Review Article

Brain serotonin and the control of food intake under physiological and pathological conditions

A. LAVIANO, A. MOLFINO, I. PREZIOSA, M. MUSCARITOLI, A. CASCINO, F. ROSSI FANELLI

Department of Clinical Medicine, University La Sapienza, Rome - Italy

ABSTRACT: *Food intake is tightly controlled by a number of central and peripheral factors and systems which ensure, under physiological conditions, an almost perfect match between energy intake and energy expenditure. Although most of the factors and systems involved in the control of energy homeostasis are redundant and their inhibition does not result in significantly changed food intake, a few of them appear critical and their block induces the onset of anorexia or hyperphagia. Among these systems, the brain monoaminergic system plays an important role in the control of eating behavior. In this article, we will review the existing literature dealing with the role of brain serotonin in the regulation of food intake and its contribution to the pathogenesis of hyperphagia of obesity. With the use of a number of models, it appears that brain serotonin contributes to food intake regulation by acting within the brain in a coordinated manner with another monoamine involved in food intake regulation, dopamine. Also, hyperphagia of obesity is associated with changes in brain monoamine concentrations, but it is still difficult to ascertain whether these defects are an acquired response to chronic overingestion leading to obesity, which then drives further increases in food intake to preserve the status quo, or whether they are due to primary central factors. The pivotal role of central serotonin in food intake regulation and particularly in obesity is also strengthened by the evidence that the drugs licensed to interfere with food intake in obese patients act on the serotonergic system.* (Nutritional Therapy & Metabolism 2007; 25: 49-55)

KEY WORDS: *Serotonin, Dopamine, Obesity, Hypothalamus, VMN, LHA, Monoamines, Food intake, Leptin, Diet-induced obesity*

INTRODUCTION

Under physiological conditions, energy homeostasis, ie, the balance between energy intake and energy expenditure, should be tightly controlled to avoid pathological changes in body weight, leading to increased risk of serious disorders. If we consider that the average energy intake over a year is approximately 650,000 kcal, then this energy intake should be matched by energy expenditure with a 99.9% precision, to avoid a >2 kg increase in body weight over the same period. Therefore, it is not surprising that energy homeostasis is under the control of a number of different, and frequently redundant, central and peripheral factors.

Although extremely complex, the general frame of food intake regulation can be summarized in the gut-brain axis hypothesis, ie, a brain area located in the hypothalamus receives and integrates inputs from the periphery. When the sum of these inputs indicates that an energy deficit exists in the periphery, hypothalamic orexigenic pathways are activated and food intake is elicited. In contrast, when the messages arriving to the brain signal an excess of energy availability, then hypothalamic anorexigenic pathways are activated and food intake is inhibited. Consequently, energy homeostasis results from the interactions at the hypothalamic level between peripheral signals, reaching the brain as hormones (among which insulin appears to play an important role), peptides, or neural inputs, and a number of hypothalamic pathways involved in their integration and in eliciting the adequate behavioral response. Among the different hypothalamic pathways, the brain monoaminergic system, and particularly brain serotonin, appears to play a critical role in controlling food intake under physiological conditions. Moreover, its derangement seems to contribute to the development of hyperphagia, thereby strengthening its role as a critical mediator of eating behavior and as an attractive putative therapeutic target for hyperphagic obese patients.

MONOAMINE AND THE CONTROL OF FOOD INTAKE

In the effort to crack the riddle of food intake control, it is useful to base investigations on a simple formula reflecting the integrative behavior of spontaneous food intake, i.e. food intake = meal number x meal size (1). Under normal circumstances, counterbalancing controls for each feeding index exist, such that a change in one is likely to produce a compensatory change in the other to preserve the relative consistency of daily food intake (2). This reciprocal relationship between meal number and meal size that maintains homeostasis of food intake under normal conditions and leads to its disruption under different experimental conditions has been repeatedly demonstrated (see ref. 3 for a review). To function as a complementary system, it is likely that under normal and stable metabolic conditions meal size (reflecting short-term food intake controls) and meal number (reflecting long-term food intake controls) are independently regulated in a way analogous to the reciprocal innervation controlling spinal reflexes. It is also likely that they are regulated by different but connected anatomical sites in the hypothalamus. Thus, putative hypothalamic areas involved in the control of appetite and food intake are those loci whose anatomical and functional relationships, as they relate to regulation of food intake and metabolism, are well established. Among other hypothalamic areas, the lateral hypothalamic area (LHA) and the ventromedial nucleus of the hypothalamus (VMN) are known to be anatomically linked (3). Functional reciprocity between LHA and VMN has been established by a number of studies. Finally, serotonin and dopamine, 2 neurotransmitters whose role in food intake control is well established, exert their action via different areas of the hypothalamus, including the VMN and LHA (4).

In the past years, intra-LHA and intra-VMN changes in neurotransmitter levels have been demonstrated to be related to the relationship between meal size and meal number (4). Conceptually, it could be hypothesized that an interaction between LHA and VMN and between at least 2 neurotransmitters, dopamine and serotonin, within these brain areas, may significantly participate in food intake control in health and disease by their influences on meal size and meal number, probably via modulation of gastrointestinal function and motility (4). In particular, it appears that an increase in hypothalamic serotonin is involved in the regulation of satiation and thus of meal number, while an increase in hypothalamic dopamine is involved in sustaining feeding activity and thus in the regulation of meal size.

Serotonin, as well as dopamine, is a monoamine acting as a neurotransmitter and is involved in different biological responses. Although the exact role of monoamines in the central regulation of food intake and body weight still awaits clarification, their involvement in this process has been repeatedly confirmed. Now it is clear that monoaminergic neurotransmitters act in conjunction with neuropeptides and peripheral hormones to bring about physiological states such as hunger, satiation and satiety (5). Supporting this view, it has been recently shown that fenfluramine, a serotonergic drug, acts in the arcuate nucleus of the hypothalamus (the integrating center receiving information from the periphery) by stimulating a specific neuronal population, the pro-opiomelanocortin neurons (POMC), which is involved in mediating satiety (6).

The particular role of monoamines in the regulation of specific behavior such as food intake is probably related to their mechanism of synthesis, which is different from that of neuropeptides. In short-term regulation, monoamine synthesis is dependent on the availability of substrate and enzyme activity and less dependent on the gene level of expression. Thus, the monoaminergic system is able to adjust its own activity both to immediate needs and to long-term regulation, which includes the level of gene expression of their rate-limiting enzymes and pre- and postsynaptic receptors. The importance of serotonin in food intake regulation was demonstrated in mice lacking serotonergic receptors, which display food intake– and body weight–related abnormalities (7). Similarly, dopamine has been shown to be indispensable for feeding behavior, so that mice with a knockout tyrosine hydroxylase gene are aphagic (8), while their eating behavior can be restored by transfection of the tyrosine hydroxylase gene into the striatum (9).

The release of dopamine and serotonin in the LHA and VMN occurs during eating and the amount of dopamine release is proportional to meal size (10, 11). Since serotonin and dopamine are known to modulate the activity and gene expression of peptidergic neurons (12), it is likely that these monoamines can target feeding-related peptidergic neurons in the LHA and VMN to influence food intake. Finally, a number of studies have shown that serotonin release in the hypothalamus is enhanced during feeding to promote satiation (13), and reflects carbohydrate ingestion (14). The observation that food deprivation brings about an opposite direction of changes in dopamine and serotonin VMN concentrations points to the reciprocal roles in the relationship between dopamine and serotonin.

SEROTONIN AND EXPERIMENTAL OBESITY

Two main experimental models have been developed to reproduce obesity in animals: the leptin signaling–deficient model and the diet-induced obesity model.

The leptin signaling–deficient model

Leptin is a peptide which is mainly produced by adipocytes in proportion to body fat stores. It reaches the arcuate nucleus in the hypothalamus, where it activates the anorexigenic neuronal pathway (ie, the POMC neurons) while simultaneously inhibiting the prophagic neuronal pathway (ie, the NPY/AgRP neurons) (15). Then, via second-order neuronal pathways, the information brought by leptin, ie, an increase in body fat stores, triggers the behavioral response of stopping eating (15). In humans, obesity due to a point mutation of the leptin gene or of its receptor is rare, but clinical obesity is characterized by leptin resistance (16). Its pathogenesis includes neurochemical changes downstream of the neurons possessing leptin receptors affecting central regulation of food intake and body weight, via altered gene expression of neuropeptides.

The Zucker rat is a well-established model of obesity caused by leptin signaling deficiency, particularly due to a mutation of the leptin receptor. The feeding pattern of the obese Zucker rat versus its lean counterpart demonstrates a consistently larger meal size throughout the 24-hour light-dark cycle; thus, the obese Zucker rat consistently consumes more food than its lean counterpart (17). Hypothalamic monoaminergic activity has been reported to be different between lean and leptin-resistant obese Zucker rats (18, 19). Thus, it is conceivable that monoaminergic hypothalamic systems, together with the peptidergic system, contribute to the pathogenesis of leptin-resistant obesity.

To confirm this hypothesis, serotonin and dopamine concentrations in the VMN were studied in vivo using microdialysis, as they relate to eating after food deprivation in obese and lean Zucker rats (20). The data obtained suggest that in obese rats with altered leptin signaling the pattern of serotonin and dopamine release associated with food deprivation and refeeding is unaltered, but the levels of these neurotransmitters are lower than those observed in lean rats. This points to an impaired postsynaptic monoaminergic action to produce an adequate metabolic response in obese Zucker rats in response to feeding state.

To better understand these data, it must be considered that leptin rapidly modulates synaptic transmission in the hypothalamus (21), inhibiting dopamine and norepinephrine release from the neuronal endings (22). In the light of these reports, it could be reasoned that a decrease in leptin secretion during food deprivation (23) would stimulate dopamine release in the hypothalamus, while a transitory leptin increase during refeeding (24) would inhibit dopamine release. Such a pattern of dopamine release associated with food deprivation and refeeding has been described and suggests a functional link between leptin and dopamine in the VMN. However, this pattern was observed in both obese and lean rats, which implies that activation of monoamine release related to feeding status is unaltered in leptin-resistant obese Zucker rats. These observations point to the conclusion that monoamine release associated with food deprivation and refeeding is a leptin-independent phenomenon, or rather that obese Zucker rats are still able to respond to leptin changes via monoamine release. Indeed, obese Zucker rats do not show complete absence of leptin action in intracellular signal transduction, but only a reduction in this effect (25). Moreover, dopamine levels were found to be lower in obese than in lean rats, which can be due to the enhanced suppressive effect of leptin on dopamine release because of the hyperleptinemia in obese rats. However, food deprivation and refeeding bring about a suppression and increase, respectively, of dopamine release in the lateral hypothalamus in both obese and lean Zucker rats (26). This phenomenon can be explained as a secondary effect of leptin via the neurons of the arcuate nucleus and the VMN to stimulate dopamine release in the lateral hypothalamus.

The lower concentrations of serotonin found in obese versus lean Zucker rats is in agreement with previously reported low VMN serotonin concentrations (27). The opposite dynamics of serotonin and dopamine changes after food deprivation and refeeding suggests that serotonin release could be also related to leptin secretion. Hence, low leptin secretion during food deprivation can be associated with low serotonin release in the VMN (23). Moreover, a stimulatory effect of leptin on serotonin turnover has been reported, although indirectly via the inhibition of nitric oxide (28).

The consistent pattern of dopamine and serotonin changes in the VMN during food deprivation and refeeding indicates an involvement of these monoamines in the long-term regulation of metabolism associated with states of hunger and satiety. Most neurotransmitters relevant to the regulation of metabolism have an effect on both energy intake and expenditure (5). Thus, even though obese Zucker rats have a similar pattern of dopamine and serotonin change to lean rats during food deprivation and refeeding, it is possible that in obese rats the monoamines are unable to produce the same metabolic effect as in lean rats. Such impaired function of monoamines may include their altered func-

tion on a postsynaptic level, where they play a role as neuromodulators of food intake–related peptidergic motoneurons.

To further explore and support the role of hypothalamic serotonin and dopamine in the regulation of feeding pattern during obesity, dopaminergic and serotonergic neurons were grafted into the LHA of obese Zucker rats in order to create an experimental model of chronic physiological over-release of dopamine or serotonin in the LHA; the feeding pattern was studied before and after the transplant (29). Compared to the pregrafting period, a smaller increase in meal size occurred in both serotonin-grafted and dopamine-grafted rats versus control rats. There was also a smaller decrease in meal number in both serotonin-grafted and dopamine-grafted rats versus control animals. Although the changes in feeding pattern resulted in a decrease in total food intake in serotonin-grafted rats versus control rats, no differences in body weight gain were observed in grafted versus control rats for the duration of the study. The present data show that dopamine and serotonin in the LHA can also modulate the feeding pattern and hence can contribute to the formation of feeding patterns in the obese Zucker rat.

The ability of dopamine and serotonin to influence feeding pattern in the LHA can be explained by recently reported data that provided the putative neurochemical basis for food intake control. Two neuronal populations in the LHA expressing melanin-concentrating hormone (30) and hypocretin/orexin (31, 32) were discovered; both neuropeptides strongly stimulate food intake. Although so far there have been no studies exploring the relationships between the LHA monoaminergic system and the newly discovered peptidergic system, it is possible that they involve a single regulatory pathway influencing food intake and body weight control.

It has been demonstrated that an increase in food intake is not essential for the development of obesity in Zucker rats (33), indicating that this obesity is due to abnormal regulation of the metabolism and not to food intake *per se*. These data explain findings as to why a decrease in total food intake in serotonin-grafted rats did not affect body weight gain, and suggest that relatively small changes in LHA monoamine concentrations produced by the graft are sufficient to affect the feeding pattern controlling mechanism, but not to affect the body weight set-point.

Beside its role in influencing food intake, hypothalamic serotonin appears also to impact energy expenditure. In a recent report, Ohliger-Frerking et al studied dorsal raphe nucleus serotonergic neurons, projecting to the VMN to influence feeding (34). They showed that the neurons from obese Zucker rats exhibited a larger depolarization and increased firing rate in response to phenylephrine than did cells from lean rats, thus suggesting that dorsal raphe nucleus serotonergic neurons of obese rats have an enhanced adrenergic drive. Furthermore, serotonin, acting through 5-HT$_{1B/2C}$ receptors, reduces food intake and augments sympathetic activity, thus promoting weight loss (35).

From these data obtained in the leptin signaling–deficient model, we can conclude that hypothalamic serotonin and dopamine are involved in the modulation of feeding pattern in lean rats, while the alterations in their baseline levels and in response to feeding may be responsible for the altered feeding pattern of obese rats. Considering that serotonin influences energy expenditure via the sympathetic nervous system, it can be concluded that hypothalamic serotonin and dopamine contribute to the pathogenesis of obesity. However, it is not yet clear whether the alterations in monoaminergic neurotransmission are primary in nature or secondary to changes in the diet. An answer to this question may result from studies in the diet-induced obesity model.

The diet-induced model of obesity

When Sprague-Dawley rats are placed on a diet relatively high in fat and calories, approximately half develop diet-induced obesity (DIO) while the rest are diet-resistant. When fed a low-fat diet from weaning, DIO- and diet-resistant–prone rats weigh the same, but DIO-prone rats have a number of abnormalities of neural function, many of which are normalized when they become obese after chronic exposure to a high-fat diet. In the effort to better explore these neurochemical alterations, Hassanain and Levin recently reported that DIO-prone rats show abnormalities of diurnal and fasting-induced alterations in brain serotonin turnover which may predispose them to becoming obese when dietary fat and caloric density are increased (36). Once obesity develops, these abnormalities, like those of several other hypothalamic neurotransmitters and peptides, are normalized. This may contribute to the persistence of obesity once it develops.

One of the major contributions of the DIO model to the understanding of the mechanisms regulating food intake in obese rats is the demonstration that changes in diet modulate gene expression. In a recent study, Schaffauser et al. studied rats fed a low- or a high-fat diet for 14 days (37). Then, the mRNA for 5-HT$_{2C}$ receptor and NPY receptor was measured. The results showed that serotonin receptor expression was reduced, while NPY mRNA was increased. These data indicate that dietary fat may modulate serotonergic activity by influencing the expression of serotonin receptor genes, and thus pos-

sibly contributing to DIO. However, this change is accompanied by profound changes in the expression of other hypothalamic genes involved in food intake, and it is not yet clear whether these changes are concomitant or one is brought about by the other.

The data obtained in the DIO model point to a critical role of genetic background in determining the occurrence of obesity. In particular, it appears that changes in the composition of the diet may largely influence hypothalamic neurotransmission (both aminergic and peptidergic) via changes in gene expression in prone animals, thus leading to a positive energy balance.

SEROTONIN AND CLINICAL OBESITY

As outlined in the previous sections, a number of experimental studies have consistently indicated that, in leptin-resistant obesity, abnormal hypothalamic dopamine and serotonin activities contribute to hyperphagia and body-weight gain, and modulation of hypothalamic dopamine and serotonin levels may result in reduced food intake and weight loss. Also, it appears that abnormalities of the brain serotonergic system are involved in mediating the onset of diet-induced obesity. When considered together, these data suggest that brain neurotransmission may represent a common step on which different appetite-related messengers converge. More simplistically, it can be hypothesized that most of the abnormality existing in the cascade of signaling pathways of the obese rat results in a disturbed hypothalamic monoaminergic neurotransmission.

Translating this evidence into human obesity, it might be speculated that abnormalities of brain serotonin function are involved in the pathogenesis of clinical obesity. However, human obesity is a multifactorial disease, so it is unlikely that serotonin could represent the only factor involved in its pathogenesis, unless null mutations of specific genes involved in serotonin activity and metabolism occur. Rather, it is likely that polymorphisms of specific serotonin-related genes may confer, or contribute to confer, the susceptibility to develop obesity in the presence of favoring environmental factors. From the clinician's perspective, this hypothesis might yield interesting results in an attempt to develop effective therapeutic approaches to disturbed eating behavior. Specifically, the inhibitory effect on food intake of hypothalamic serotonin may be exploited to reduce food intake and achieve weight loss in hyperphagic obese patients (38). We recognize that serotonergic agents have been used in the treatment of hyperphagia, but it must be emphasized that their side effects may limit their use (39).

A more physiological and safer approach may be based on the distinct characteristics of the enzymatic pathways transforming the amino acid tryptophan into serotonin. Tryptophan is readily transformed into serotonin, whose concentrations do not limit the enzyme activity; consequently, the more tryptophan that reaches the brain, the more serotonin is produced (40). Thus, by providing the brain with pharmacological doses of the precursor tryptophan, more serotonin should be produced, also within the hypothalamus; consequently, reduced food intake and body-weight loss should be achieved. To test this hypothesis, we used the direct precursor of serotonin, 5-hydroxy-tryptophan. In a series of clinical, placebo-controlled, double-blind studies, we consistently demonstrated that the oral administration of 5-hydroxy-tryptophan at a dose ranging from 750 to 900 mg/day reduces food intake in dietary-unrestricted obese patients (41), enhances the adherence to a hypocaloric dietary regimen (42), and reduces carbohydrate craving in non-insulin-dependent diabetic patients (43), supporting the proposed role of brain serotonin in determining macronutrient selection (38). The clinical relevance of brain-neurotransmission modulation is also emphasized by the promising results obtained in the opposite clinical syndrome, ie, anorexia associated with tumor growth. In this setting, preliminary data have indicated that the reduction of the supply of tryptophan to the brain achieved by the manipulation of the plasma amino-acid profile is associated with increased food intake (44). In our opinion, these data support the hypothesis that brain monoaminergic neurotransmission may represent a common step on which different appetite-related messengers converge.

CONCLUSION

A tight control of energy homeostasis is critical in maintaining adequate nutritional status and body composition over time. To this end, a complex regulatory system evolved based on the interaction between peripheral factors, informing the brain about the metabolic status of peripheral tissues, and hypothalamic integrating areas, which elicit the appropriate behavioral response. Among the hypothalamic circuitries, the monoaminergic system, and particularly the serotonin system, appear to play a critical role in influencing not only food intake but energy expenditure as well. In this context, the contribution of brain serotonin to hyperphagia and obesity, as well as disease-related anorexia, has been investigated in animal models. The results obtained demonstrate that abnormalities of the serotonergic system may contribute to the development of hyperphagia and obesity.

This experimental evidence suggests that brain serotonin could be involved in human obesity by favoring the accumulation of adipose tissue via yet to be determined polymorphisms of serotonin-related genes, which disturb the physiological anorexigenic effects of this neurotransmitter.

Address for correspondence:
Dr. Alessandro Laviano
Department of Clinical Medicine
University La Sapienza
Viale dell'Università, 37
00185 Rome, Italy
e-mail: alessandro.laviano@uniroma1.it

REFERENCES

1. Meguid MM, Laviano A, Rossi Fanelli F. Food intake equals meal size times mean number. Appetite 1998; 31: 404.
2. Becker EE, Kissileff HR. Inhibitory controls of feeding by the ventromedial hypothalamus. Am J Physiol 1974; 226: 383-96.
3. Meguid MM, Yang Z-J, Gleason JR. The gut-brain brain-gut axis in anorexia: toward an understanding of food intake regulation. Nutrition 1996; 12: S57-62.
4. Meguid MM, Fetissov SO, Varma M, et al. Hypothalamic dopamine and serotonin in the regulation of food intake. Nutrition 2000; 16: 843-57.
5. Havel PJ, Larsen PJ, Cameron JL. Control of Food Intake. In Neuroendocrinology in Physiology and Medicine; Conn PM, Freeman ME, Eds.; Humana Press: Totowa, NJ, 1999; pp. 335-52.
6. Heisler LK, Cowley MA, Tecott LH, et al. Activation of central melanocortin pathways by fenfluramine. Science 2002; 297: 609-11.
7. Nonogaki K, Strack AM, Dallman MF, Tecott LH. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene. Nature Med 1998; 4: 1152-6.
8. Zhou Q-Y, Palmiter RD. Dopamine-deficient mice are severely hypoactive, adipsic, and aphagic. Cell 1995; 83: 1197-209.
9. Szczypka MS, Mandel RJ, Donahue BA, Snyder RO, Leff, SE, Palmiter, RD. Viral gene delivery selectively restores feeding and prevents lethality of dopamine-deficient mice. Neuron 1999; 22: 167-78.
10. Meguid MM, Yang Z-J, Koseki M. Eating induced rise in LHA-dopamine correlates with meal size in normal and bulbectomized rats. Brain Res Bull 1995; 36: 487-90.
11. Meguid MM, Yang Z-J, Laviano A. Meal size and number: relationship to dopamine levels in the ventromedial hypothalamic nucleus. Am J Physiol 1997; 272: R1925-R1930.
12. Smialowska M, Baikowska M, Heilig M, et al. Pharmacological studies on the monoaminergic influence on the synthesis and expression of neuropeptide Y and cortico-tropin releasing factor in rat brain amygdala. Neuropeptides 2001; 35: 82-91.
13. Schwartz DH, Hernandez L, Hoebel BG. Serotonin release in lateral and medial hypothalamus during feeding and its anticipation. Brain Res Bull 1990; 25: 797-802.
14. Rouch C, Nicolaidis S, Orosco M. Determination, using microdialysis, of hypothalamic serotonin variations in response to different macronutrients. Physiol Behav 1999; 65: 653-7.
15. Schwartz MW, Woods SC, Porte D Jr, et al. Central nervous system control of food intake. Nature 2000; 404: 661-71.
16. Esler M, Rumantir M, Wiesner G, et al. Sympathetic nervous system and insulin resistance: from obesity to diabetes. Am J Hypertens 2001; 14: 304S-309S.
17. McLaughlin CL, Baile CA. Ontogeny of feeding behavior in the Zucker obese rat. Physiol Behav 1981; 26: 607-12.
18. Levin BE, Sullivan AC. Catecholamine levels in discrete brain nuclei of seven month old genetically obese rats. Pharmacol Biochem Behav 1979; 11: 77-82.
19. Orosco M, Trouvin JH, Cohen Y, Jaquot C. Ontogeny of brain monoamines in lean and obese female Zucker rats. Physiol Behav 1986; 36: 853-6.
20. Meguid MM, Fetissov SO, Blaha V, Yang Z-J. Dopamine and serotonin VMN release is related to feeding status in obese and lean Zucker rats. NeuroReport 2000; 11: 2069-72.
21. Glaum SR, Hara M, Bindokas VP, et al. Leptin, the obese gene product, rapidly modulates synaptic transmission in the hypothalamus. Mol Pharm 1996; 50: 230-5.
22. Brunetti L, Michelotto B, Orlando G, Vacca M. Leptin inhibits norepinephrine and dopamine release from rat hypothalamic neuronal endings. Eur J Pharmacol 1999; 372: 237-40.
23. Trayhurn P, Thomas ME, Duncan JS, Rayner DV. Effects of fasting and refeeding on ob gene expression in white adipose tissue of lean and obese (oblob) mice. FEBS Lett. 1995; 368: 488-90.
24. Saladin R, De Vos P, Guerre-Millo M, et al. Transient increase in obese gene expression after food intake or insulin administration. Nature 1995; 377: 527-9.

25. Yamashita T, Murakami T, Iida M, et al. Leptin receptor of Zucker fatty rat performs reduced signal transduction. Diabetes 1997; 46: 1077-80.

26. Yang Z-J, Meguid MM. LHA dopaminergic activity in obese and lean Zucker rats. NeuroReport 1995; 6: 1191-4.

27. Routh VH, Stern JS, Horwitz BA. Serotonergic activity is depressed in the ventromedial hypothalamic nucleus of 12-day-old obese Zucker rats. Am J Physiol 1994; 267: R712-R719.

28. Calapai G, Corica F, Corsonello A, et al. Leptin increases serotonin turnover by inhibition of brain nitric oxide synthesis. J Clin Invest 1999; 104: 975-82.

29. Meguid MM, Fetissov SO, Miyata G, Torelli GF. Feeding pattern in obese Zucker rats after dopaminergic and serotonergic LHA grafts. NeuroReport 1999; 10: 1049-53.

30. Qu D, Ludwig DS, Gammeltoft S, et al. A role for melanin-concentrating hormone in the central regulation of feeding behaviour. Nature 1996; 380: 243-7.

31. de Lecea L, Kiduff TS, Payron C, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA 1998; 95: 322-7.

32. Sakurai T, Amemiya A, Ishii M, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 1998; 92: 573-85.

33. Cleary MP, Vasseli JR, Greenwood MRC. Development of obesity in Zucker obese (fafa) rat in absence of hyperphagia. Am J Physiol 1980; 238: E284-E292.

34. Ohliger-Frerking, P, Horowitz JM, Horwitz BA. Enhanced adrenergic excitation of serotonergic dorsal raphe neurons in genetically obese rats. Neurosci Lett 2002; 332: 107-10.

35. Bray, G.A. Reciprocal relation of food intake and sympathetic activity: experimental observations and clinical implications. Int J Obes Relat Metab Disord 2000; 24 (Suppl. 2): S8-S17.

36. Hassanain M, Levin BE. Dysregulation of hypothalamic serotonin turnover in diet-induced obese rats. Brain Res 2002; 929: 175-80.

37. Schaffhauser A, Madiche AM, Braymer HD, Bray GA, York DA. Effects of a high-fat diet and strain on hypothalamic gene expression in rats. Obes Res 2002; 10: 1188-96.

38. Liebowitz SF. The role of serotonin in eating disorders. Drugs 1990; 39 (Suppl. 3): 33-48.

39. Jung RT. Animal models of obesity. In Clinical Obesity; Kopelman PG, Stock MJ, Eds.; Blackwell Science: London, 1998; pp. 469-80.

40. Tagliamonte A, Bigio G, Vargiu L, Gessa GL. Free tryptophan in serum controls brain tryptophan level and serotonin synthesis. Life Sci 1973; 12: 277-87.

41. Ceci F, Cangiano C, Cairella M, et al. The effects of oral 5-hydroxytryptophan administration on feeding behavior in obese adult female subjects. J Neural Transm 1989; 76: 109-17.

42. Cangiano C, Ceci F, Cascino A, et al. Eating behavior and adherence to dietary prescriptions in obese adult subjects treated with 5-hydroxytryptophan. Am J Clin Nutr 1992; 56: 863-7.

43. Cangiano C, Laviano A, Del Ben M, et al. Effects of oral 5-hydroxy-tryptophan on energy intake and macronutrient selection in non-insulin dependent diabetic patients. Int J Obes Relat Metab Disord 1998; 22: 648-54.

44. Cangiano C, Laviano A, Meguid MM, et al. Effects of administration of oral branched-chain amino acids on anorexia and caloric intake in cancer patients. J Natl Cancer Inst 1996; 88: 550-2.