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REVIEW ARTICLE

Regulation of Appetite: Role of Serotonin and Hypothalamus

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ABSTRACT

Serotonin (5-HT), a mono-aminergic neurotransmitter is biochemically derived from tryptophan and is mainly found in gastrointestinal tract, platelets and central nervous system of animals. Serotonin (5-HT) in coordination with hypothalamus plays an important role in the CNS control of appetite, eating behavior, and energy balance and body weight. It has a special role in control of carbohydrate intake. It has been observed that reduction in serotonin level causes hyperphagia. As the result, carbohydrate intake increases and hence results in obesity. Inversely-increased level of serotonin level leads to hypophagia, as a result carbohydrate intake decreases. That is why serotonergic agonists are clinically useful in treatment of obesity. Obesity (body mass index [BMI] > 30) is a risk factor for major causes of death, including cardiovascular disease, numerous cancers, diabetes, and metabolic syndrome and is linked with markedly diminished life expectancy. The energy regulation of 5-HT is mediated in part, by 5-HT receptors located in various medial hypothalamic nuclei. Along with serotonin, other hormones like insulin; leptin and corticosteron are also involved in the energy control and regulation. Though large numbers of serotonergic drug like selective serotonin reuptake inhibitors (SSRI), such as sibutramine, or serotonin $5HT_2c$ agonists are available to treat this deadly disease, these drugs are associated with large number of side effects. Thus, the increasing global prevalence of obesity has renewed interest in the serotonin-hypothalamic regulation of energy balance to find the drugs having maximum pharmacological and minimum toxicological effects. In this review article, attempts have been made to provide the detailed role of serotonin in the appetite regulation so that new targets and new sites can be created for the therapy of obesity.

Keywords: *Obesity, Satiety, Eating behavior, Serotonin, Hypothalamus, Appetite*

Appetite is a psychological desire to eat. Appetite, an expression of numerous regulatory processes, determine the initiation and termination of meals, the amount and type of food consumed, meal length and frequency, and governs the duration between meal intervals. Signals are generated from the very commencement of consumption, the short term consequences of which serve to terminate eating behavior and act as powerful inhibitors for further intake. This process signals to brain and estimation of a meal as opposed to an accurate analysis of content. This is an important distinction between the short term satiety signals produced by the physiological consequences of meal intake and the longer signal secreted by the body's constant metabolic need for energy intake, and is critical to both the appetite fluctuation and patterns of eating behavior 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].

Appetite and energy homoeostasis

A complex physiological system balances energy intake and expenditure, comprising afferent signals and efferent effectors. Hunger leads to initiation of eating. When a meal is ingested, satiety hormones contribute to

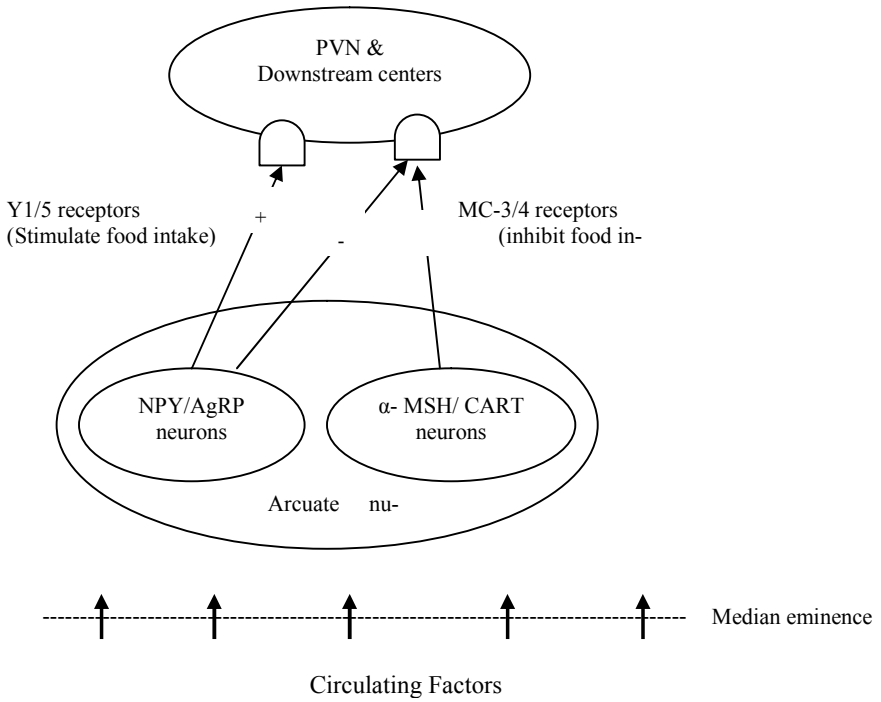

Fig 1. The central regulation of appetite (Chaudhri et al, 2006 [6])

digestion and a feeling of fullness. Central circuits in the
brain integrate satiety signals and signals of long term energy status to produce a coordinated response to the change in nutritional status [2].

Regulation of Appetite

Appetite is controlled at both the central and peripheral sites.

Central regulation

The nuclei of the hypothalamus and brain stem are important regions for regulation of energy homoeostasis. Various gut hormones act on hypothalamic and brainstem centers of appetite control. This provides one means by which the gut may signal energy status to the seat of satiety, the central nervous system (CNS). Arcuate nucleus (ARC) acts as the site of integration of a number of neurological and blood-borne signals, due to its privileged location near the median eminence. This latter region lacks a complete blood–brain barrier [3], and therefore some investigators have argued that the ARC is rendered susceptible to be influenced by circulating factors. Circulating factors modify the activity of two populations of neuron within the ARC. One population co-expresses cocaine- and amphetamine-related transcript (CART) and pro-opio-melanocortin (POMC) and inhibits food intake. Among the products of cleavage of POMC is a-melanocyte-stimulating hormone, which is a ligand for the melanocortin-4 receptor [4].

The second population of neurons increases food intake and co-expresses neuropeptide Y (NPY) and agouti-related protein [5]. Both populations project to the paraventricular nucleus (PVN) and other areas important in the regulation of food intake (Fig 1) [6]. Extensive reciprocal connections exist between the hypothalamus and the brainstem, particularly the nucleus of the tractus solitaries [7]. Like the ARC, the brainstem is well placed to receive signals from the blood due to its proximity to other regions with an incomplete blood–brain barrier, e.g. the area postrema. In addition, the brainstem receives vagal afferent neurons from the gastrointestinal tract, and therefore acts as another site of integration between endocrine and neuronal signals.

Peripheral regulation

Ghrelin, which is synthesised predominantly by the stomach, is the endogenous ligand for the growth hormone secretagogue receptor which is expressed in brain stem and hypothalamic nuclei including the ARC [8]. In rodents, ghrelin is a potent stimulus to feeding as it was reported that chronic ghrelin administration induces adiposity [9], and CNS injection of anti-ghrelin antibodies inhibits the normal feeding response after fasting [10]. Human data support a role for ghrelin in appetite regulation. Plasma levels of ghrelin are high in the fasted state and fall after eating [11], and exogenous infusion of ghrelin increased food intake at a buffet meal by

28% compared with saline control. Indeed, it was found that individuals with Prader–Willi syndrome have grossly increased ghrelin levels, and this could be a cause of their hyperphagia [4].

Meal termination and satiety factors

Control of meal size is largely determined by the onset of satiety. This involves messages from mechano- and chemo-receptors from the oral cavity and gastrointestinal tract. In addition, gut peptides are released in response to a meal. These optimize digestion and signal a change in energy status, with subsequent influence on both physiology and behavior [2]. Various gut hormones are thought to play a part in the process. These include:

Cholecystokinin

The first gut peptide to be implicated in the control of appetite was cholecystokinin (CCK). CCK is synthesized in a number of tissues in humans, including the I-cells of the small intestine [12], from where it is rapidly released into the circulation in response to a meal [13]. Other hormones include peptideYY [14], glucangon-like peptide [15], and pancreatic peptide [16].

Serotonin

Neuronal serotonin is synthesized from the essential amino acid trypyophan, in the cell body cytoplasm. The enzyme tryptophan hydroxylase hydroxylates dietary I-tryptophan to 5-hydroxytryptophan (5-HTP). 5-HTP is then rapidly decarboxylated at the terminal, by the enzyme I-aminoacid decarboxylase, to produce serotonin (5-HT). The majority of serotonin is taken up via a vesicle membrane transport mechanism and stored in presynaptic vesicles. After release, synaptic serotonin continues to stimulate pre- and post-synaptic receptors until it is either converted to 5-hydroxyindole acetic acid by monoamine oxidase or reabsorbed into the presynaptic neuron for reuse [17].

Role of serotonin in eating behavior

Energy balance is regulated by the hypothalamic nuclei by peripherally-generated signals via various neuropeptides. These neuropeptides are linked with the serotonergic system, which controls the eating behavior. An interaction between neuropeptide Y (NPY) and serotonin was suggested early by studies [18] in which NPY-induced hyperphagia was shown to be blocked by the serotonin receptor agonist fenfluramine. Serotonin and orexin are both involved in feeding regulation, in addition to their roles in sleep-wake cycle. Orexin has been shown to alter serotonin release in the hypothalamus [19]. It has been indicated that serotonin has a suppressive effect on food intake and body weight [20]. This effect of serotonergic stimulation has been demonstrated with both peripheral and central injections of serotonergic agonists. Moreover, the opposite effect, an enhancement of food consumption, has been observed with receptor antagonist and other drugs which reduce serotonin activity.

Serotonergic receptors involved in feeding behavior

Evidences suggest that central 5-HT_1; as opposed to 5-HT_2 or 5-HT_3 receptor subtypes mediate the feeding suppressive action of serotonergic stimulation in the medial hypothalamus. This is supported by the studies [21] in which peripheral and hypothalamic injections of serotonergic or β-adrenergic antagonists with relatively high affinity for 5-HT_1 receptors, but not selective antagonists of 5-HT_2 or 5-HT_3 receptors, significantly attenuate the feeding-suppressive action of serotonergic agonists injected peripherally or into the PVN. Further differentiation of the 5-HT_1 receptor indicates that, in the rat, the 5-HT_{1B} and possibly 5-HT_{1C} subtypes are specifically involved in 5-HT-induced hypophagia, in contrast to the 5-HT_{1A} receptor, which may mediate the opposite response, hyperphagia [21]. The role of 5-HT_{2C} receptor [22] subtype has been demonstrated to upregulate the expression of hypothalamic NUCB2 and induces anorexia via leptin-independent pathway in mice. Further, it has been suggested that the mice lacking functional 5-HT_{2C} receptor becomes obese as adults [23] as these mice exhibit hyperphagia and consume larger meals, indicating a deficit in satiety. In another mutant mouse, *anx,* the anorexic behavior of the animal at a young age is suggested to be attributed, in part, to an overactive 5-HT innervation of the medial hypothalamic nuclei [24].

Impact of serotonin on macronutrient ingestion

Hypothalamic as well as peripheral administration of serotonergic agonist affects feeding patterns by producing a significant decrease in the size and duration of individual meals in association with the reduced trait of eating. As the latency to meal onset and the frequency of the meal taken are not affected, it is proposed that endogeneous 5-HT may influence primarily the termination rather than the initation of eating. Through hypothalamic administration of 5-HT, as well as studies employing systemic injection of serotonergic agents, evidence has accumulated to indicate a role for 5-HT in the modulation of the animals appetite for the specific foods [25]. This role has been proposed to involve the control of carbohydrate and protein intake or perhaps the ratio of these two macronutrients, with serotonergic stimulation reducing the proportion of carbohydrate in the diet. This phenomenon was initially demonstrated in a two-diet self- selection paradigm, first with peripherally administrated fenfluramine and fluoxetine [26] and then with PVN injection of 5-HT or norfenfluramine [25]. The opposite pattern has been detected with the reduction in brain 5-HT after intraventricular injection of serotonergic injection [27]. Some studies reveal that injections of 5-HT or the serotonergic agonist d-norfenfluramine and fluoxetine directly into the medial hypothalamus preferentially and dose-dependently suppress carbohydrate consumption while having little or no effect on or possibility enhancing the ingestion of protein or fat. This effect, similarly seen with central injection of 5-HT in mice [28], can be detected in sever-

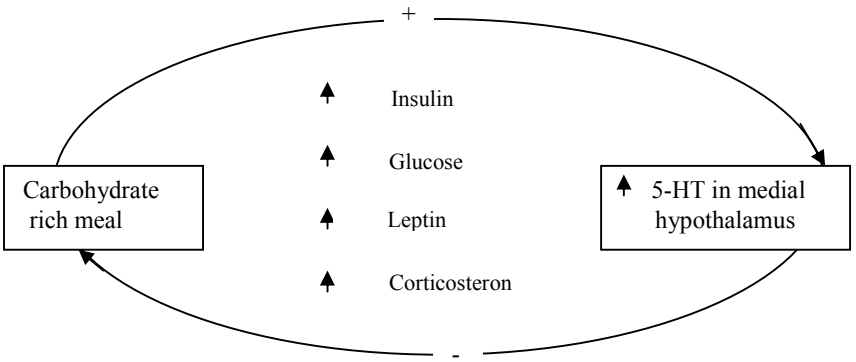

Fig 2. Feedback loop in Control of meal size (Leibowitz et al, 1998 [29])

al medial hypothalamic nuclei, although the PVN and VMN are most responsive. Peripherally-administered d-fenfluramine, fluoxetine and quipazine also suppress carbohydrate intake. However, depending upon the drug dose and nutritional state of the animal, they may be less selective in their effect on macronutrient choice [25]. Particularly at higher doses, they cause reduction in fat as well as carbohydrate ingestion while having less impact or sometimes enhancing effect on protein consumption.

Impact of carbohydrate ingestion on serotonin

A link between the serotonin and a specific macronutrient is substantiated by results showing a feedback effect of carbohydrate ingestion itself on 5-HT in the hypothalamus and brain stem (Fig 2) [29]. Animals consuming a high carbohydrate diet, compared to a low carbohydrate-high protein diet, show increased level of tryptophan (TRP), the 5-HT aminoacid precursor

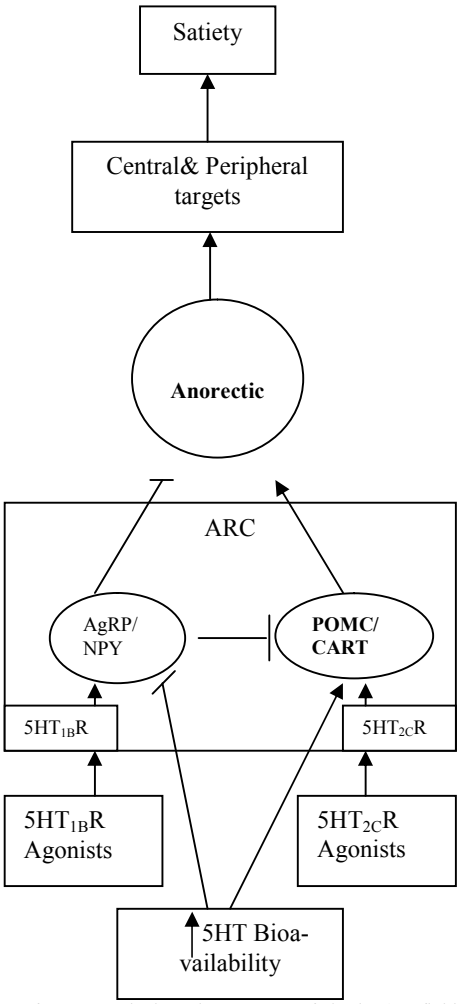

Fig 3. Working of serotonergic drugs in treatment of obesity (Garfield and Heisler, 2009; [42])

[31,31] and an increased level of 5-HT content in whole hypothalamus [32]. This diet promotes up ɛ of TRP into the brain and its subsequent conversion to 5-HT and also reduces concentrations of other amino acids that compete with TRP for transport into the brain. Insulin, which is released after a high carbohydrate meal stimulates the absorption of these large neutral amino acids (LNAA), by increasing the ratio of TRP:LNAA. This feedback mechanism may be disturbed in the condition of decreased insulin sensitivity e.g obesity resulting in an over-consumption of carbohtdrate [30]. Thus, the ingestion of the macronutrient, carbohydrate, stimulates the production of the monoamine, which then performs the function of terminating the ingestion of this nutrient and producing satiety. With excess serotonergic stimulation of medial hypothalamus, anorexia results e.g in the *anx* mouse [24]. On the other hand, with the deficiency of 5-HT function, e.g with lesions or receptor antagonist of the 5-HT system, hyperphagia and weight gain become evident [33].

Serotonergic drugs food intake and feeding behavior

Effect of various serotonergic drugs have been studied to check their effect on food intake and feeding behavior. These drugs include 5-HT precursor, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), serotonin–norepinephrine reuptake inhibitors (SNRI), and serotonin antagonists. Studies suggested that administration of 5-HT precursor [34], serotonin agonists and its metabolites [35], SSRI which include fluoxetine [36], sertaline and SNRI like sibutramine [37] decreases food intake. Combination of sibutramine and naloxone shows synergestic effect in decreasing food intake in rats [38]. Administration of serotonergic antagonists like metergoline-α $5HT_{1/2}$ receptor antagonist showed a dose-dependent increase of food intake in rats [39].

Serotonergic drugs and obesity

Early pharmacological manipulations identified an inverse relationship between the biogenic amine neurotransmitter serotonin and food intake. More specifically, a selective reduction in serotonin bioavailability was associated with hyperphagia and subsequent weight gain, whilst diminished food intake was induced by an increase in serotonin efficacy [40]. Hypothalamus is the key component in mediated feeding behavior [41]. Acute administration of serotonergic compounds altered the expression of such peptidergic appetitive effectors within the hypothalamus, namely an increase in anorectic pro-opiomelanocortin (POMC) mRNA and a decrease in orexigenic neuropeptide Y (NPY) mRNA [40], both of which are synthesized within discrete neuronal populations of the ARC. Recently, it has been shown that manipulation of these first order hypothalamic POMC/cocaine and amphetamine-regulated transcript (CART) and agouti-related protein (AgRP)/NPY neurones is a mechanism through which serotonergic compounds reduce food intake as shown in Fig 3 [42]. Specifically, the serotonin system concomitantly regulates the antagonistic functions of POMC/CART and AgRP/NPY neurones through neurotransmitter binding of two spatially distinct G-protein-coupled receptor subtypes: depolarizing POMC/CART neurons via action at G_q-coupled 5-HT_{2C}Rs [43] and hyperpolarizing AgRP/NPY neurons through action at G_i-coupled 5-HT_{1B}Rs [44]. Furthermore, the anorectic effect of compounds increasing serotonergic bioavailability and 5-HT_{2C} receptor and 5-HT_{1B} receptor agonists is contingent upon the downstream activation of the melanocortin 4 receptors (MC4Rs) [45]. It is noteworthy that these serotonergic compounds, which are highly effective in reducing food intake, are rendered ineffective by pharmacological or genetic inactivation of this single downstream melanocortin receptor target [44]. These data elucidate that the melanocortin pathway is a key downstream target for serotonergic compound.

Recent research has further clarified that the key population of MC4Rs influencing appetite is expressed in the PVH and/or amygdala [46]. Fenfluramine, an amphetamine derivative lacking psychostimulant properties, was synthesized in the 1970s, and was followed 20 years later by the more efficacious enantiomer, dexfenfluramine. Both compounds were successfully prescribed (often in combination with phentermine) as anorectic treatments for obesity until their withdrawal from clinical use in 1997, due to corollary incidences of cardiopulmonary complications. Mechanistically, these drugs are analogous to amphetamine, causing reversal and blockade of the serotonin transporter and a consequential increase in serotonin efflux and synaptic persistence [46]. Genetic and pharmacological studies demonstrated that action at the 5-HT_{2C}Rs and 5-HT_{1B}Rs is required for fenfluramine to influence ingestive behaviour [46].

REFERENCES

1. Halford JCG, Blundell JE. Separate systems for serotonin and leptin in appetite control. *Ann Med* 2000; 32:222-32.
2. Druce M, Bloom SR. The regulation of appetite. *Arch Dis Child* 2006; 91:183-87.
3. Peruzzo B. Pastor FE, Blazquez JL, Schobitz K, Pelaez B, Amat P & Rodriguez EM. A second look at the barriers of the medial basal hypothalamus. *Exp Brain Res* 2000; 132:10–26.
4. Wynne K, Stanley S, McGowan B, Bloom S. Appetite control. *J Endocrinol* 2005; 184:291–318.
5. Ellacott KL, Cone RD. The central melanocortin system and the integration of short- and long-term regulators of energy homeostasis. Recent Prog. *Horm Res* 2004; 59: 395–408.
6. Chaudhri O, Small C, Bloom S. Gastrointestinal hormones regulating appetite. *Philos Trans R Soc Lond B Biol Sci* 2006; 361:1187-209.
7. Van der Kooy D, Koda LY, McGinty JF, Gerfen CR & Bloom FE. The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat. *J Comp. Neurol* 1984; 224:1–24.
8. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999; 402:656–60.

9. Wren AM, Small CJ, Abbott CR, Dhillo WS, Seal LJ, Cohen MA, Batterham RL, Taheri S, Stanley SA, Ghatei MA, Bloom SR. Ghrelin causes hyperphagia and obesity in rats. *Diabetes* 2001; 50:2540–7.
10. Nakazato M, Murakami N, Date Y, et al (2001) . A role for ghrelin in the central regulation of feeding. *Nature* 409:194–8.
11. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ. Plasma ghrelin levels after dietinduced weight loss or gastric bypass surgery. *N Engl J Med* 2002; 346:1623–30.
12. Buffa R, Solcia E, Go VL. Immunohistochemical identification of the cholecystokinin cell in the intestinal mucosa. *Gastroenterology* 1976; 70:528–32.
13. Liddle RA, Goldfine ID, Rosen MS, Taplitz RA, Williams JA. Cholecystokinin bioactivity in human plasma. Molecular forms, responses to feeding, and relationship to gallbladder contraction. *J Clin Invest* 1985; 75:1144–52.
14. Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature* 2002; 418:650–4.
15. Schirra J, Katschinski M, Weidmann C, Schäfer T, Wank U, Arnold R, Göke B. Gastric emptying and release of incretin hormones after glucose ingestion in humans. *J Clin Invest* 1996; 97:92–103.
16. Adrian TE, Bloom SR, Bryant MG, Polak JM, Heitz PH, Barnes AJ. Distribution and release of human pancreatic polypeptide. *Gut* 1976; 17:940–4.
17. Halford JCG, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic Drugs, Effects on appetite expression and use for the treatment of obesity. *Drugs* 2007; 67:27-55.
18. Rogers P, McKibbin PE, Williams G. Acute fenfluramine administration reduces neuropeptide Y concentrations in specific hypothalamic regions of the rat: possible implications for the anorectic effect of fenfluramine. *Peptides* 1991; 12:251-55.
19. Orlando G, Brunetti Ll, Di Nisio C. Effects of cocaine and amphetamine regulated transcript peptide, leptin and orexins on hypothalamic serotonin release. *Eur J Pharmacol* 2001; 430:269-72.
20. Cruzon G. Serotonin and appetite. *Ann NY Acad Sci* 1990; 600:521-30.
21. Nonogaki K, Ohba Y, Sumii M, Oka Y. Serotonin systems upreglate the expression of hypothalamic NUCB2 via 5HT2C receptors and induce anorexia via a leptin-independent pathway in mice. *Biochem Biophys Res Commu* 2008; 372:186-190.
22. Tecott LH, Nonogaki k, strack AM, Vickers SP, Dourish CT, clifton PG. A primary satiety defects leads to adult onset obesity in serotonin 5-HT2C receptor mutated mice. *Soc Neurosci Abs* 1997; 23:514.
23. Son JH, Baker H, Park DH, Joh TH. Drastic and selective hyperinnervation of central serotonergic neurons in a lethal neurodevelopmental mouse mutant, Anorexia (anx). *Brain Res Mol Brain Res* 1994; 25:129-34.
24. Shor-Posner G, Grinker JA, MarinescuC, Brown O, Leibowitz SF. Hypothalamic serotonin in the control of meal patterns and macronutrient selection. *Brain Res Bull* 1986; 17: 663-71.
25. Wurtman JJ, Wurtman RJ. Fenfluramine and fluoxetine spare protein consumption while suppressing caloric intake by rats. *Science* 1977; 198:1178-80.
26. Li ET, Anderson GH. 5-Hydroxytryptamine: A modulator of food consumption but not quantity? *Life Sci* 1984; 34:2453-60.
27. Currie PJ. Differential effects of NE, CLON, and 5-HT on feeding and macronutrient selection in genetically obese (ob/ob) and lean mice. *Brain Res Bull* 1993; 32:133-42.
28. Fernstrom JD, Faller DV, Shabshelowitz H. Acute reduc tion of brain serotonin and 5-HIAA following food consumption: Correlation with the ration of serum tryptophan to the sum of conpeting amino acids. *J Neural Transm Gen Sect* 1975; 36: 113-21.
29. Leibowitz SF, Alexander JT. Hypothalamic serotonin in control of eating behavior, meal size, and body weight. *Biol Psychiatry* 1998 Nov 1; 44(9):851-64.
30. Wurtman RJ, Wurtman JJ. Brain serotonin, carbohydrate carving, obesity and depression. *Obes Res* 1995; 3:477S-80S.
31. Thibault L. Dietary carbohydrates: Effects on self selection, plasms glucose and insulin, and brain indinoleaminergic systems in rat. *Appetite* 1994; 23:275-86.
32. Lambert PD, Wilding JP, al-Dokhayel AA, Bohuon C, Comoy E, Gilbey SG. A role for neuropeptide Y, dynorphin, and noradrenaline in the central control of food intake after food deprivation. *Endocrinology* 1993; 133:29-32.
33. Cangiano C, Ceci F, Casinco A. Eating behavior and adherence to dietary prescription in obese adult subjects treated with 5-Hydroxytryptophan. *Am J Clin Nutr* 1992; 56:863-67.
34. 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.
35. Pijl H, Koppeschaar HPF, Willekens FLA, Op de Kamp I, Veldhuis HD, Meinders AE. Effect of serotonin reuptake inhibition by fluoxetine on body weight and spontaneous food choice in obesity. *Int J Obesity* 1991; 15:237-42.
36. Chapelot D, Mamonier C, Thomas F, Hanotin C. Modalities of the food intake-reducing effect of sibutramine in humans. *Physiol Behav* 2000; 68:299-308.
37. Tallett AJ, Blundell JE, Rodgers RJ. Sibutramine & naloxone: Infra-additive interaction in the regulation of appetite? *Behavioural Brain Res* 2010; 207:174-81.
38. Zittel TT, Glatzle J, Weimar T, Kless S, Becker HD, Jehle EC. Serotonin receptor blockade increases food intake and body weight after total gastretomy in rats. *J Surg Res* 2002; 106:273-81.
39. Fletcher PJ, Paterson IA. A comparison of the effects of tryptamine and 5-hydroxytryptamine on feeding following injection into the paraventricular nucleus of the hypothalamus. *Pharmacol Biochem Behav* 1989; 32:907-11.
40. Heisler LK, Cowley MA, Tecott LH, Fan W, Low MJ, Smart JL, Rubinstein M, Tatro JB, Marcus JN, Holstege H, Lee CE, Cone RD, Elmquist JK. Activation of central melanocortin pathways by fenfluramine. *Science* 2002; 297:609-11.
41. Choi S, Blake V, Cole S, Fernstrom JD. Effects of chronic fenfluramine administration on hypothalamic neuropeptide mRNA expression. *Brain Res* 2006; 1087:83-6.
42. Garfield AS, Heisler LK. Pharmacological targeting of the serotonergic system for the treatment of obesity. *J Physiol* 2009; 587(Pt 1):49-60.
43. Heisler LK, Jobst EE, Sutton GM, Zhou L, Borok E, Thornton-Jones Z, Liu HY, Zigman JM , Balthasar N, Kishi T, Lee CE, Aschkenasi CJ, Zhang CY, Yu J, Boss O, Mountjoy KG, Clifton PG, Lowell BB, Friedmann JM, Horvath T, Butler AA, Elmquist JK, Cowley MA. Serotonin reciprocally regulates melanocortin neurons to modulate food intake. *Neuron* 2006; 52:239-49.
44. Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, Ferreira M, Tang V, McGovern RA, Kenny CD, Christiansen LM, Edelstein E, Choi B, Boss O, Aschkenasi C, Zhang CY, Mountjoy K, Kishi T, Elmquist JK, Lowell BB. Divergence of melanocortin pathways in the control of food intake and energy ecpenditure. Cell 2005; 123:493-505.
45. Crespi D, Mennini T, Gobbi M. Carrier-dependent and Ca2+-dependent 5-HT and dopamine release induced by (+)-amphetamine,3,4-methylendioxymethamphetamine, p-chloroamphetamine and (+)- fenfluramine. *Br J Pharmacol* 1997; 121:1735-43.
46. Vickers SP, Clifton PG, Dourish CT, Tecott LH. Reduced satiating effect of d-fenfluramine in serotonin 5-HT2C receptor mutant mice. *Psycopharmacology* 1999; 143:309-14.

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