933 from Biovitrum and GlaxoSmithKline and YM348 from Yamanouchi Pharmaceuticals.[2] Some of the compounds have passed into phase I and (in the case of BVT-933) phase II trials; it is regrettable that their effects on

human appetite, food intake and bodyweight remain largely unknown. One issue may have been drug affinity to serotonin receptors other than 5-HT_{2C}, causing adverse effects during the clinical trial studies.

However, lorcaserin (Arena Pharmaceuticals) is known to be currently undergoing clinical trials[140-142] and, according to the company, in a phase Ia study the drug significantly reduced meal size. A single 10mg dose produced a statistically significant 10.7% (122.5 kcal) mean reduction in meal size relative to placebo. The drug also completed a phase Ib safety dose-escalation study, and no effect on heart valves or pulmonary artery pressure was observed, so phase II trials were carried out in 2005. The results of these, again according to the company, are promising.[140] In phase IIa trials, a 15mg daily dose produced a statistically significant mean weight loss of 1.3kg (compared with 0.4kg in the placebo group) over a 28-day treatment period.[142] Recently, results of the phase IIb trials have also been published, showing that treatment with lorcaserin was associated with a highly significant average weight loss of 1.8, 2.6 and 3.6kg at daily doses of 10, 15 and 20mg, respectively, over the 12-week treatment period. In comparison, those in the placebo group lost just 0.3kg in that time. This drug is expected, funding permitted, to enter phase III clinical trials in the second half of 2006. The structure of lorcaserin is undisclosed, but it is likely to have come from a series of novel 3-benzazepine derivatives.[141]

Halford et al.[143] described the ideal attributes of any appetite suppressant anti-obesity drug in 2003. An ultimate appetite suppressant anti-obesity drug should ideally:

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

All future serotonergic drugs should be measured by these criteria, above and beyond those for anti-obesity drugs in general. Furthermore, in order to make a sizeable impact on the market, any drug will need to produce placebo-subtracted weight loss over 1 year that is greater than that currently produced by anti-obesity drugs orlistat (less than 4kg) and sibutramine (over 4kg), and that reported to be produced by novel anti-obesity agent rimonabant (approximately 5–6kg).[144]

9. Novel Serotonergic Targets for Weight Control

While most of the focus on serotonin and weight control has been on drugs agonising the 5-HT_{2C} receptor, other targets in the serotonin system exist. The 5-HT_6 receptor is one of the most recent additions to the serotonin receptor family. It is almost exclusively expressed within the CNS with high levels in cortical and limbic regions.[145] The recent development of specific 5-HT_6 receptor ligands has indicated potential roles for this receptor in a number of physiological processes, including feeding.[146] Selective 5-HT_6 receptor antagonists have been reported to produce significant reductions in food intake when administered to *ob/ob* mice, with these hypophagic effects being accompanied by significant reductions in bodyweight and insulin levels.[147] Such results identify 5-HT_6 receptor antagonists as potential anti-obesity agents. Notably a number of companies have recently indicated they have preclinical 5-HT_6 receptor-based anti-obesity drug development programmes and presumably a

number of suitable 5-HT_6 receptor antagonists now exist. 5-HT_6 antagonists such as PRX-08034 (Epix Pharmaceuticals) and BVT 74316 (Biovitrum AB) have recently entered clinical trials.[148,149]

10. Summary

Anti-obesity treatments have targeted and will continue to target the endogenous serotonin satiety system. As levels of endogenous serotonin respond to both deprivation and energy excess, and a reduced caloric intake lowers CNS serotonin levels and turnover, serotonin appears to play a key role in appetite. Moreover, susceptibility to weight gain in both rodents and humans may be attributable to low levels of endogenous serotonin and serotonin dysfunction. The hypothalamic serotonin satiety system is known to interact with orexigenic systems such as orexin and NPY. Serotonin may inhibit feeding behaviour by, among other means, blocking these hunger signals. In addition, the hypophagic effects of serotonergic drugs appear to be mediated by the anorexigenic melanocortin system. Therefore, as an episodic satiety transmitter, serotonin (like the tonic adiposity signal leptin) influences feeding behaviour via both stimulatory and inhibitory effects on several regulatory neuropeptide systems in the hypothalamus.

Drugs that either directly or indirectly stimulate hypothalamic 5-HT_{2C} receptors in rodents produce both changes in the structure of feeding behaviour and reductions in food intake that are consistent with the satiety process. These drugs cause an enhancement of the post-meal satiety potency of fixed caloric loads and reduce pre-meal appetite and food intake at ad libitum meals in both lean and obese humans. Reductions in bodyweight gain and decreases in bodyweight from baseline are strongly associated with the hypophagic action of these drugs in both rodent dietary-induced obesity models and human clinical trials. Moreover, antagonism of 5-HT_6 receptors also appears to reduce food intake and block weight gain in rodents. Whether drug-induced hypophagia and associated effects on weight are due to selective action on appetite is unclear.

A new generation of selective 5-HT_{2C} receptor agonists have been developed and some have passed into clinical testing. The selectivity of these compounds should ensure that they avoid the adverse effects associated with their predecessors. However, it is essential that these new drugs produce marked effects on appetite and feeding behaviour, and are able to induce substantial and sustained hypophagia that is sufficient to produce clinically significant weight loss. When assessing the effects of these drugs, it is important to examine not just kilocalorie or gram reduction in intake, but also observed changes in appetite (such as hunger, prospective consumption, fullness, etc.) and feeding behaviour (eating rate, meal size, daily meal and snack number). As obesity is known to be linked to the consumption of highly palatable, energy-dense foods (high in fat and/or sugar) it is necessary to establish how a drug modifies the type of food chosen in terms of energy density, macronutrient composition and palatability. Any drug able to reduce the liking for or the wanting of highly palatable foods that are known to promote overconsumption and weight gain is likely to be of significant therapeutic value. There are also a number of non-serotonergic treatments undergoing clinical trials. Many of these are also entering phase II studies or preparing for phase III trials.[150] Ultimately, it is against these drugs, as well as existing treatments, that the efficacy of any serotonin-targeted anti-obesity treatment will be judged.

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Correspondence and offprints: Dr *Jason C.G. Halford*, School of Psychology, University of Liverpool, Liverpool, L69 7ZA, UK.

E-mail: j.c.g.halford@liverpool.ac.uk