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Serotonin and Appetite Regulation

Implications for the Pharmacological Treatment of Obesity

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Summary

It is approximately 20 years since the serotonin (5-hydroxytryptamine; 5-HT) hypothesis of appetite control was formally stated. In that time, evidence has accumulated to confirm the role of serotonergic mechanisms in appetite control. At present, it is believed that serotonin 5-HT_{1B} and 5-HT_{2C} receptor subtypes mediate the capacity for an inhibition of food intake. Animal studies show that serotonin-induced suppression of eating generally preserves the behavioural satiety sequence, which is widely regarded as an indication of the operation of the natural physiological processes for meal termination and sustained post-meal satiety.

The precise nature of the human serotonin feeding control system is less well understood. However, the 5-HT_{2C} receptor has been implicated in human eating, although any role for the 5-$HT_{1D\beta}$ (h5-HT_{1B}) receptor has yet to be determined.

A consistent pattern of reduction in hunger motivation and energy intake is seen in human studies with a variety of serotonergic agents. With some drugs, but not all, a controlled restraint of appetite can be observed for at least 1 year. Patients receiving drugs report both a lower frequency and a reduced strength of urges to eat, together with the feeling of being more in control of their eating. Some serotonergic drugs, such as dexfenfluramine, can exert a continued suppression of appetite even following substantial bodyweight loss brought about by a period of following a very low calorie diet.

Recent evidence has outlined the effects of diet composition on energy balance and bodyweight gain. This has generated interest in the effect of serotonergic drugs on preference for high fat diets and diets characterised by energy dense foods coupled with potent palatability, and carbohydrate craving. The experimental evidence is not unanimous on whether manipulation of serotonergic systems can selectively adjust macronutrient intake and food choice. Animal studies indicate that certain serotonergic drugs such as dexfenfluramine are potent inhibitors of the consumption of high fat diets. Human studies confirm that there is a suppression of the consumption of highly palatable high fat foods, and some studies indicate a possible selective avoidance of fat after the administration of dexfenfluramine and sumatriptan.

Serotonergic drugs may be particularly helpful in curtailing episodes of overconsumption. However, it remains to be clearly demonstrated whether serotonin-based interventions are appropriate for the binge eating subpopulation of obese people and for those individuals displaying binge eating disorder.

Despite the recent withdrawal from the market of appetite suppressants containing dexfenfluramine and fenfluramine, evidence suggests that serotonergic drugs can continue to play a useful role in the treatment of obesity. Their effects are achieved by adjusting biological mechanisms, which in turn reduce the impact of risk factors that facilitate the development of positive energy balance and bodyweight gain. Although the recent development of sibutramine as an appetite suppressant is encouraging, further research in this area is required to develop well tolerated and effective serotonergic appetite suppressants. Furthermore, an improvement in methodology in clinical research is required to enable detection of a selective modulation of high fat (high energy dense) foods.

By far the largest body of evidence relating to the role of the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) in appetite regulation comes from animal studies. Such studies have informed us of the limbic structures and specific serotonin receptors involved in appetite regulation and how serotonin contributes to the expression of feeding behaviour. Thus, analysis of this literature is essential to understand the effects of serotonergic drugs on human eating behaviour.

In this review, we first detail what animal studies (predominantly rodent studies) have revealed about the role of serotonin in appetite regulation. Subsequently, we look at the effect of available serotonergic drugs on human appetite, feeding behaviour and bodyweight of both lean and obese individuals.

1. The Serotonergic System

Neuronal serotonin is synthesised from the essential amino acid tryptophan, which crosses the blood-brain barrier and enters the CNS. In the cytoplasm, neuronal tryptophan is hydroxylated by tryptophan hydroxylase (with the co-factor piteridine) to produce 5-hydroxytryptophan (5-HTP) [see fig. 1]. 5-HTP is then decarboxylated by aro-

matic acid decarboxylase (with the co-factor pyridoxal phosphate) into serotonin.

Cytoplasmic serotonin is stored in a dense core of vesicles near the presynaptic membrane and is released into the synaptic cleft in response to an arriving action potential (a calcium-dependent effect). The released serotonin stimulates both pre- and postsynaptic serotonin receptors and continues to do so until it is either re-absorbed into the presynaptic neuron for re-use or is oxidised to 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase (MAO) [fig. 2].

Consequently, a variety of mechanisms can be pharmacologically targeted to increase synaptic serotonergic activity. Synaptic levels of serotonin could be increased by: (i) augmenting serotonin synthesis with the provision of more serotonin precursors (i.e. tryptophan or 5-HTP); and (ii) promoting its release from, and preventing reuptake into, the presynaptic membrane. Serotonin transmission could also be increased by directly activating the postsynaptic serotonin receptors.

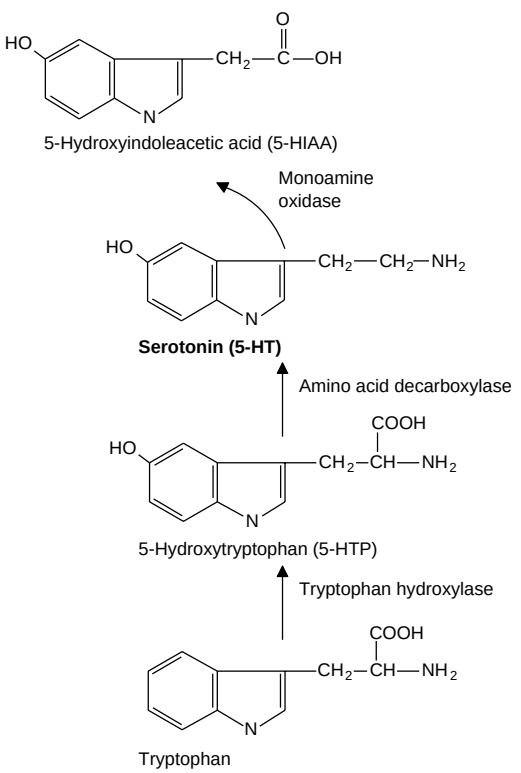

Fig. 1. The synthesis of serotonin (5-hydroxytryptamine; 5-HT).

In 1957, Gaddum and Picarelli[1] suggested the possibility of 2 types of serotonin receptors, which they labelled D and M (later termed 5-HT_2 and 5-HT_3). 22 years later, Peroutka and Snyder,[2] using radioligand labelling techniques, also identified 2 distinct serotonin receptor subtypes (termed 5-HT_1 and 5-HT_2). In 1986, the Committee on Receptor Nomenclature classified serotonin receptors into 3 subtypes: 5-HT_1, 5-HT_2 and 5-HT_3.[3]

Over the past 10 years, radioligand and cloning techniques have allowed the further subdivision of serotonin receptors. The 5-HT_1 group has been further subdivided into 5-HT_{1A},[4] 5-HT_{1B},[5] 5-$HT_{1D\alpha}$, 5-$HT_{1D\beta}$,**1**[7] 5-ht_{1E},**2**[8,9] and 5-ht_{1F}.[10] The 5-HT_2 group is further divided into 5-HT_{2A},[11] 5-HT_{2B}**3** and 5-HT_{2C}**4**.[6] Other current serotonin receptor subtypes agreed on by the International Union of Pharmacology Committee on Drug Classification and Receptor Nomenclature (NC-IUPHAR) subcommittee on serotonin receptors include the original 5-HT_3[1] and the 5-HT_4,[12,13] 5-$HT_{5\alpha}$, 5-$ht_{5\beta}$, 5-HT_6 and 5-HT_7 subtypes (for a review, see Hoyer and Martin[6]). Thus, to date there are 14 recognised serotonin receptors. It is not yet possible to predict any further reclassification.

2. Animal Studies

2.1 Serotonin and Food Intake

The first studies to demonstrate a link between serotonin and food intake were performed over 20 years ago. These studies demonstrated that increased serotonin levels in the CNS had a dra-

1 The 5-$HT_{1D\beta}$ receptor is now regarded as the human equivalent of the rodent 5-HT_{1B} receptor (h5-HT_{1B} and r5-HT_{1B}, respectively).[6]

2 The use of 'ht' in lower case indicates this is a recombinate receptor with as yet no proven functional significance (for a full explanation see Hoyer and Martin[6]).

3 Previously termed 5-HT_{2F}.

4 Previously termed 5-HT_{1C}.

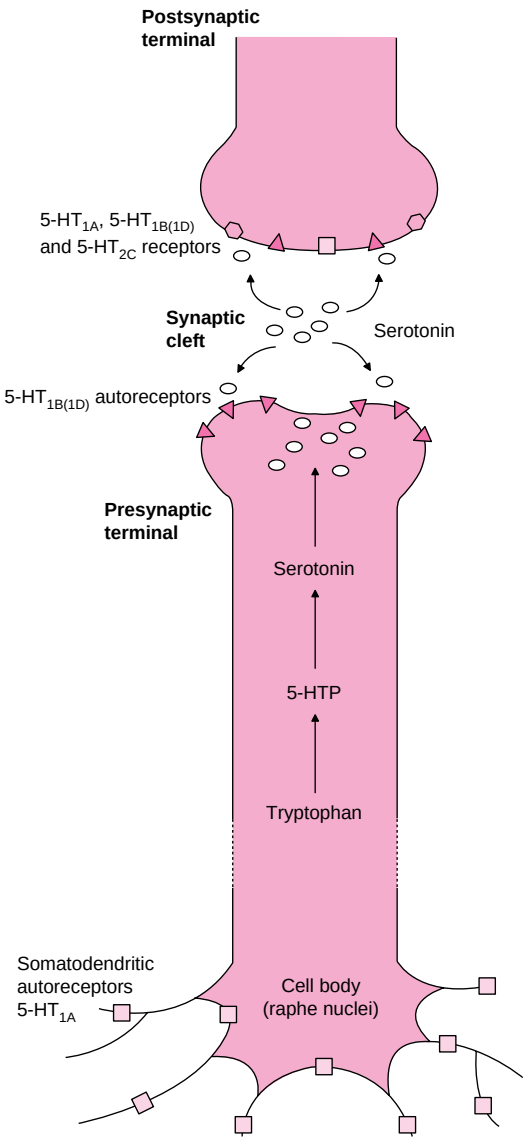

Fig. 2. A serotonin (5-hydroxytryptamine; 5-HT) neuron, showing the serotonin receptors implicated in feeding.

matic effect on food intake and feeding behaviour. Increasing serotonin activity by a variety of mechanisms such as enhancing the synthesis or blocking the breakdown of serotonin or directly stimulating serotonin receptors all produced a strong hypophagic response.[14-17] In the earliest studies, serotonin or its precursors, tryptophan and 5-HTP, were administered to rats. Bray and York[18] noted that serotonin directly administered into the CNS of both lean and obese rats decreased feeding rates and meal sizes. Tryptophan also decreased feeding rates, meal size and food intake,[19] while 5-HTP decreased meal size and food intake.[20] Conversely, blocking the synthesis of serotonin from its processors, using p-chlorophenylalanine (PCPA), increased food intake.[21] It was subsequently proposed that the serotonergic system was directly implicated in the control of food intake.[22]

2.1.1 Mechanism

According to present data, the serotonin receptors most directly implicated in the control of food intake appear to be presynaptic 5-HT_{1A} and postsynaptic 5-HT_{1B} (5-$HT_{1D\beta}$ in humans)[23] and 5-HT_{2C} receptors (see fig. 2). Activation of 5-HT_{1A} receptors is associated with increases in food intake[24] and so this receptor is unlikely to be involved in the hypophagic action of any drugs.

The availability of serotonin-specific drugs such as dexfenfluramine (a serotonin releaser and reuptake inhibitor) and fluoxetine (a selective serotonin reuptake inhibitor, SSRI), and more recently selective agonists and antagonists of specific serotonin receptor subtypes, have allowed a fuller exploration of the role of serotonergic mechanisms in satiety.

Studies Using Receptor Antagonists

A common method used to study the mechanism by which serotonin controls appetite has been to oppose the anorectic action of serotonin releasers or reuptake inhibitors by means of a selective receptor antagonist. Indeed, this procedure has indicated that the hypophagic effect of dexfenfluramine is most likely to be mediated by 5-HT_{1B} and/or 5-HT_{2C} receptors. It was originally considered that fenfluramine-induced hypophagia was mediated by 5-HT_{1B} receptors alone,[25] since antagonists of 5-$HT_{1A/1B}$ receptors blocked the hypophagia but the 5-$HT_{2A/2C}$ receptor antagonist ritanserin did not.[26-28] However, in a later study, dl-fenfluramine–induced hypophagia was reversed by the 5-$HT_{2B/2C}$ receptor antagonist SB-200646C but not by the 5-$HT_{1B/1D}$ antagonist GR-127935.[24]

This would suggest instead that dl-fenfluramine–induced hypophagia is mediated by 5-HT_{2C} receptors.

The hypophagic effect of fluoxetine is not as easily blocked with serotonergic antagonists.[29-31] This has led some researchers to reasonably question the significance of the serotonergic system in fluoxetine-induced hypophagia. However, the 5-$HT_{1/2}$ receptor antagonist metergoline has been shown to partially[31] and fully[32] block fluoxetine-induced hypophagia. This would implicate 5-HT_{1B} and/or 5-HT_{2C} receptors in fluoxetine-induced hypophagia.

At very high dosages, fluoxetine-induced anorexia may also be dependent on catecholamine mechanisms.[32] This would explain the difficulty some researchers have had in blocking fluoxetine-induced hypophagia using solely serotonergic antagonists. It is also worth noting that some authors have suggested that both fenfluramine and fluoxetine (generally believed to be indirectly acting agents) may have direct effects on serotonin or non-serotonin receptors.[33,34] Indeed, it has been suggested that fluoxetine may act as an antagonist of 5-HT_{2C} receptors;[35] if so, fluoxetine-induced hypophagia could be mediated by 5-HT_{1B} receptors.

The hypophagic effects of sertraline (another SSRI)[36] can be blocked using the serotonergic antagonists metergoline (5-$HT_{1/2}$ receptor–specific) and methysergide (5-$HT_{1A/1B/2C}$ receptor–specific), which suggests roles for 5-HT_{1B} and/or 5-HT_{2C} receptors in feeding behaviour.[37] The hypophagia induced by sibutramine [a mixed serotonin and noradrenaline (noradrenaline) reuptake inhibitor (SNRI)][38] can also be partially antagonised by metergoline, ritanserin and SB-200646, thus suggesting a role for 5-HT_{2C} receptors in its anorectic action.[39] However, studies have indicated that noradrenergic mechanisms, mediated by α_1- and β_1-adrenoceptors, may also contribute to sibutramine-induced anorexia.[39]

Studies Using Receptor Agonists

The serotonergic suppression of food intake has also been investigated using specific receptor agonists. Unfortunately, partially selective agonists (like the selective antagonists) generally have affinity for more than one serotonin receptor subtype. One current exception to this is CP-94253, which selectively acts on 5-HT_{1B} receptors.[40] This highly selective agonist CP-94253 also potently reduces food intake in the rat,[40] without inducing any behavioural disruption.[41] This suggests that activation of the r5-HT_{1B} receptor alone is sufficient to reduce food intake. In contrast, the less selective agonist RU-24969 (which has affinity for 5-HT_{1A} and r5-HT_{1B} receptors) reduces food intake, but also has a marked effect on other behaviours.[42,43] This may partly explain the nature of RU-24969–induced hypophagia (see section 2.2.1). These 2 drugs have similar, but not identical, pharmacological actions, but very different effects on behaviour.

Trifluoromethylphenylpiperazine (TFMPP) and *m*-chlorophenylpiperazine (mCPP) [a metabolite of the antidepressant trazodone] are selective agonists at both r5-HT_{1B} and 5-HT_{2C} receptors. Blockade of 5-HT_{2C} receptors reverses the hypophagic effects of these drugs.[44,45] This seems to indicate that activation of 5-HT_{2C} receptors is sufficient to produce a reduction in food intake. However, there is evidence for some involvement of r5-HT_{1B} sites, and it is possible that the activation of r5-HT_{1B} receptors is needed for the expression of hypophagia produced by 5-HT_{2C} receptor stimulation.[46,47] The selective 5-$HT_{2B/2C}$ receptor antagonist SB-200646A partially blocked mCPP-induced anorexia, which would appear to support the 2-receptor theory.[48]

MK-212, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and (–)-2-5-dimethoxy-4-methylamphetamine (DOM) act directly on 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, but not on 5-HT_{1B} receptors. All these drugs reduce food intake.[49-52] This again suggests that activation of 5-HT_{2C} receptors is sufficient to reduce food intake. However, behavioural analysis suggests that the effects on intake of at least 2 of these drugs (MK-212 and DOI) may be the result of a marked alteration of behaviour.[53,54] Therefore, MK-212– and DOI-induced hypophagia may not

be dependent on a 5-HT_{2C} receptor–mediated satiety mechanism (discussed in section 2.2.1). Recent cross-tolerance studies (with mCPP) suggest both DOI- and DOM-induced hypophagia is mediated by 5-HT_{2A} and not 5-HT_{2C} receptors.[51,52]

Further evidence for the role of 5-HT_{2C} receptors in the control of food intake comes from transgenic studies. Tecott et al.[55] successfully bred a strain of mice that had no functional 5-HT_{2C} receptors. These mice showed hyperphagia and obesity.

2.2 Serotonin and Satiety

Just as agonist-antagonist studies have been used to disclose receptor involvement underlying hypophagic drug effects, behavioural monitoring has been used to disclose the form of the hypophagia.

Monitoring eating behaviour itself in addition to measuring food intake has been a common method of examining the satiating effects of drugs. Satiation is defined as the inhibitory process that causes meal termination, while satiety is defined as post-ingestion appetite suppression. It is important to distinguish drugs that reduce food intake by a specific action on the satiety system from those that reduce food intake by other means.[56] Satiating effects are indicated by changes in feeding parameters such as the eating rate, the number of eating bouts or the size of each bout.[20,54,57,58] This measurement of feeding behaviour is essential to diagnose the likely cause of a reduction in food intake.

Precise measurement of animal feeding behaviour can act as a bio-behavioural assay for potential anti-obesity compounds. Rats display a specific sequence of behaviour after finishing a meal.[59] After the animal finishes eating it starts to display grooming and active behaviour that eventually gives way to resting. This is termed the 'behavioural satiety sequence' (BSS) and has been used repeatedly to study the nature of drug-induced hypophagia. Hypophagia produced by means other than caloric ingestion (e.g. aversive food or nausea) fails to produce a BSS profile.

2.2.1 Feeding Behaviour

Anorectic doses of the catecholaminergic drug amphetamine have been shown to disrupt the BSS.[60,61] Amphetamine fragments feeding behaviour into short and numerous bouts and the eating rate is increased. The accompanying increase in active behaviour prevents the onset of resting behaviour that characterises the later stage of the BSS. Amphetamine-treated rats appear to eat in a frantic and hurried manner.

In comparison, an anorectic dose of the serotonergic drug dl-fenfluramine (and dexfenfluramine) produces a normal BSS with an early onset of resting similar to that produced by pre-feeding.[43,57,60,62] However, other studies have shown that resting behaviour in the BSS may be delayed by dl-fenfluramine in a similar manner to amphetamine.[63-65]

Fluoxetine has also been shown to produce a normal BSS,[32,62,64] while other SSRIs such as sertraline,[54] femoxitine and paroxetine[66] have been shown to enhance the BSS. Like fluoxetine, the SNRI sibutramine produces a normal BSS.[67]

Of the selective serotonin receptor agonists, both mCPP and TFMPP have been shown to preserve the structure of the BSS, enhancing the onset of resting.[54,61,68] This would confirm that hypophagia caused by activation of post-synaptic 5-HT_{2C} and possible 5-HT_{1B} receptors was sufficient to enhance satiety. Since the selective r5-HT_{1B} receptor agonist CP-94253 produced a similar BSS profile,[41] activation of the r5-HT_{1B} receptor alone would appeared to be sufficient to enhance satiety.

However, the 5-$HT_{1A/1B}$ receptor agonist RU-24969 disrupts the BSS.[41,43,68] Active behaviour is increased, eating becomes fragmented into small bouts and resting is delayed. These effects of RU-24969 are distinct from those of CP-94253. RU-24969 may induce some hypophagia by activation of post-synaptic r5-HT_{1B} receptors,[42] but this is secondary to dopaminergic hyperactivity.[45] As RU-24969 has not been shown to directly activate dopamine receptors, dopaminergic hyperactivity may be mediated indirectly via 5-HT_{1A} receptors of the raphe nuclei. The nature of RU-24969–

induced behavioural hyperactivity has yet to be determined.

The 5-HT_2 receptor agonist DOI does not preserve the BSS, producing a form of behavioural hyperactivity similar to RU-24969.[68] Hypophagia arising from the behavioural disruption may be due to activation of 5-HT_{2A} receptors.[51,52] Similarly, the 5-HT_2 receptor agonist MK-212 does not preserve the BSS, but paradoxically produces a profile of severe sedation.[53] Consequently, drug-induced behavioural under- or overactivity can prevent the appearance of a normal BSS.

In conclusion, studies of the BSS support the evidence from the serotonin agonist-antagonist studies. The BSS studies suggest that activation of r5-HT_{1B} receptors alone, and r5-HT_{1B} and 5-HT_{2C} receptors together, produces both a reduction in food intake and a post-ingestive satiety response in rats. Reductions in food intake due to direct activation of other serotonin receptors, such as 5-HT_{2A} and 5-HT_{1A}, do not appear to be due to a satiety mechanism. Activation of the 5-HT_{2A} receptor may contribute to hypophagia.

2.2.2 Interactions With Other Systems

The nature of the integration of the central mechanisms controlling appetite and the peripheral feedback mechanisms that inform the CNS of the nutritional status of the body remains unclear. However, many studies have already provided convincing evidence of links between the serotonergic appetite control system and systems that feed back gastric and metabolic information. One major link is between serotonin and the pre-absorptive gut satiety factor cholecystokinin (CCK).

It has been demonstrated that both serotonin- and dexfenfluramine-induced hypophagia can be blocked by devazepide, an antagonist of CCK_A receptors.[69,70] Anorexia induced by CCK-8 is also reversed by the 5-HT_1 and 5-HT_2 receptor antagonist metergoline,[70] the 5-HT_{1A} receptor antagonist WAY-100135[71] and the 5-HT_2 receptor antagonist ketanserin.[72] CCK-8 blocks the hyperphagia induced by activation of the 5-HT_{1A} autoreceptor by 8-hydroxy-2-(propylamine)tetraline (8-OH-DPAT),[71] and 8-OH-DPAT blocks CCK-8–induced hypophagia.[73] This would implicate both 5-HT_{1A} and 5-HT_{2C} receptors in mediating satiety signals received from peripheral CCK receptors. However, some care is necessary in the interpretation of these drug interaction studies, since not all causes of apparent blockade need to involve action at a common receptor subtype. Nonetheless, it seems likely that CCK, released as a consequence of the presence of food in the gut, stimulates afferent vagal receptors (CCK_A receptors) that connect indirectly (via the nucleus tractus solitarius) to a CNS serotonergic satiety mechanism located in or near to the paraventricular nucleus (see fig. 3).[74]

Another chemical closely associated with this region of the brain is neuropeptide Y. Neuropeptide Y potently stimulates food intake and appears to counterbalance the hypophagic effects of serotonin. It has been shown that serotonergic drugs block the increase in feeding induced by neuropeptide Y.[75,76] Blocking serotonin synthesis or antagonising serotonin receptors results in increases in the levels of neuropeptide Y in the paraventricular nucleus.[77,78]

There is a current controversy over whether 5-HT_{1B} receptor–induced hypophagia is mediated in the paraventricular nucleus itself[73,79] or in adjacent hypothalamic nuclei.[80-82] This debate is based on the accuracy of drug administration and/or paraventricular nucleus lesion procedures in the earlier studies. However, as stated above, serotonergic drugs do potently affect the levels of neuropeptide Y in the paraventricular nucleus.

Serotonin, like leptin and insulin (feedback factors in the CNS that control energy intake), influences the synthesis of neuropeptide Y, thereby interfering with the initiation of food intake.[83] Consequently, central networks may involve interactions among leptin, neuropeptide Y and serotonin at their specific receptors (see fig. 3). As the stores of body fat increase, a resulting increase in circulating leptin may activate hypothalamic receptors that trigger serotonin activity and inhibit food intake. An interesting question is: do mice

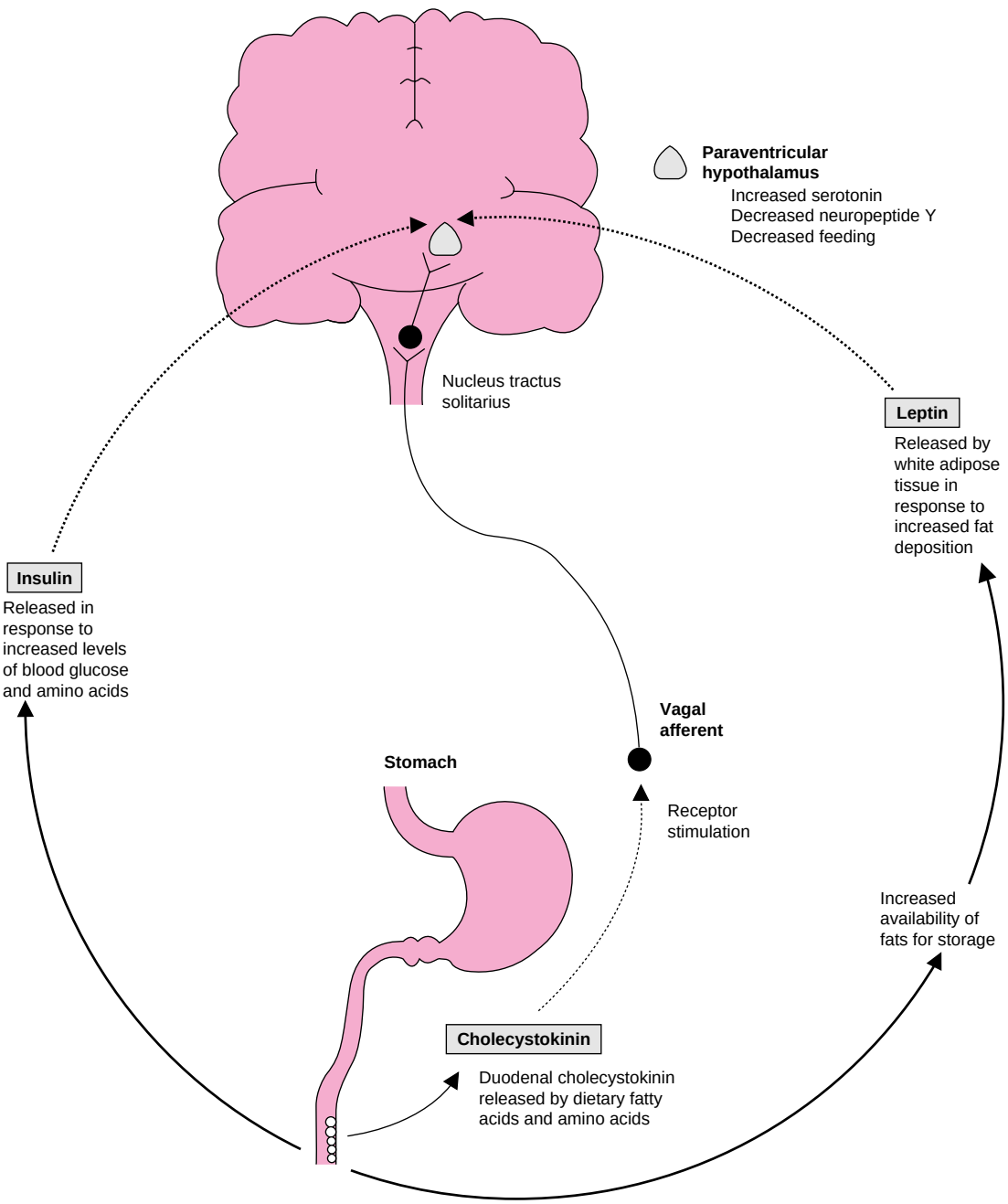

Fig. 3. Humoral and neural connections to the brain, indicating where serotonin (5-hydroxytryptamine; 5-HT) may be involved in the control of energy intake.

lacking 5-HT_{2C} receptors[55] lose weight if given leptin? If leptin has no effect in these transgenic mice, it would suggest that the anorectic effects of leptin may be mediated by 5-HT_{2C} receptors.

2.2.3 Peripheral Serotonin

The gastrointestinal tract (GIT) is estimated to contain 90% of the serotonin found in the body. Serotonin in the GIT is implicated in a variety of processes such as emesis, diarrhoea, abdominal pain and gastrointestinal reflexes (for a review, see Read and Gwee[84]). Serotonin and serotonergic drugs have potent effects on both gastric motility and stomach emptying.[85] Peripheral serotonergic mechanisms enable the body to respond to the content of the gut. The 5-HT_3 receptor is implicated in most of these processes.

Additionally, peripheral serotonin may be directly involved in the process of satiety (as indicated by the BSS).[86] Agonist-antagonist studies suggest it is likely that 5-HT_1 and 5-HT_2 receptors, rather than 5-HT_3 receptors, are responsible for this peripheral satiety effect.[87]

2.3 Serotonin and Dietary Composition

One of the most intriguing and important issues concerning the treatment of obesity through appetite modulation is the possibility of altering food choice. The importance of this rests on the recognition that a positive energy balance and bodyweight gain can arise, in part, from selecting a diet rich in energy-dense foods. Since fat is the macronutrient that contributes the greatest to the energy density of food (twice the kilocalories per gram of other macronutrients),[88] a diet of high fat foods is a predisposing factor for bodyweight gain.[89] However, there is also evidence that obligatory consumption of excess carbohydrate can also lead to significant energy storage.[90] Therefore, there is considerable interest in the development of pharmaceutical agents that can selectively reduce the intake of foods believed to favour a positive energy balance and subsequent energy storage (i.e. foods containing large amounts of fats and refined sugars).

2.3.1 Neural Mechanisms

In 1973, Fernstom and Wurtman[91] proposed that serotonergic neurons appeared to function as plasma amino acid 'ratio sensors',[91] informing the body of its general nutritional state.[92] This was based on the observation of a relationship between the tryptophan : large neutral amino acid (T : LNAA) ratio in plasma and the proportions of dietary carbohydrate and protein. Increased intake of carbohydrate raises the T : LNAA ratio, which theoretically leads to increased serotonin synthesis and release. Indeed, there are reports of high carbohydrate consumption resulting in a raised T : LNAA ratio in humans.[93] This altered ratio could act as a 'diet composition' signal to the brain. Some researchers believe that this ratio determines the synthesis and release of CNS serotonin and ultimately drives feeding behaviour. Evidence for this is still mixed.[94] However, the T : LNAA ratio is one way in which nutritional information could influence CNS serotonergic appetite systems and quickly modulate feeding behaviour.

Further evidence indicates that the effect of carbohydrate and protein meals on plasma T : LNAA ratios is altered in patients with anorexia nervosa[95] and in certain types of obesity.[96] This altered ratio is not adequately corrected by a glucose load. There is also evidence of disordered CNS serotonin metabolism in individuals with eating and bodyweight disorders, suggesting serotonin dysregulation.[97] Other evidence has shown that the prolactin response to tryptophan is significantly elevated in women but not men following a 3-week adherence to a low energy 1000 kcal/day diet.[98] The gender-specific neuroendocrine response indicates a shift in the sensitivity of serotonin-mediated processes caused by a relatively mild dietary adjustment. Additionally, this same degree of dieting leads to a fall in plasma tryptophan levels and decreases the T : LNAA ratio.[99]

2.3.2 Study Results

Collectively, these findings indicate a sensitive connection between nutrition and serotonin metabolism in the CNS and the periphery. This biobehavioural loop has provided the theoretical basis

for numerous studies of the action of serotonergic drugs on macronutrient selection in the form of animals offered a choice of differing diets (diet selection paradigms). However, the methodological problems associated with such studies are formidable.[100] Additionally, definitive results following pharmacological treatments are rare.

A key issue in the results obtained from choice paradigms is the number of diets from which the animal is to choose. In studies of the effects of serotonergic agents on protein versus carbohydrate intake (with fat levels in both diets held constant to preclude any treatment effect on fat intake), serotonergic drugs selectively reduced carbohydrate intake.[101] In other studies, these drugs selectively spared carbohydrate intake and suppressed the intake of the other diets.[102,103] What is clear is that serotonergic suppression of food intake is not dependent on the food containing large amounts of carbohydrate. Nor does low carbohydrate content prevent serotonergic suppression of intake.

Other diet selection studies have used 3 diets to identify specific macronutrient selection. The diet choices offered consisted largely of one macronutrient or were pure forms of macronutrients.[104] In these 3-choice paradigms, serotonin appears to selectively reduce fat intake. When serotonergic agents are administered directly into the paraventricular nucleus the intakes of both carbohydrate and fat are reduced.[105]

The cafeteria diet model is a type of choice paradigm often used to induce bodyweight gain. The animal chooses between a supplemented, or cafeteria, diet (standard laboratory food with extra macronutrient) or a standard food control.[106] Dietary-induced obesity[107] in the rat is a reliable phenomenon that can be utilised to directly assess the effect of the macronutrient supplement (cafeteria minus normal food control). During dietary-induced obesity, daily energy intake is significantly increased, largely through an increase in meal size (grams).[106,108] Rats treated long term with dexfenfluramine and exposed to a cafeteria choice diet with a fat supplement did not display dietary-induced obesity, unlike control animals that were treated with placebo. Furthermore, the dexfenfluramine-treated rats displayed decreased feeding (of all diet) and reduced bodyweight.[109]

A second procedure to induce bodyweight gain in rats is to administer specially formulated hyperfat diets (50 to 60% fat by kilocalorie) and compare this with the effects with a low fat diet (4 to 5% fat by kilocalorie). In Osborne-Mendel rats, which are sensitive to high-fat feeding, dexfenfluramine totally abolished the excess food intake and bodyweight gain associated with the high fat diet.[110] This is consistent with previous data demonstrating that dexfenfluramine was effective at reducing both energy intake and bodyweight gain induced by a high fat diet (65% fat by kilocalorie).[111] No tolerance to this dexfenfluramine-induced suppression of energy intake and bodyweight gain was observed, even after 40 days.

These animal studies demonstrate 2 key points. First, exposure to high fat diets does not block the bodyweight reducing and food intake suppressing effects of serotonergic drugs. Dexfenfluramine appears particularly effective, and for long periods, with very high fat diets. Secondly, in some paradigms, where rats were given a choice of diets including fat, serotonergic drugs have been shown to suppress fat choices and consumption of high fat diets. Although most animal studies have not provided an opportunity to observe any selective effects of serotonergic manipulation on fat preference, it is clear that administration of dexfenfluramine is a sufficient stimulus to block hyperphagia and antagonise the bodyweight gain associated with high levels of dietary fat. This would obviously have therapeutic value in the treatment of obesity.[112]

3. Human Studies

The animal studies described in section 2 clearly indicate that a reduction in food intake follows activation of postsynaptic serotonin receptors. The small number of human studies that are available also indicate that serotonergic agents can reduce food intake. Due to the availability of fenfluram-

ine, dexfenfluramine and fluoxetine, most human serotonergic data are based on these 3 compounds.

3.1 Effects of Serotonergic Drugs on Hunger

Because of the theoretical significance of hunger in the conceptualisation of appetite control, and its perceived importance in the control of eating, the effects of serotonergic drugs on hunger sensations (or conversely increase sensations of fullness) in humans have been investigated.

Many studies have demonstrated a short term inhibition of hunger, both before and after the meal, in both lean and obese individuals when dexfenfluramine was given acutely (see reviews by Hill and Blundell[113] and Goodall and Silverstone[114]). In obese patients, dexfenfluramine had a similar effect to glucose on hunger,[115] suggesting a common effect on satiety. In a later study that tracked daily hunger sensations across the day in obese individuals, it became clear that dexfenfluramine maintained a suppression of post-prandial hunger,[116] which was most potent after a high protein (iso-caloric) meal. This is indicative of enhanced post-meal satiety.

Because of these nutrient-drug interactions it has been suggested that serotonergic systems mediate the processes of satiation and satiety. It follows from this that the action of many serotonergic drugs would be to intensify the satiating action of foods.[111] Interestingly, with extended administration (over several weeks) to obese women, dexfenfluramine reduced hunger at specific points during the diurnal cycle (before and after a midday meal, before the evening meal and before going to bed)[117] and also reduced the perceived frequency and strength of urges to eat. The drug also reduced the willingness to initiate (reduced hunger) and maintain (increase within-meal satiation) eating episodes.

In a 2-week study of fluoxetine (60 mg/day), hunger was significantly reduced before and after the midday meal when food intake was also measured.[118] More recently, administration of sibutramine 10 or 30 mg/day for 14 days caused a significant reduction in hunger.[119]

3.2 Effects of Serotonergic Drugs on Food Intake

Most human research into the effects of serotonergic drugs on food intake has investigated the effects of dexfenfluramine, dl-fenfluramine and fluoxetine, which are believed to act through presynaptic mechanisms to modulate serotonergic activity. In addition, there are some data available on the 5-HT_{2C} receptor–selective drug mCPP,[120] the serotonin precursors tryptophan[115] and 5-hydroxytryptophan,[121] the SSRI sertraline[122] and the SNRI sibutramine.[119] Table I summarises the results from important selected studies with each compound to give a representation of the effects achieved.

3.2.1 Dexfenfluramine

For dexfenfluramine, the extent of the observed reduction in energy (calorie) intake varies from 11 to 40% and depends on experimental or clinical circumstances. A reduction in daily intake is apparent in treatment regimens varying from 1 day to 6 months (table I).

Importantly, the restraint of the motivation to eat and of food consumption is maintained for considerable periods of time. In a 12-month multicentre international trial, the withdrawal of dexfenfluramine at the end of the 1-year treatment period led to an immediate rise in daily energy consumed.[132] This indicated that the drug had continued to hold food intake in check for the entire period of administration.

This phenomenon is important since bodyweight loss ceased for most individuals at 6 months, but bodyweight was maintained steadily for the next 6 months. This does not indicate that tolerance had developed to dexfenfluramine, but demonstrates that the physiological resistance to the decline in energy intake had eventually reached an equilibrium with the anorectic potency of the drug. When the drug was withdrawn (after 12 months), the continued suppression and lack of tolerance became apparent.

Knowing the amount of energy lost during 12 months, and considering the approximate energy

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

Reference	Drug	Study design	No. of study participants (status)	Duration of treatment	Hunger and food preference	Caloric intake
Silverstone & Goodall[123]	Tryptophan	Laboratory study	16 (healthy)	1 day	NR	↓ Intake
Cangiano et al.[121]	5-HTP	Laboratory study	20 (obese)	6 wks	↓ Carbohydrate intake, early post meal satiety	↓ Intake and bodyweight over 6-wk period
Rogers & Blundell[124]	Fenfluramine	Laboratory study	12 (normal bodyweight)	1 day	NR	↓ Test meal intake and eating rate
Hill & Blundell[116]	Dexfenfluramine	Laboratory study	8 (obese)	3 days	↓ Hunger, ↑ fullness after first meal	↓ Intake after second meal (11-19%)
Wurtman et al.[125]	Dexfenfluramine	Laboratory study	24 (obese)	2 wks	↓ Carbohydrate snack intake	NR
Wurtman et al.[126]	Dexfenfluramine	Laboratory study	20 (obese)	8 days	↓ Carbohydrate intake at meal, ↓ snack intake	↓ Intake
Goodall & Silverstone[114]	Dexfenfluramine	Laboratory study	13 (healthy men)	1 day	↓ Hunger	↓ Intake
Blundell & Hill[115]	Dexfenfluramine	Laboratory study	10 (lean women), 11 (obese women)	1 day	↓ Hunger	↓ Intake
Goodall et al.[127]	Dexfenfluramine	Laboratory study	12 (healthy men)	1 day	↓ Fat intake	No overall effect
McGuirk & Silverstone[128]	Fluoxetine	Laboratory study	11 (healthy men	2 wks	↓ Hunger on days 8 and 15, but not on day 1	↓ Intake on days 1 and 8, but not on day 15
Lawton et al.[118]	Fluoxetine	Laboratory study	12 (obese women)	14 days	No macronutrient preference, ↓ hunger	↓ Intake (22.4%)
Wadden et al.[122]	Sertraline	Relapse prevention trial	53 (obese women)	6 wks	↓ Hunger, ↓ food preoccupation	NR
Walsh et al.[129]	mCPP	Laboratory study	12 (healthy women)	1 day	NR	↓ Test meal intake
Sargent et al.[130]	mCPP	Laboratory study	18 (obese)	2 wks	↓ Hunger, ↓ bodyweight	NR
Boeles et al.[131]	Sumatriptan	Laboratory study	15 (healthy women)	1 day	No change in hunger, ↓ fat intake	↓ Intake
Rolls et al.[119]	Sibutramine	Laboratory study	12 (obese women)	14 days	↓ Hunger	↓ Daily intake

Abbreviations and symbols: mCPP = *m*-chlorophenylpiperazine; 5-HTP = 5-hydroxytryptophan; NR = not reported; ↑ indicates an increase; ↓ indicates a decrease.

cost of 0.5kg (1lb) of fat (3500 kcal), it can be deduced that a serotonergic drug can maintain an average reduction of daily energy intake of between 6 and 10% over the course of 1 year. Naturally the inhibition of food intake will be greater during early treatment; later intake is held at a reduced level, probably not declining further. This continued restraint of food intake provides an explanation why the suppression of rated hunger (compared with placebo) is not seen after a few months of treatment. The drug has not lost its power to inhibit hunger, but the findings mean that a reduced energy intake (and bodyweight) is maintained with no compensatory rise in hunger motivation.

The potency of serotonergic drugs at inhibiting food intake in humans is illustrated by the continuing action of dexfenfluramine when administered to obese patients receiving a very low calorie diet

(VLCD). Patients receiving dexfenfluramine and placebo were placed on a VLCD for 8 weeks and lost an average of 14kg. The VLCD naturally creates a strong disposition to resume normal eating (or over-eating) and to regain the bodyweight lost. This phenomenon was apparent in those patients randomised to placebo treatment;[133] in contrast, those patients who received dexfenfluramine continued to lose bodyweight (fig. 4). This study illustrates the power of dexfenfluramine to overcome the physiological (and psychological) drive to eat following bodyweight reduction. In contrast, a similar study using the SSRI sertraline showed that following a VLCD, sertraline-treated individuals regained most of the bodyweight lost.[122]

Mechanism

There is some evidence implicating serotonin receptor subtypes in the suppression of human feeding. Following the demonstration that the effects of mCPP on the inhibition of food intake in rats is mediated by 5-HT_{2C} receptors, it was reported that mCPP reduced food intake in humans[129] and produced a small but significant loss of bodyweight that was associated with a decrease in hunger in obese individuals[130] (table I). In addition, mCPP enhanced plasma levels of prolactin following a period of dieting.[120] Together with previous work indicating the effects of dieting on plasma tryptophan levels and serotonin sensitivity in the brain,[129,134] these data suggest a mediating role for 5-HT_{2C} receptors in appetite control in humans.[120] Further circumstantial evidence is provided by the finding that ritanserin (a 5-HT_2 receptor antagonist) antagonises the suppressive effect of dexfenfluramine on food intake in human volunteers.[127]

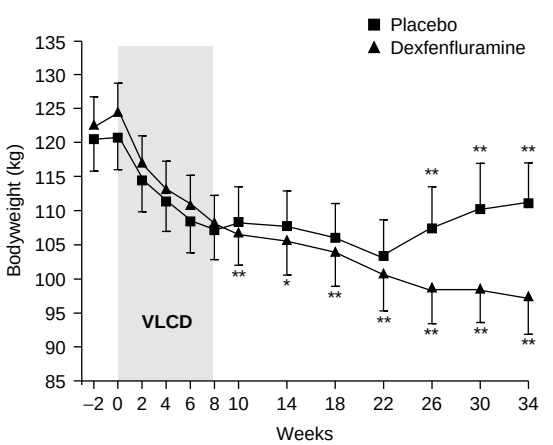

Fig. 4. The effect of dexfenfluramine or placebo on bodyweight following considerable weight reduction in obese patients who were placed on a very low calorie diet (VLCD) for 8 weeks (reproduced from Finer,[133] with permission). *Symbols:* * $p < 0.01$ and ** $p < 0.001$ compared with bodyweight at week 8.

Further experimentation awaits the development of well tolerated selective serotonin receptor antagonists for use in human research. For the moment, it can be concluded that human studies suggest the involvement of 5-HT_{2C} receptors in the inhibition of appetite. Indeed, the development of specific 5-HT_{2C} receptor agonists would be an appropriate strategy for the drug treatment of obesity. The role of the human 5-$HT_{1D\beta}$ receptor (or the h5-HT_{1B} receptor, as it may soon become known) in human feeding behaviour has yet to be fully determined. If this receptor is the functional, as well as the pharmacological, equivalent of the rodent 5-HT_{1B} (r5-HT_{1B}) then pharmacological targeting of this receptor may also prove useful. Indeed, it was recently demonstrated that the selective 5-$HT_{1B/1D}$ receptor agonist sumatriptan decreases food intake, specifically the proportion of dietary fat consumed, in lean women.[131]

3.2.2 Sibutramine

Sibutramine has been shown to effectively reduce bodyweight in human studies. In a double-blind, placebo-controlled trial, Weintraub et al.[135] found that sibutramine induced a significant dose-related bodyweight loss in obese patients over 8 weeks. A similar effect was demonstrated in a longer trial (24 weeks) with the addition of diet restrictions and lifestyle changes (see fig. 5).[136] Over a 1-year period, patients who showed an initial sensitivity to sibutramine-induced bodyweight loss (greater than 2kg in first 4 weeks) lost between 5 and 10% of their baseline bodyweight at 3 months, and appeared to remain at that level up to 1 year after the treatment started.[137] In the labo-

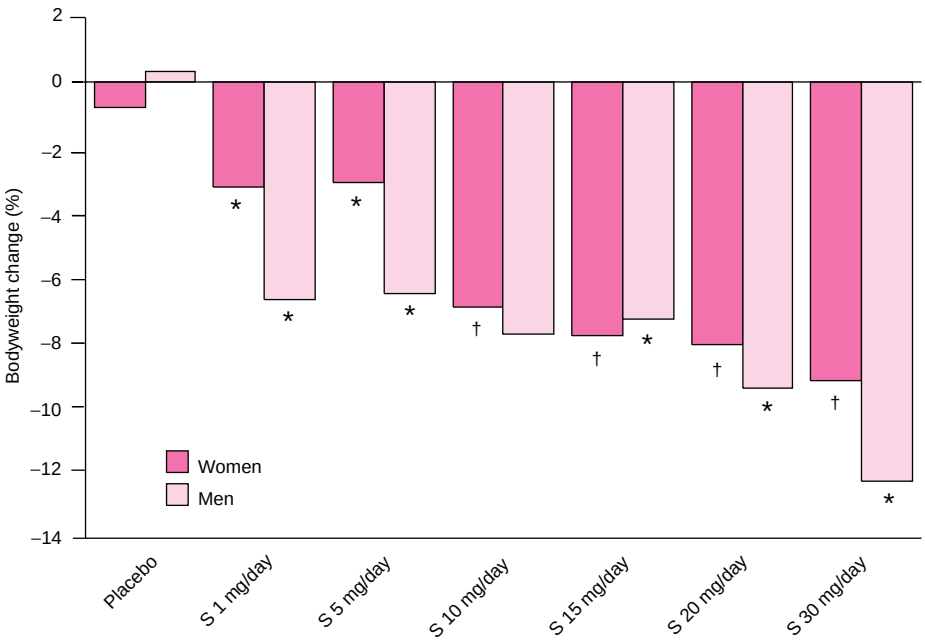

Fig. 5. Effect of 24 weeks of treatment with sibutramine (S) 1 to 30 mg/day on bodyweight in obese men and women. Weight loss is expressed as a percentage of initial bodyweight.[136] *Symbols:* * $p \leq 0.001$ versus baseline; † $p \leq 0.001$ versus placebo and baseline.

ratory, sibutramine has been shown to reduce hunger and daily intake in obese females.[119]

3.3 Effects of Serotonergic Drugs on Food Choice

The results of human studies of the effect of serotonergic drugs on food choice are as affected by methodological differences as the animal studies (see section 2.3).[138] As with the animal work, human studies initially tested the effect of drugs on protein and carbohydrate consumption.

In studies using set meals, fat was held constant whilst protein and carbohydrate levels were varied.[125,126] All foods appeared to contain high levels of fat.[126] Serotonin reduced carbohydrate more than protein intake, but this also involved an obligatory reduction in fat intake. In free feeding studies, the consumption of high protein snacks was specifically reduced.[125] These snacks also had a high fat content. In all these studies the greatest effect of serotonin appeared to be on fat intake.

Fats form a large proportion of the energy in snack foods.[139] With double the energy density of protein or carbohydrate, fats make the largest contribution to the over-consumption of energy. It is noteworthy that the predominant effect of dexfenfluramine on the human feeding pattern is the reduction of snacking (see below). Again, this leads to a dramatic (if obligatory) reduction in fat intake. However, do serotonergic drugs directly suppress fat intake? Free selection designs, in which a variety of foods differing in all macronutrients are available, have been used to answer this question. Some free feeding studies have shown that dexfenfluramine reduces the consumption of all macronutrients equally.[113] Other studies have shown that dexfenfluramine, like fluoxetine, reduces fat selectively.[127,128]

Clinical studies in obese people have provided further evidence of a selective action of dexfenfluramine on fat intake.[140] At the end of a 3-month study, the energy intake of the dexfenfluramine

group was 16% lower than that of the placebo group. This was due to a 13% reduction in energy intake from meals and a 23% reduction in energy intake from snacks. This energy reduction was characterised by a selective decrease in dietary lipids of between 30 to 34%, which represents an overall 25% reduction in total fat consumed (table II). These particular obese individuals given dexfenfluramine displayed selective avoidance of high fat food.

In a short term study, fluoxetine did not give rise to a selective macronutrient effect.[118] Rolls et al.[119] showed that sibutramine caused a significant reduction in percentage energy from fat consumed, but an increase in percentage energy from carbohydrate. No information is yet available on whether sibutramine selectively affects the consumption of energy dense snacks.

In conclusion, it remains to be demonstrated whether different serotonergic drugs, in differing clinical circumstances, exert specific and distinguishable effects on food selection. Recent evidence suggested that dexfenfluramine produces a greater reduction in energy balance when the diet is high in fat[141] and that the largest reduction in daily energy intake is observed when the eating pattern contains high fat sweet snacks.[142] These effects may be particularly useful considering the relationship between dietary fat and obesity[143] and the preference shown by obese women for sweet high fat foods.[144]

4. Tolerability Issues

All drugs produce side effects along with the adjustment of the major symptom for which they are prescribed. Sometimes, side effects may constitute health hazards. In most patients, drugs that are used to control appetite should result in health benefits arising from a reduction in the level of obesity that are greater than the risks engendered by the drugs themselves. However, for fenfluramine and dexfenfluramine the occurrence of two health hazards has resulted in the withdrawal of these drugs from the market – primary pulmonary hypertension[145] and valvular heart disease symptoms.[146]

More than 25 years ago there was an outbreak of pulmonary hypertension in Europe, which was linked to the appetite suppressant drug aminorex. The drug caused a mortality rate of 50% and was rapidly withdrawn. The pulmonary hypertension associated with fenfluramine derivatives occurred at a much lower frequency,[145] but was still above the (very low) background level of the disease. Some of the cases occurred when fenfluramine was taken together with phentermine (the so-called 'fen-phen combination').[147,148]

The initial reports of valvular heart disease were diagnosed by echocardiography in female patients taking the fenfluramine-phentermine combination.[146] Subsequently, the condition appeared in women taking fenfluramine[149] or dexfenfluramine[150] alone. Apparently, the histological picture is virtually indistinguishable from that seen in carcinoid disease or in valvular conditions induced by ergot alkaloids such as ergotamine or methysergide.

As a result of the identification of these adverse effects, a commonly asked question is: Are these problems likely to occur with other serotoninergic drugs? Because serotonin is a neurotransmitter involved in a wide variety of biological actions in the body, serotoninergic drugs always have the po-

Table II. Energy and nutrient intakes in obese individuals measured over the course of 1 day in a metabolic unit 3 months after treatment with dexfenfluramine or placebo was initiate. The bodyweight change over the 3 months of treatment was –4.6kg for dexfenfluramine and +0.4 kg for placebo recipients[140]

Treatment	Kcal/day	Total energy (%)		
		carbohydrate	protein	fat
Placebo	1574 ± 142	45	21	34
Dexfenfluramine	1353 ± 109*	49	22	30**

Symbols: * p = 0.025; ** p = 0.04 versus placebo.

tential to influence more than one end-point or biological system. This is likely to be most apparent with indirectly acting nonspecific serotoninergic drugs, such as releasers or reuptake blockers, and least apparent with selective direct acting receptor agonists. However, the distribution throughout biological tissues of specific serotonin receptor subtypes may lead to undesirable concomitant actions even with drugs that are regarded as having a selective action.

Serotonin itself is known to be a vasoconstrictor at high doses, but has the opposite effect at low doses. Primary pulmonary hypertension associated with fenfluramine derivatives is not a frequent occurrence, but seems to occur in certain susceptible individuals; in much the same way as some people spontaneously develop pulmonary hypertension by living at high altitude for a period of time.[151] It is not known if fenfluramine-induced primary pulmonary hypertension is mediated by serotonin itself or by some action of the fenfluramine molecule. Specific receptors have not so far been implicated.

The presence of valvular disease in the carcinoid syndrome implicates serotonin in its aetiology, but whereas circulating levels of the neurotransmitter are high in carcinoid syndrome, serotoninergic drugs such as fenfluramine and fluoxetine lead to a reduction in the levels of circulating serotonin. At present, it is not known whether valvular heart disease arises from the effects of serotonin itself or the action of either specific molecules or specific receptor subtypes. Further light may be shed on this issue with the publication of findings from much larger groups of unselected patients in specific placebo-controlled trials.

The action of sibutramine, which has recently been approved by the US Food and Drug Administration, is, at least in part, mediated via serotonergic mechanisms. Encouragingly, to date, sibutramine has not been associated with either pulmonary hypertension or valvular heart disease, but it has, as yet, been administered to a relatively small number of patients. Clinical data indicate that sibutramine increases blood pressure,[152,153] probably due to the noradrenergic component of its mechanism of action, and should not be prescribed to obese hypertensive patients.

5. Future Possibilities

5.1 Other Eating Disorders

It is widely believed that the conditions of obesity and eating disorders such as bulimia nervosa and binge eating disorder are closely linked. Indeed, it has been estimated that a sizeable proportion of obese individuals may display subclinical binge eating, i.e. the frequent consumption of abnormally large amounts of food in a single meal. This is not to suggest that all obese people binge, or all bingers are chronically overweight. Indeed, excess food intake, and consequent obesity, can be achieved purely by consuming energy dense, high fat meals and snacks, without the necessity of binge eating. However, binge eating as a distinct factor in the eating patterns of some obese individuals was first noted by Stunkard as early as 1959.[154] Estimates of binge eating in the obese obviously vary depending on the diagnostic criteria of binge eating used. Spitzer et al.,[155] using criteria of the frequency and size of binges and lack of control of eating episodes, found that 30.1% of obese individuals displayed binge eating without purging, compared with a prevalence of only 2% in individuals of normal bodyweight. In addition females, both obese and normal, were more likely to binge.

There is a large body of evidence implicating serotonin in bulimia nervosa, binge eating disorder and obesity. Bulimic symptomatology has been explained in terms of a dysregulation of serotonergic function.[97,156,157] Repeated bingeing may alter CNS serotonin receptor sensitivity and functioning. Reduced levels of serotonin due to bingeing could lead to both feelings of depression and sustain inadequate control of food intake. This would account for both the affective symptomatology of bulimia and the impaired satiety response of the bulimic individual during the binge episode.[158] Alternatively, reduced serotonin respon-

siveness could lead to, as well as sustain, both binge eating and affective symptomatology.[159]

Obviously, serotonergic drugs that are used to treat bulimia are chosen to reduce all bulimic symptomatology including vomiting and other purging behaviours. As the critical symptom of bulimia nervosa, purging is a rare occurrence in obesity (according to diagnostic criteria for bulimia nervosa) compared with clinical binge eating. A variety of different serotonergic drugs have been shown to be beneficial in patients who display binge eating (bulimia nervosa or binge eating disorder): fluoxetine significantly reduces bingeing in bulimic patients,[160-162] fluvoxamine (another SSRI used for treating obsessive-compulsive disorder) also significantly reduces binge eating episodes[163] and trazodone reduces bingeing in people with bulimia nervosa.[164-166]

Thus, serotonergic intervention seems appropriate in treating normal bodyweight bingers. In obese women whose binge eating fitted criteria for binge eating disorder (display binge eating for 6 months, and not 3 months as in criteria for bulimia nervosa), dexfenfluramine proved effective in normalising eating patterns.[167] In theory, drugs that increase CNS serotonin levels, should sustain satiety. They should also counteract the effects of serotonergic dysregulation and may prevent the process of disinhibition that is reported to lead to a binge eating episode.

Not all studies have found serotonergic drugs to be particularly useful in treating binge eating in either normal bodyweight or obese bingers. For example, the benefits of fluoxetine were approximately equal in obese women with and without binge eating disorder[168] and Fahy et al.[169] found that dexfenfluramine performed no better than placebo in their patients with bulimia nervosa. However, despite some contradictory preliminary results, serotonergic drugs appear to possess potential therapeutic value in treating bingeing (and also purging). This may be above and beyond their effects on appetite control.

A range of serotonergic drugs have been used to treat binge eating. Fluoxetine, fluvoxamine and dexfenfluramine have 3 distinct clinical applications (an antidepressant drug, an anti-compulsion drug and an anti-obesity drug, respectively). Drugs that increase CNS serotonin levels, or stimulate serotonin receptors directly, may prove useful anti-bingeing agents and become a part of the treatment of binge eating disorder, normal bodyweight individuals with bulimia nervosa, and the large subgroup of the obese population who display clinical and subclinical episodes of binge eating behaviour. Which of these patient groups will benefit most from which serotonergic drug, and in what treatment regimen, remains to be determined.

The therapeutic effect of other serotonin drugs such as mCPP, sertraline and other SSRIs (or SNRIs) on bingeing has yet to be determined. The effectiveness of trazodone may be partly due to its metabolite mCPP.[164-166] Future possibilities for the treatment of obesity and binge eating disorder may include matching the therapeutic profiles of differing serotonergic drugs with individual patient's symptomatology.

5.2 Risk Factors for Bodyweight Gain: Repair or Protection?

There appear to be 2 schools of thought about the regulation of bodyweight. Some researchers point to the impressive degree of bodyweight stability over the life span of animals and humans, and argue for a mechanism which actively regulates bodyweight (or body fat). It follows that the presence of obesity arises from a defect in this regulatory system. In turn, it follows that pharmacological treatment (possibly arising from developments in molecular biology or genetics) should seek to 'repair' this defect.

An alternative view is that bodyweight represents a level attained by the equilibration of biological dispositions (facilitatory and inhibitory) and environmental forces. Here it is argued that people are vulnerable to bodyweight gain because of a permissive physiological system in the presence of a potent and stimulating food supply in a provocative environment. It follows that pharmacological treatment should seek to 'protect' indi-

viduals from those forces (mainly environmental) that generate a positive energy balance.

It is worth keeping in mind that risk factors for obesity can be recognised in the biological domain, in the environment, and in the patterns of behaviour that link biology with the environment. For example, risk factors may exist at the level of the gene, product of gene expression, tissue, organ and system, and may include low resting metabolic rate, inappropriately high respiratory quotient (low fat oxidation) or weak short term satiety signals. Other types of risk factor include the availability of food supply containing high energy dense foods, predilection to select high fat items, poor control over meal size and large daily fluctuations in energy (and fat) intake.

Any pharmacological treatment for obesity should obviously seek to nullify the impact of biological, nutritional or behavioural risk factors. The concept of 'repair and protect' can be a heuristic device to focus attention on those features that provoke a positive energy balance and that can be targets for pharmaceutical agents. There is evidence to suggest that serotonergic drugs could be involved in the treatment of obesity through a repair or protection role. The possibility raised by animal studies that a defect in the expression of the 5-HT_{2C} receptor may constitute a risk factor (see section 2.1.1) could be the basis for a therapeutic strategy. Alternatively, there is ample evidence that serotonergic drugs can protect against the impact of environmental risk factors.

Current surveys of obesity world wide indicate that human beings are finding it increasingly difficult to prevent themselves attaining a positive energy balance and gaining bodyweight. Equally, evidence suggests that obese people find it almost impossible to maintain, for a sufficiently long period, the necessary adjustments required to enforce a negative energy balance and the attainment of a lower stable weight. Serotonergic drugs are likely to continue to be useful in helping a certain number of obese people to reduce the impact of the risk factors that promote bodyweight gain.

6. Conclusion

Despite the recent withdrawal of some serotonergic appetite suppressants from the market, drugs that have a serotonergic mechanism of action have a useful role in the treatment of obesity by adjusting the biological mechanism involved in appetite control and preventing the occurrence of a positive energy balance and hence bodyweight gain. Many individuals are vulnerable to bodyweight gain because of a permissive physiological system in the presence of a potent and stimulating food supply in a provocative environment. This combination appears to lead easily to a positive energy balance. Experimental and clinical evidence indicates that serotonergic drugs can effectively reduce the potency of these risk factors (i.e. hunger, urges to eat, intake of energy dense foods and high levels of fat, large meals and frequent snacks, strong sensory attractiveness of foods, lack of control over eating, and relatively weak satiety signals) and thereby lessen their impact on energy intake. Thus, serotonergic drugs can provide biological assistance to obese people to control those risk factors for bodyweight gain that operate via overconsumption.

Given that there is evidence that the 5-HT_{1B} and 5-HT_{2C} receptors are involved in mediating the effects of serotonergic drugs on food intake, the development of well tolerated and effective selective agonists for these receptors may be the next phase of pharmacological therapy for obesity.

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References

1. Gaddum JH, Picarelli ZP. Two kinds of tryptamine receptor. Br J Pharmacol 1957; 12; 323-8
2. Peroutka SJ, Snyder SH. Multiple serotonin receptors: different binding of 3H-5-hydroxytryptamine, 3H-lysergic acid and diethylamide and 3H-spiroperidol. Mol Pharmacol 1979; 16; 687-99
3. Bradley P, Engel G, Feniuk W, et al. (nomenclature committee) Proposals for the classification and nomenclature of func-

tional receptors for 5-hydroxytryptamine. Neuropharmacology 1986; 25: 563-76
4. Fargin A, Raymond JR, Regan JW, et al. Effector coupling mechanisms of the cloned 5-HT1A receptor. J Biol Chem 1989; 264: 14848-52
5. Hoyer D, Pazos A, Probst A, et al. Serotonin receptors in the human brain. I. Characterisation and autoradiographic localization of 5-HT1A recognition sites: apparent absence of 5-HT1B recognition sites. Brain Res 1988; 376: 85-96
6. Hoyer D, Martin GR. Classification and nomenclature of 5-HT receptors: a comment on current issues. Behav Brain Res 1996; 73: 263-8
7. Humphrey PPA, Hartig P, Hoyer D. A proposed new nomenclature for 5-HT receptors. Trends Pharmacol Sci 1993; 14: 233-6
8. McAllister G, Charlesworth A, Snodin C, et al. Molecular cloning of a serotonin receptor from human brain (5-HT1E): a fifth 5-HT1-like sub-type. Proc Natl Acad Sci USA 1992; 89: 5517-21
9. Amlaiky N, Ramboz S, Boschert U, et al. Isolation of a mouse 5-HT1E-like receptor expressed predominantly in the hippocampus. J Biol Chem 1992; 92: 19761-4
10. Adham N, Kao H-T, Schechter L.E, et al. Cloning of another human serotonin receptor (5-HT1F): a fifth 5-HT1 receptor subtype coupled to the inhibition of adenylate cyclase. Proc Natl Acad Sci USA 1993; 89: 408-12
11. Hoyer D. Agonists and antagonists at 5-HT receptor subtypes. Adv Biosci 1992; 85: 29-47
12. Dumuis A, Boulelal R, Sebben M, et al. A 5-HT receptor in the nervous system positively coupled with adenylate cyclase is antagonised by ICS 205 930. Eur J Pharmacol 1988; 146: 187-8
13. Dumuis A, Sebben M, Bockaert J. The gastrointestinal prokinetic benzamide derivatives are agonists at a non-classical 5-HT receptor (5-HT4) positively coupled to adenylate cyclase in neurons. Naunyn Schmiedebergs Arch Pharamacol 1989; 340: 403-10
14. Jesperson S, Scheel-Kruger J. Evidence for a difference in mechanism of the action between fenfluramine and amphetamine induced anorexia. J Pharm Pharmacol 1973; 22: 637-8
15. Barrett AM, McSherry L. Inhibition of drug-induced anorexia in rats by methysergide. J Pharm Pharmacol 1975; 27: 889-95
16. Pinder BM, Brogden RN, Sawyer PR, et al. Fenfluramine: a review of the pharmacological properties and therapeutic efficacy in obesity. Drugs 1975; 10: 241-323
17. Garattini S, Samanin R. Anorectic drugs and brain neurotransmitters: food intake and appetite. Silverstone T, editor. Berlin: Dahlem Konferenzen, 1976: 82-208
18. Bray GA, York DA. Studies on food intake of genetically obese rats. Am J Physiol 1972; 223: 176-9
19. Latham CJ, Blundell JE. Evidence for the effect of tryptophan on the pattern of food consumption in rats. Life Sci 1979; 24: 1271-8
20. Blundell JE, Latham CJ. Serotoninergic influences on food intake: effect of 5-hydroxytryptophan on parameters of feeding behaviour in deprived and free-feeding rats. Pharmacol Biochem Behav 1979; 11: 431-7
21. MacKenzie RG, Hoebel BG, Ducret RP, et al. Hyperphagia following intraventricular p-chlorophenylalanine-, leucine- or tryptophan-methyl esters: lack of correlation with whole brain serotonin level. Pharmacol Biochem Behav 1979; 10: 951-5
22. Blundell JE. Is there a role for serotonin (5-hydroxytryptamine) in feeding? Int J Obes 1977; 1: 15-42
23. Jin H, Oksenberg D, Askenzai A, et al. Characterization of the human 5-HT1B receptor. J Biol Chem 1992; 267 (9): 5735-8
24. Dourish CT. Multiple serotonin receptors: opportunities for new treatments for obesity. Obes Res 1995; 3 Suppl.: 449-62s
25. Clifton PG. The neuropharmacology of meal patterning. In: Cooper SJ, Hendrie CA, editors. Ethology and psychopharmacology. Chichester: Wiley, 1994: 313-28
26. Neill JC, Cooper SJ. Evidence that d-fenfluramine anorexia is mediated by 5-HT1 receptors. Psychopharmacology 1989; 97: 213-8
27. Samanin R, Mennini T, Bendotti C, et al. Evidence that central 5-HT2 receptors do not play an important role in the anorectic activity of d-fenfluramine in the rat. Neuropharmacology 1989; 28: 465-9
28. Neill JC, Bendotti C, Samanin R. Studies on the role of 5-HT receptors in satiation and the effect of d-fenfluramine in the runway test. Eur J Pharmacol 1990; 190: 105-12
29. Wong DT, Reid LR, Threlkeld PG. Suppression of food intake in rats by fluoxetine: comparison of enantiomers and effects of serotonin antagonists. Pharmacol Biochem Behav 1988; 31: 475-9
30. Grignaschi G, Samanin R. Role of serotonin and catecholamines in brain in feeding suppressant effects of fluoxetine. Neuropharmacology 1992; 31: 445-9
31. Lee MD, Clifton PG. Partial reversal of fluoxetine anorexia by the 5-HT antagonist metergoline. Psychopharmacology 1992; 107: 359-64
32. Halford JCG, Blundell JE. Metergoline antagonizes fluoxetine-induced suppression of food intake but not changes in the behavioural satiety sequence. Pharmacol Biochem Behav 1996; 54: 745-51
33. Curzon G, Gibson EL, Oluyomi AO. Appetite suppression by commonly used drugs depends on 5-HT receptors but not on 5-HT availability. Trends Pharmacol Sci 1997; 18: 21-5
34. Raiteri M, Bonanno G, Vallebouona F. *In vitro* and *in vivo* effects of d-fenfluramine: no apparent relation between 5-hydroxytryptamine release and hypophagia. J Pharmacol Exp Ther 1995; 273: 643-9
35. Lightowler S, Kennett GA, Wood MD, et al. Hypophagic effect of fluoxetine in rats is not mediated by inhibition of 5-HT re-uptake or an agonist action at 5-HT2C receptors. Br J Pharmacol 1994; 112: 359-64
36. Koe BK, Weissman A, Welch WM, et al. Sertraline, 1S,4S-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine, a new uptake inhibitor with selectivity for serotonin. J Pharmacol Exp Ther 1983; 266: 686-700
37. Lucki I, Kreider MS, Simansky KJ. Reduction of feeding behaviour by the serotonin uptake inhibitor sertraline. Psychopharmacology 1988; 96: 289-95
38. Heal DJ, Frankland ATJ, Gosden J, et al. A comparison of the effects of sibutramine hydrochloride, bupropion and methamphetamine on dopaminergic function: evidence that dopamine is not a pharmacological target for sibutramine. Psychopharmacology 1991; 107: 303-9
39. Jackson HC, Bearham MC, Hutchins LJ, et al. Investigation of the mechanisms underlying the hypophagic effects of the 5-HT and noradrenaline re-uptake inhibitor, sibutramine, in the rat. Br J Pharmacol 1997; 121: 1613-8
40. Koe BK, Nielsen JA, Macor JE, et al. Biochemical and behavioural studies of the 5-HT1B receptor agonist, CP-94,253. Drug Dev Res 1992; 26: 241-50

41. Halford JCG, Blundell JE. The 5-HT1B receptor agonist CP-94,253 reduces food intake and preserves the behavioural satiety sequence. Physiol Behav 1996; 60: 933-9
42. Kennett GA, Dourish CT, Curzon G. 5-HT1B agonists induce anorexia at a post synaptic site. Eur J Pharmacol 1987; 141: 429-35
43. Blundell JE, Alikhan H. Analysing the structure and sequence of feeding in animals and man. In: Christie WM, Weinman J, editors. Microcomputers, psychology and medicine. Chichester: Wiley, 1990: 203-25
44. Kennett GA, Curzon G. Evidence that mCPP may have behavioural effects mediated by central 5-HT1C receptors. Br J Pharmacol 1988; 94: 137-47
45. Kennett GA, Curzon G. Evidence that the hypophagia induced by mCPP and TFMPP requires 5-HT1C and 5-HT1B receptors; hypophagia induced by RU-24969 only requires 5-HT1B receptors. Psychopharmacology 1988; 96: 93-100
46. Curzon G. Serotonin and appetite. Ann NY Acad Sci 1990; 600: 521-30
47. Curzon G. Effects of tryptophan and 5-hydroxytryptamine receptor subtype agonists on feeding. Adv Exp Med Biol 1991; 294: 377-88
48. Kennett GA, Wood MD, Glen A, et al. *In vivo* properties of SB 200646A, a 5-HT2c/2b receptor antagonist. Br J Pharmacol 1994; 111: 797-802
49. Clineschmidt BV, McGuffen JC, Pfleuger AB. A 5-hydroxytryptamine-like mode of action for 6-chloro-2-[1-piperazinyl]-pyrazine (MK-212) Br J Pharmacol 1978; 62: 579-89
50. King BH, Brazell C, Dourish CT. MK-212 increases rat plasma ACTH concentration by activation of the 5-HT1c receptor subtype. Neurosci Lett 1989; 105: 174-6
51. Aulakh CS, Mazzola-Pomietto P, Wozniak KM, et al. 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane-induced hypophagia and hyperthermia in rats is mediated by serotonin-2A receptors. J Pharmacol Exp Ther 1994; 270: 127-52
52. Aulakh CS, Mazzola-Pomietto P, Hulihan-Giblin BA, et al. Lack of cross tolerance for hypophagia induced by DOI versus mCPP suggests separate mediation by 5-HT2A and 5-HT2c receptors respectively. Neuropsychopharmacology 1995; 13: 1-8
53. Halford JCG, Lawton CL, Blundell JE. The 5-HT receptor agonist MK-212 reduces food intake but disrupts the behavioural satiety sequence. Pharmacol Biochem Behav 1997; 56: 41-6
54. Simansky KJ, Vaidya, AH. Behavioural mechanisms for the anorectic actions of the serotonin (5-HT) uptake inhibitor sertraline in rats: comparison with directly acting agonists. Brain Res Bull 1990; 25: 953-60
55. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2C serotonin receptors. Nature 1995; 374 (6522): 542-6
56. Blundell JE, Latham CJ. Pharmacological manipulations of feeding behaviour: possible influences of serotonin and dopamine on food intake. In: Garattini S, Samanin R, editors. Central mechanisms of anorectic drugs. New York: Raven Press, 1978: 83-109
57. Blundell JE, Latham CJ. Characteristic adjustments to the structure of feeding behaviour following pharmacological treatments: effects of amphetamine and fenfluramine and the antagonism produced by pimozide and metergoline. Pharmacol Biochem Behav 1980; 12: 717-22
58. Blundell JE, Rogers PJ, Hill AJ. Behavioural structure and mechanisms of anorexia: calibration of normal and abnormal inhibition of eating. Brain Res Bull 1985; 15: 319-26
59. Antin J, Gibbs J, Holt J, et al. Cholecystokinin elicits the complete behavioural sequence of satiety in rats. J Comp Physiol Psych 1975; 89: 784-60
60. Blundell JE, McArthur RA. Behavioural flux and feeding: continuous monitoring of food intake and food selection, and the video-recording of appetitive and satiety sequences for the analysis of drug action. In: Samanin R, Garittini S, editors. Anorectic agents: mechanisms of action and tolerance. New York: Raven Press, 1981: 19-43
61. Halford JCG. Analysis of the behaviour associated with feeding in drug induced anorexia in the rat. [Ph.D thesis]. Leeds: University of Leeds, 1994
62. Halford JCG, Blundell JE. 5-hydroxytrytaminergic drugs compared on the behavioural sequence associated with satiety [abstract]. Br J Pharmacol 1993; 100: 95p
63. Montgomery AMJ, Willner P. Fenfluramine disrupts the behavioural satiety sequence in rats. Psychopharmacology 1988; 94: 397-401
64. Willner P, McGuirk J, Phillips G, et al. Behavioural analysis of the anorectic effects of fluoxetine and fenfluramine. Psychopharmacology 1990; 102: 273-7
65. McGuirk J, Muscat R, Willner P. Effects of chronically administered fluoxetine and fenfluramine on food intake, body weight and the behavioural satiety sequence. Psychopharmacology 1992; 107: 401-7
66. McGuirk J, Muscat R, Willner P. Effects of the 5-HT uptake inhibitors femoxitine and paroxetine, and the 5-HT1A agonist citalopram, on the behavioural satiety sequence. Pharmacol Biochem Behav 1992; 41: 801-5
67. Halford JCG, Heal DJ, Blundell JE. Effects in the rat of sibutramine on food intake and the behavioural satiety sequence [abstract]. Br J Pharmacol 1995; 114: 378p
68. Kitchener SJ, Dourish CT. An examination of the behavioural specificity of hypophagia induced by 5-HT1B, 5-HT1C and 5-HT2 receptor agonists using the post-prandial satiety sequence in rats. Psychopharmacology 1994; 113: 369-77
69. Cooper SJ, Dourish CT, Clifton PG. CCK antagonists and CCK-monoamine interactions in the control of satiety. Am J Clin Nutr 1992; 55 Suppl.: 291s-295s
70. Grignaschi G, Mantelli B, Fracasso C, et al. Reciprocal interaction of 5-hydroxytryptamine and cholecystokinin in the control of feeding. Br J Pharmacol 1993; 109 (2): 491-4
71. Voigt JP, Fink H, Marsden CA. Evidence for the involvement of the 5-HT1A receptor in CCK-induced satiety in rats. Naunyn Schmiedebergs Arch Pharmacol 1995; 351: 217-20
72. Poeschla B, Gibbs J, Simansky KJ, et al. Cholecystokinin-induced satiety depends on the activation of 5-HT1C receptors. Am J Physiol 1993; 264: R62-4
73. Poeschla B, Gibbs J, Simansky KJ, et al. The 5-HT1A agonist 8-OH-DPAT attenuated the satiating action of cholecystokinin. Pharmacol Biochem Behav 1992; 42: 541-3
74. Macor JE, Burkhart CA, Heym JH, et al. 3-(1,2,5,6-Tetrahydropyrid-4-yl)pyrrolo[3,2-b]pyrid-5-one: a potent and selective 5-HT1B agonist and rotationally restricted phenolic analogue of 5-methoxy-3-(1,2,5,6-tetrahydropyid-4-yl)indole. J Med Chem 1990; 33: 2087-93
75. Grignaschi G, Sironi F, Samanin R. The 5-HT1B receptor mediates the effect of d-fenfluramine on eating caused by intrahypothalamic injection of neuropeptide Y. Eur J Pharmacol 1995; 274: 221-4

76. Dryden S, Wang Q, Frankish HM, et al. The serotonin (5-HT) antagonist methysergide increases neuropeptide Y (NPY) synthesis and secretion in the hypothalamus of the rat. Brain Res 1995; 699: 12-8
77. Dryden S, Frankish HM, Wang Q, et al. Increased feeding and neuropeptide Y (NPY) but not NPY mRNA levels in the hypothalamus of the rat following central administration of the serotonin synthesis inhibitor p-chlorophenylalanine. Brain Res 1996; 724: 232-7
78. Dryden S, Frankish HM, Wang Q, et al. The serotonergic agent fluoxetine reduces neuropeptide Y levels and neuropeptide Y secretion in the hypothalamus of lean and obese rats. Neuroscience 1996; 72: 557-66
79. Hutson PH, Donohoe TP, Curzon G. Infusion of the 5-hydroxytryptamine agonists RU-24969 and TFMPP into the paraventricular nucleus of the hypothalamus causes hypophagia. Psychopharmacology 1988; 97: 550-2
80. Fletcher PJ, Coscina DV. Injecting 5-HT into the PVN does not prevent feeding induced by 8-OH-DPAT into the raphe. Pharmacol Biochem Behav 1993; 46: 487-91
81. Coscina DV, Feifel D, Nobrega JN, et al. Intra-ventricular but not intra-paraventricular nucleus metergoline elicits feeding in satiated rats. Am J Physiol 1994); 266: r1562-7
82. Currie PJ, Coscina DV. Metergoline potentiates natural feeding and antagonizes the anorectic action of medial hypothalamic 5-HT. Pharmacol Biochem Behav 1996; 53: 1023-8
83. Dryden S, Williams G. The role of hypothalamic peptides in the control of energy balance and body weight. Curr Opin Endocrinol Diabetes 1996; 3: 51-8
84. Read NW, Gwee KA. The importance of 5-hydroxytryptamine receptors in the gut. Pharmacol Ther 1994; 62: 159-73
85. Francis J, Critchley D, Dourish CT, et al. Comparisons between the effects of 5-HT and dl-fenfluramine on food intake and gastric emptying in the rat. Pharmacol Biochem Behav 1995; 50: 581-5
86. Edwards S, Stevens R. Peripherally administered 5-hydroxytryptamine elicits the full behavioural satiety sequence. Physiol Behav 1991; 50: 1075-7
87. Simansky KJ. Serotoninergic control of the organization of feeding and satiety. Behav Brain Res 1996; 73: 37-42
88. Poppitt SD, Prentice AM. Energy density and its role in the control of food intake: evidence from metabolic and community studies. Appetite 1996; 26: 153-74
89. MacDiaramid JI, Cade JE, Blundell JE. High and low fat consumers, their macronutrient intake and body mass index: further analysis of the National Diet and Nutrition Survey of British adults. Eur J Clin Nutr 1997; 50 (8): 505-12
90. Horton TJ, Drougas H, Brachey A, et al. Fat and carbohydrate overfeeding in humans: different effects on energy storage. Am J Clin Nutr 1995; 62: 19-29
91. Fernstrom JD, Wurtman RJ. Control of brain 5-HT content by dietary carbohydrates. In: Barchas J, Usdin E, editors. Serotonin and behaviour. New York: Academic Press, 1973: 121-8
92. Wurtman RJ, Fernstrom JD. Effects of diet on brain neurotransmitters. Nutr Rev 1974; 32: 193-200
93. Teff KL, Young SN, Blundell JE. The effect of protein or carbohydrate breakfasts on subsequent plasma amino acid levels, satiety and nutrient selection in normal males. Pharmacol Biochem Behav 1989; 34: 410-7
94. Blundell JE, Hill AJ. Nutrition, serotonin and appetite: case studying the evolution of a scientific idea. Appetite 1987; 8: 183-94
95. Pirke KM, Schweiger U, Laessle RG. Effect of diet composition on affective state in anorexia nervosa and bulimia. Clin Neuropharmacol 1986; 9: 513-5
96. Ashley DVM, Fleury MO, Golay A, et al. Evidence for diminished brain 5-HT biosynthesis in obese diabetic and non-diabetic humans. Am J Clin Nutr 1985; 42: 1240-5
97. Brewerton TD. Toward a unified theory of serotonin dysregulation in eating and related disorders. Psychoneuroendocrinology 1995; 20: 561-90
98. Goodwin GM, Fairburn CG, Cowen PJ. Dieting changes 5-HT function in women, not in men: implications for the aetiology of anorexia nervosa? Psychol Med 1987; 17: 839-42
99. Goodwin GM, Cowen PJ, Fairburn CJ, et al. Plasma concentrations of tryptophan and dieting. BMJ 1990; 300: 1499-500
100. Blundell JE. Problems and processes underlying the control of food selection and nutrient intake. In: Wurtman RJ, Wurtman JJ, editors. Nutrition and the brain. Vol 6. New York: Raven Press, 1983: 163-222
101. Luo S, Li ETS. Food intake and selection pattern of rats treated with dexfenfluramine, fluoxetine and RU-24969. Brain Res Bull 1990; 24: 729-33
102. Lawton CL, Blundell JE. The effects of d-fenfluramine on intake of carbohydrate supplements is influenced by the hydration of the test diets. Physiol Behav 1992; 3: 517-23
103. Lawton CL, Blundell JE. 5-HT manipulation and dietary choice: variable carbohydrate (polycose) suppression demonstrated only under specific experimental conditions. Psychopharmacology 1993; 112: 375-82
104. Kanarek RB. Dushkin H. Serotonin administration selectively reduces fat intake in rats. Pharmacol Biochem Behav 1988; 13: 133-22
105. Leibowitz SF, Shor-Posner G. Brain serotonin and eating behaviour. Appetite 1986; 7: 1-14
106. Rogers PJ, Blundell JE. Meal patterns and food selection during the development of obesity in rats fed a cafeteria diet. Neurosci Biobehav Rev 1984: 8: 441-53
107. Sclafani A. Animal models of obesity: classification and characterisation. Int J Obes 1984; 8: 491-508
108. Prats E, Monfar M, Castella J, et al. Energy intake of rats fed a cafeteria diet. Physiol Behav 1989; 45: 2263-72
109. Blundell JE, Hill AJ. Effects of dexfenfluramine in feeding and body weight: relationship with food consumption and palatability. In: Vague J, Guy-Grand B, Bjontroup P, editors. Metabolic complication of human obesities. Nordlolland: Elsevier, 1985: 199-206
110. Fisler JS, Underberger SJ, York DA, et al. d-fenfluramine in a rat model of dietary fat-induced obesity. Pharmacol Biochem Behav 1993; 45: 487-93
111. Blundell JE, Hill AJ. Do serotoninergic drugs decrease energy intake by reducing fat or carbohydrate intake? Effect of d-fenfluramine with supplemented weight increase diets. Pharmacol Biochem Behav 1989; 31: 773-8
112. Blundell JE, Lawton CL, Halford JCG. Serotonin, eating behaviour and fat intake. Obes Res 1995; 3 Suppl. 4: 471-6
113. Hill AJ, Blundell JE. Model system for investigating the actions of anorectic drugs: effects of d-fenfluramine on food intake, nutrient selection, food preferences, meal patterns, hunger and satiety in healthy human subjects. Advances in the biosciences. Oxford: Pergamon Press, 1986: 377-89
114. Goodall EM, Silverstone T. Differential effect of d-fenfluramine and metergoline on food intake in human subjects. Appetite 1988; 11: 215-8

115. Blundell JE, Hill AJ. On the mechanism of action of dexfenfluramine: effect on alliesthesia and appetite motivation in lean and obese subjects. Clin Neuropharmacol 1988; 11 Suppl. 1: 121S-34S
116. Hill AJ, Blundell JE. Sensitivity of the appetite control system in obese subjects to nutritional and serotoninergic challenges. Int J Obes 1990; 14: 219-33
117. Hill AJ, Rogers PJ, Blundell JE. Techniques for the experimental measurement of human eating behaviour: a practical guide. Int J Obes 1995; 19: 361-75
118. Lawton CL, Wales JK, Hill AJ, et al. Serotoninergic manipulation, meal-induced satiety and eating pattern: effects of fluoxetine in obese female subjects. Obes Res 1995; 3: 345-56
119. Rolls BJ, Shide DJ, Thorwart ML, et al. Sibutramine reduces food intake in non-dieting women with obesity. Obes Res 1998; 6: 1-11
120. Cowen PJ, Clifford EM, Walsh AE, et al. Moderate dieting causes 5-HT2C supersensitization. Psychol Med 1996; 26: 1156-9
121. Cangiano C, Ceci F, Casinco A, et al. Eating behaviour and adherence to dietary prescription in obese adult subjects treated with 5-hydroxytryptophan. Am J Clin Nutr 1992; 56: 863-7
122. Wadden TA, Bartlett SJ, Foster GD, et al. Sertraline and relapse prevention following treatment by a very low calorie diet: a controlled clinical trial. Obes Res 1995; 3 (6): 549-7
123. Silverstone T, Goodall E. The clinical pharmacology of appetite suppressant drugs. Int J Obes 1984; 8 (1): 23-33
124. Rogers PJ, Blundell JE. Effect of anorexic drugs on food intake and the micro-structure of eating in human subjects. Psychopharmacology 1979; 66: 159-65
125. Wurtman JJ, Wurtman RJ, Growdon JH, et al. Carbohydrate craving in obese people: suppression by treatments affecting serotoninergic transmission. Int J Eat Disord 1982; 1: 2-15
126. Wurtman JJ, Wurtman RJ, Mark S, et al. d-Fenfluramine selectively suppresses carbohydrate snacking in obese subjects. Int J Eat Disord 1985; 4: 89-99
127. Goodall EM, Cowen PJ, Franklin M, et al. Ritanserin attenuates anorectic endocrine and thermic responses to d-fenfluramine in human volunteers. Psychopharmacology 1993; 112: 461-6
128. McGuirk J, Silverstone T. The effect of 5-HT re-uptake inhibitor fluoxetine on food intake and body weight in healthy male subjects. Int J Obes 1990; 14: 361-72
129. Walsh AE, Smith KA, Oldman AD, et al. m-Chlorophenylpiperazine decreases food intake in a test meal. Psychopharmacology 1994; 116: 120-2
130. Sargent PA, Sharpley AL, Williams C, et al. 5-HT2C activation decreases appetite and bodyweight in obese subjects. Psychopharmacology 1997; 133: 309-12
131. Boeles S, Williams C, Campling GM, et al. Sumatriptan decreases food intake and increases plasma growth hormone in women. Psychopharmacology 1997; 129: 179-82
132. Guy-Grand B. Clinical studies with d-fenfluramine. Am J Clin Nutr 1992; 55 Suppl.: 173s-176s
133. Finer N, Finer S, Nauova RP. Drug therapy after very-low-caloric diets. Am J Clin Nutr 1992; 56: 1955-85
134. Anderson IM, Parry-Billings M, Newsholme EA, et al. Dieting reduces plasma tryptophan and alters brain 5-HT functioning in women. Psychol Med 1990; 20: 785-91
135. Weintraub M, Rubio A, Golik A, et al. Sibutramine in weight control: a dose-ranging, efficacy study. Clin Pharmacol Ther 1997; 50 (3): 330-7
136. Bray GA, Ryan DH, Grodon D, et al. A double-blind randomized placebo-controlled trial of sibutramine. Obes Res 1996; 4 (3): 263-70
137. Smith I, Fitchet M, Kelly F. Sibutramine: predictability of long term weight loss. Int J Obes 1997; 21 Suppl. 2; s53
138. Blundell JE, Lawton CL. Serotonin and dietary fat intake: effect of dexfenfluramine. Metabol Clin Exper 1995; 44 (2): 33-7
139. Drewnowski A. Changes in mood after carbohydrate consumption [abstract]. Am J Clin Nutr 1987; 46: 703
140. Lafreniere F, Lambert J, Rasio E, et al. Effects of dexfenfluramine treatment on body weight and postprandial thermogenesis in obese subjects: a double-blind, placebo-controlled study. Int J Obes 1993; 17: 25-30
141. Poppitt SD, Murgatroyd PR, Tainsh KR, et al. The effect of dexfenfluramine on energy and macronutrient balance of obese women on high fat and low fat diets [abstract]. Int J Obes 1997; 21 Suppl. 2: s65
142. Green S, Lawton C, Wales J, et al. Risk factors for overeating: dexfenfluramine suppresses the intake of sweet high fat or carbohydrate foods in obese women [abstract]. Int J Obes 1997; 21 Suppl. 2: s64
143. Golay A, Bobbioli E. The role of dietary fat in obesity. Int J Obes 1997; 21 (3 Suppl.): s2-11
144. Drewnowski A, Kurth C, Holden-Wiltse J, et al. Food preferences in human obesity: carbohydrates verses fats. Appetite 1992; 18: 207-1
145. Abenhaim L, Moride Y, Benot F, et al. Appetite suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996; 335: 609-16
146. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997; 337: 581-8
147. Dillon KA, Putnam KG, Avorn JL. Death from irreversible pulmonary hypertension associated with short-term use of fenfluramine and phentermine [letter]. JAMA 1997; 278: 1320
148. Mark EJ, Patalas ED, Chang HT, et al. Fatal pulmonary hypertension associated with short-term use of fenfluramine and phentermine. N Engl J Med 1997; 337: 602-6
149. Food and Drug Administration. Health advisory on fenfluramine/phentermine for obesity. Media Release 1997 Aug 27
150. Cannistra LV, Davis SM, Bouman AG. Valvular heart disease associated with dexfenfluramine [letter]. New Engl J Med 1997; 337: 636
151. Davis WM, Waters IW. High altitude may be synergistic with pulmonary hazards of appetite control medications fenfluramine and dexfenfluramine. Med Hypotheses 1997; 49: 509-12
152. Knoll Meridia blood pressure elevation screen should be created; BP concerns outweigh weight loss benefit for 39%-50% patients, FDA committee concludes. F-D-C Pink Sheets 1996 Sept 39; 58: 10-1
153. Knoll's sibutramine rejected by US panel. Marketletter 1996 Oct 7: 18
154. Stunkard AJ. Eating patterns in obesity. Psychiatr Q 1959; 33: 284-92
155. Spitzer RL, Devlin M, Walsh BT, et al. Binge eating disorder: a multisite field study of the diagnostic criteria. Int J Eat Disord 1992; 11: 191-203
156. Brewerton TD, George MS. Is migraine related to the eating disorders. Int J Eat Disord 1993; 14: 75-9
157. Brewerton TD, Mueller EA, Lesam MD, et al. Neuro-endocrine responses to m-chlorophenylypiperazine and l-tryptophan in bulimia. Arch Gen Psychiatry 1992; 49: 852-61

158. Kissileff HR, Wentzlaff TH, Guss JL, et al. A direct measurement of satiety disturbance in patients with bulimia nervosa. Physiol Behav 1996; 60: 1077-85
159. Jimerson DC, Wolfe BE, Metzger ED, et al. Decrease serotonin function in bulimia nervosa. Arch Gen Psychiatry 1997; 54: 529-34
160. Solyom L, Solyom C, Ledwidge B. The fluoxetine treatment of low weight, chronic bulimia nervosa. J Clin Psychopharmacol 1990; 10: 421-5
161. Wood A. Pharmacotherapy of bulimia nervosa – experience with fluoxetine. Int Clin Psychopharmacol 1993; 8 (4): 295-9
162. Goldstein DJ, Wilson MG, Thompson VL, et al., Fluoxetine Bulimia Nervosa Research Group. Long-term fluoxetine treatment of bulimia nervosa. Br J Psychiatry 1995; 166: 660-6
163. Ayuso-Gutierrez JL, Palazon M, Ayuso-Mateos JL. Open trial of fluvoxamine in the treatment of bulimia nervosa. Int J Eat Disord 1994; 15: 245-9
164. Pope Jr HG, Keck Jr PE, McElroy SL, et al. A placebo-controlled study of trazodone in bulimia nervosa. Clin Psychopharmacol 1989; 9 (4): 254-9
165. Hudson JL, Pope Jr HG, Keck Jr PE, et al. Treatment of bulimia nervosa with trazodone: short-term response and long-term follow-up. Clin Neuropharmacol 1989; 12 (1 Suppl.): s38-46
166. Solyom L, Solyom C, Ledwidge B. Trazodone treatment of bulimia nervosa. J Clin Psychophamacol 1989; 9 (4): 287-90
167. Stunkard A, Berkowitz R, Tratikut C, et al. D-fenfluramine treatment of binge eating disorder. Am J Psychiatr 1996; 153: 1455-9
168. Greeno CA, Wing R. A double-blind, placebo-controlled trial of the effect of fluoxetine on dietary intake in overweight women with and without binge-eating disorder. Am J Clin Nutr 1996; 64: 267-73
169. Fahy TA, Elsler I, Russell GP. A placebo-controlled trial of d-fenfluramine in bulimia nervosa. Br J Psychiatry 1993; 162: 597-603

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