Serotonin and Obesity

A. Laviano[1] and M.M. Meguid[2,*]

[1]*Department of Clinical Medicine, University La Sapienza, Rome, Italy,* [2]*Department of Surgery, SUNY Upstate Medical University, Syracuse, NY 13210, USA*

Abstract: Human obesity represents a major threat to global well-being, and a better understanding of its pathogenic mechanisms may lead to the development of effective therapeutic strategies. In this article, we will review the existing literature dealing with the role of serotonin in the pathogenesis of obesity. Using a number of models, we demonstrate that abnormal hypothalamic serotonergic neurotransmission and/or deranged receptor expression/sensitivity exists, and that these are closely associated with changes in the concentrations of dopamine, another hypothalamic monoamine closely involved in the regulation of food intake. However, it is still difficult to ascertain whether these abnormalities are acquired in response to chronic overingestion resulting in obesity, which then drives further increases in food intake to preserve the status quo, or whether these are due to primary factors. The pivotal role of central serotonin in obesity is also strengthened by the evidence that the drugs licensed to interfere with food intake in obese patients involve the serotonergic system. But since their use, including sibutramine, may lead to potentially severe side effects, alternative strategy to increase hypothalamic serotonergic activity is also proposed.

Keywords: Serotonin, dopamine, obesity, hypothalamus, VMN, LHA, monoamines, food intake, leptin, diet-induced obesity

INTRODUCTION

Although obesity is not considered a disease *per se*, it represents a major threat to global well being because it predisposes the patient to the development of chronic diseases, including diabetes, coronary heart disease and certain types of cancers, thereby increasing morbidity and mortality [1]. Also, the rising prevalence of obesity worldwide has financial consequences, since it increases the costs of national healthcare systems, placing burdens on weak national economies, and resulting in weak economic growth and shrinking public funds. Thus, obesity *per se* is a significant clinical and also political issue. Finally, on pure scientific ground, it also represents an interesting model to investigate abnormalities of physiological mechanisms regulating food intake.

Human obesity represents a combination of several factors, including genetic and environmental, as well as social and cultural aspects (Fig. **1**). To this we can now also add business aspects, all of which can subtly influence an increase in food intake. An example is US Agribusiness: it currently produces 3,800 calories of food per day for every American. This is 500 calories more than was produced 30 years ago and at least 1,500 calories per day more than the average American needs. The food companies thus persuade each American to eat more, simply by increasing the size of the average meal. When chronically repeated, this elevates the body weight "set point", with a resultant increase of appetite, to vigorously defend the elevated body weight set point [2]. Thus the cost of food to the individual in the US, is much greater than inexpensive food. Ultimately it becomes the cost of obesity.

The general understanding of the pathogenesis of obesity gives priority to the resulting abnormal metabolism to fulfill metabolic needs for building and maintaining fat depot and confers only a secondary role to the control of appetite. However, mechanisms of increased appetite deserve special attention, because by better understanding the central neuronal neurochemistry involved in the regulation of overeating, and its relation to the sympathetic and parasympathetic systems, the hypothalamic-neuro-adrenal axis, as well as to peripheral organs, such as the gut, the endocrine and adipose tissue, it may be possible to interfere pharmacologically to reduce appetite and food intake, and alleviate obesity.

A simplistic view of food intake regulation is that ingested nutrients are sensed at different levels of the GI tract, including the liver. This information, together with that arising from adipose tissue, is transmitted to the brain via a series of routes (neuronal input, hormones and peptides), and is integrated in the hypothalamus, where the appropriate behavioral response is triggered (Fig. **2**). The picture is far more complex, because the hypothalamus consists of different areas and concentrations of nuclei. Within each, there exists connections to sets of effectors, consisting of neurotransmitters, neuromodulatory peptides and transmembrane proteins [3].

MONOAMINE AND THE CONTROL OF FOOD INTAKE

In an effort to crack the riddle of food intake control, it is useful to base investigations on a simple formula reflecting

*Address correspondence to this author at the Department of Surgery, University Hospital, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, USA; Tel: (315) 464-6277; Fax: (315) 464-6237; E-mail: meguidm@upstate.edu

1568-0150/03 $41.00+.00

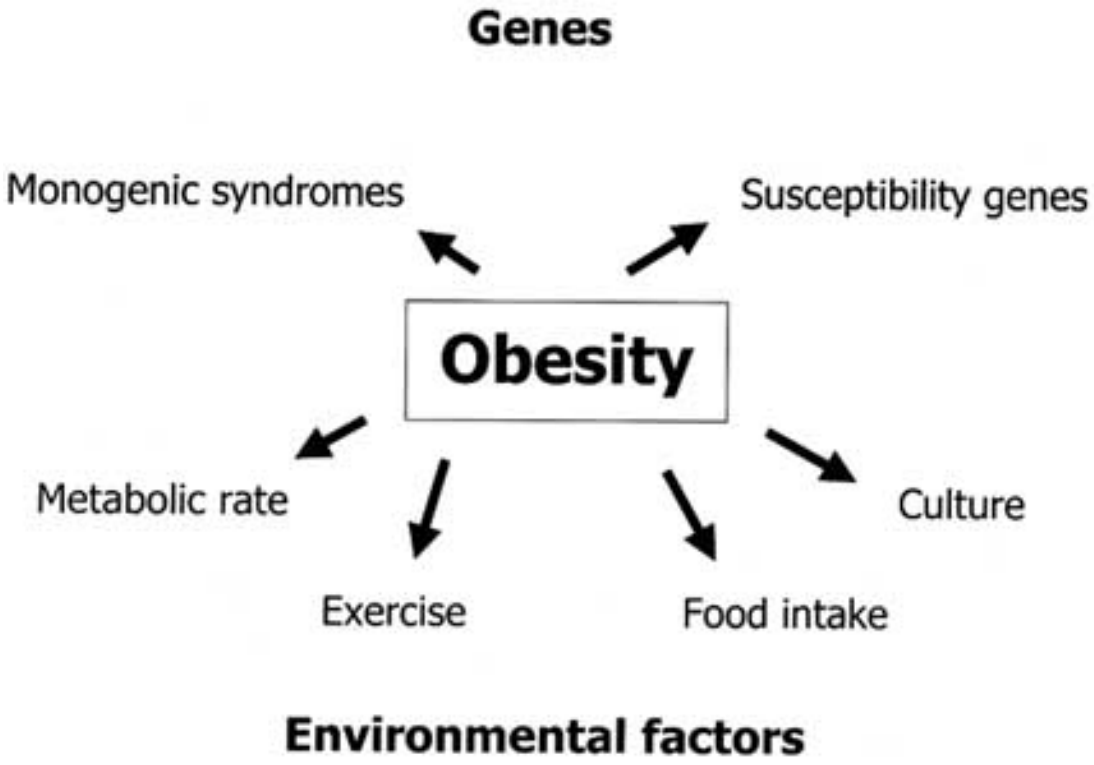

Fig. (1). Genetic and environmental determinants of obesity in humans

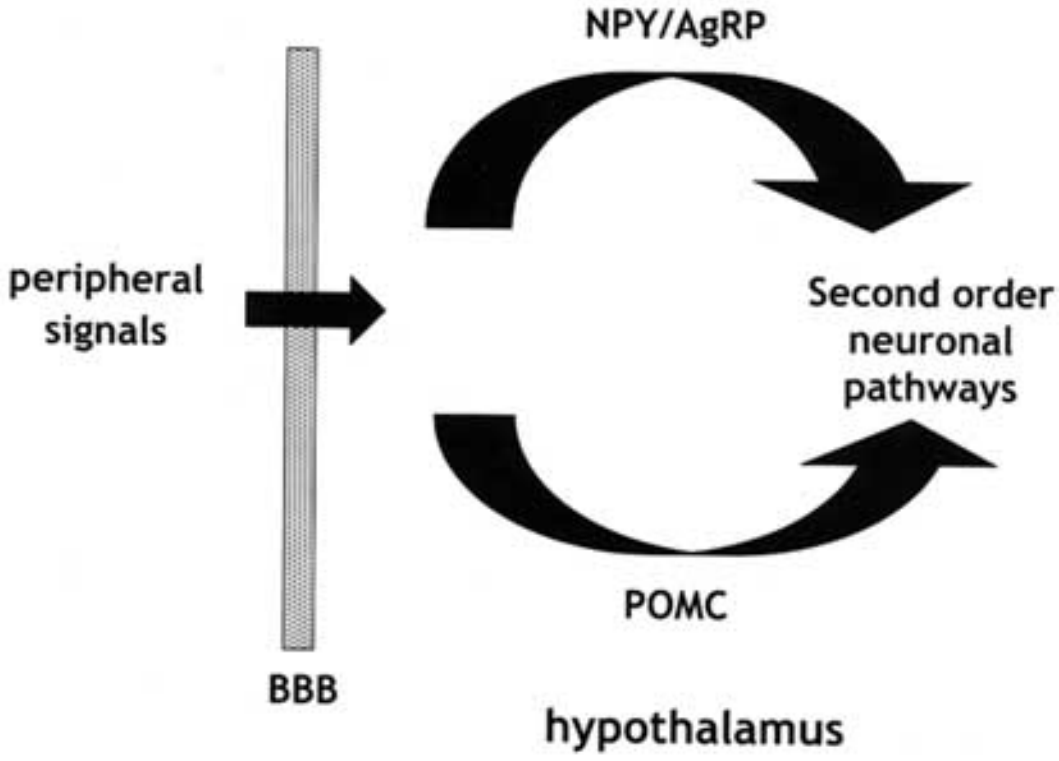

Fig. (2). Schematic view of the central mechanisms regulating food intake. NPY: neuropeptide Y; AgRP: agouti-related peptide; POMC: pro-opiomelanocortin; BBB: blood-brain barrier

integrative behavior of spontaneous food intake. Thus: food intake = meal number x meal size [4]. Under normal circumstances, counterbalancing controls for each feeding index exist, such that a change in one produces a compensatory change in the other, to preserve the relative consistency of daily food intake [5]. The reciprocal relationship between meal number and meal size, that maintains homeostasis of food intake under normal conditions, is disrupted under several different experimental conditions (for review see ref. 6). To function as a complementary system, it is likely that under normal and stable metabolic conditions, meal size (reflecting short-term food intake control) and meal number (reflecting long-term food intake control) are independently regulated in a way analogous to the reciprocal innervation controlling spinal reflexes. This suggests that different but connected anatomical sites in the hypothalamus regulate them. Among other hypothalamic areas, the lateral hypothalamic area (LHA; representing the parasympathetic system) and the ventromedial nucleus of the hypothalamus (VMN; representing the sympathetic system) are known to be anatomically linked [6]. Also, functional reciprocity between LHA and VMN has been established in a number of studies. Finally, serotonin and dopamine receptors are widely distributed within the hypothalamus [7, 8], and are recognized as two neurotransmitters whose role in food intake control is well established. They exert their action via different areas of the hypothalamus, including the VMN and LHA [9].

We have shown that intra-LHA and intra-VMN changes in neurotransmitter concentrations are related to the relationship between meal size and meal number [9]. Thus, we hypothesized that interaction between LHA and VMN and between the two neurotransmitters, dopamine and serotonin (and not any one single neurotransmitter), significantly influence food intake control in health and disease by their effect on meal size and meal number, probably via modulation of gastrointestinal function and motility [9].

Serotonin, as well as dopamine, is a monoamine acting as neurotransmitter and 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 [10]. Supporting this view, it has been recently shown that fenfluramine, a serotonergic drug, acts in the arcuate nucleus of 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 [11].

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 neuropeptides. In short-term regulation, monoamine synthesis is dependent on the availability of substrate and enzyme activity. 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 post-synaptic 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, manifested as chronic hyperphagia [12]. Similarly, dopamine has been shown to be indispensable for feeding behavior, so that mice with knockout tyrosine hydroxylase gene are aphagic [13]. Their eating behavior can be restored by the transfection of the tyrosine hydroxylase gene into the striatum [14].

The release of dopamine and serotonin in the LHA and VMN occurs during eating [15] and the amount of dopamine release is proportional to meal size [15, 16]. Since serotonin and dopamine are known to modulate activity and gene expression of peptidergic neurons [17], these monoamines can target feeding-related peptidergic neurons in the LHA and VMN to influence food intake (Fig. **3**). Finally, a number of studies showed that serotonin release in the hypothalamus is enhanced during feeding to promote satiation [18], and reflects carbohydrate ingestion [19]. The observation that food deprivation brings about an opposite direction of changes in dopamine and serotonin VMN concentration 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.

I - The Leptin Signaling Deficient Model

Leptin is a peptide that 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 (i.e., the POMC neurons) while simultaneously inhibiting the pro-phagic neuronal pathway (i.e., the NPY/AgRP neurons)[3]. Then, via second order neuronal pathways, the information brought by leptin, i.e., an increase in body fat stores, triggers the behavioral response to stop eating [3]. 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 [20]. Its pathogenesis includes neurochemical changes downstream to the neurons possessing leptin receptors affecting central regulation of food intake and body weight, via altering gene expression of neuropeptides.

The Zucker rat is a well-established model of obesity due to leptin signaling deficiency, particularly 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-h light-dark cycle; thus, the obese Zucker rat consistently consumes more food than its

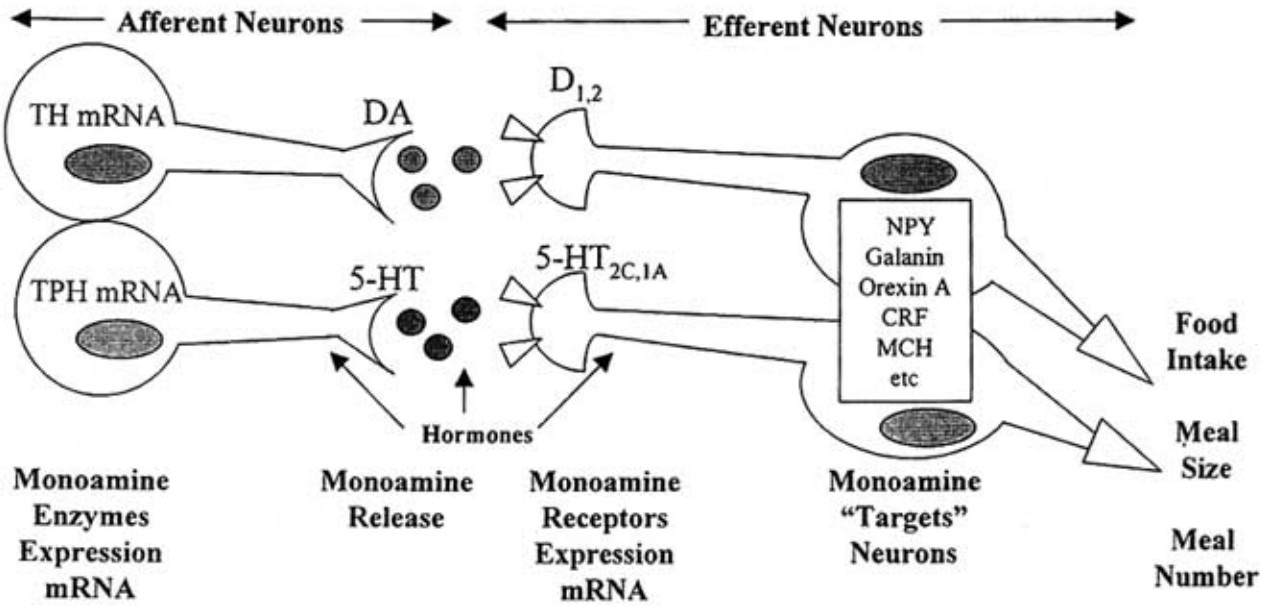

Fig. (3). Scheme showing an afferent-efferent neurotransmitter unit (from ref. 9). Serotonin and dopamine synthesis is influenced by the availability of their precursors and the expression of the synthesizing enzymes.In the hypothalamus, dopamine and serotonin influence the activity of peptidergic neurons, which in turn control food intake, by modulating meal number and meal size. Food intake regulating hormones, i.e., leptin, modulate monoamine release and the sensitivity of post-synaptic receptor, thus interefering with food intake. Serotonin also influences body weight by controlling transcription factors critical in body weight regulation.

TH: tyrosine hydroxylase; TPH: tryptophan hydroxylase; DA: dopamine; 5-HT: serotonin; $D_{1,2}$: dopamine receptors type 1 and 2; 5-$HT_{2C,1A}$: serotonin receptors type 2C and 1A

lean counterpart [21](Fig. **4**). Hypothalamic monoaminergic activity has been reported to be different between lean and leptin-resistant obese Zucker rats [22, 23]. Thus, it is conceivable that monoaminergic hypothalamic systems, together with the peptidergic system, contribute to the pathogenesis of leptin-resistant obesity.

To support this view, 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 [24]. Before food was provided, mean baseline serotonin and dopamine levels in obese rats were lower than in lean rats. Food intake was accompanied by a similar decrease in dopamine in both obese and lean rats. Serotonin levels were increased to the same degree during eating in obese and lean rats. Thus, in obese rats with altered leptin signaling the pattern of serotonin and dopamine release associated with food deprivation and refeeding is unaltered, but with presence of their low levels. 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 [25], inhibiting dopamine and norepinephrine release from the synapses [26]. In the light of these reports, we reason that a decrease of leptin secretion during food deprivation [27], would stimulate dopamine release in the hypothalamus, while a transitory leptin increase during refeeding [28] would inhibit dopamine release. Such a pattern of dopamine release (i.e., increase with food deprivation and refeeding) was found in our work and suggests a functional link between leptín 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 transductíon, but only a reduction in this effect [29]. 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, previously we found that in the lateral hypothalamus, food deprivation and refeeding bring about a suppression and increase, respectively, of dopamine release in both obese and lean Zucker rats [30]. 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 Zucker rats as compared with lean Zuckers is in agreement with previously reported low VMN serotonin concentration [31]. The opposite in dynamics of serotonin and dopamine

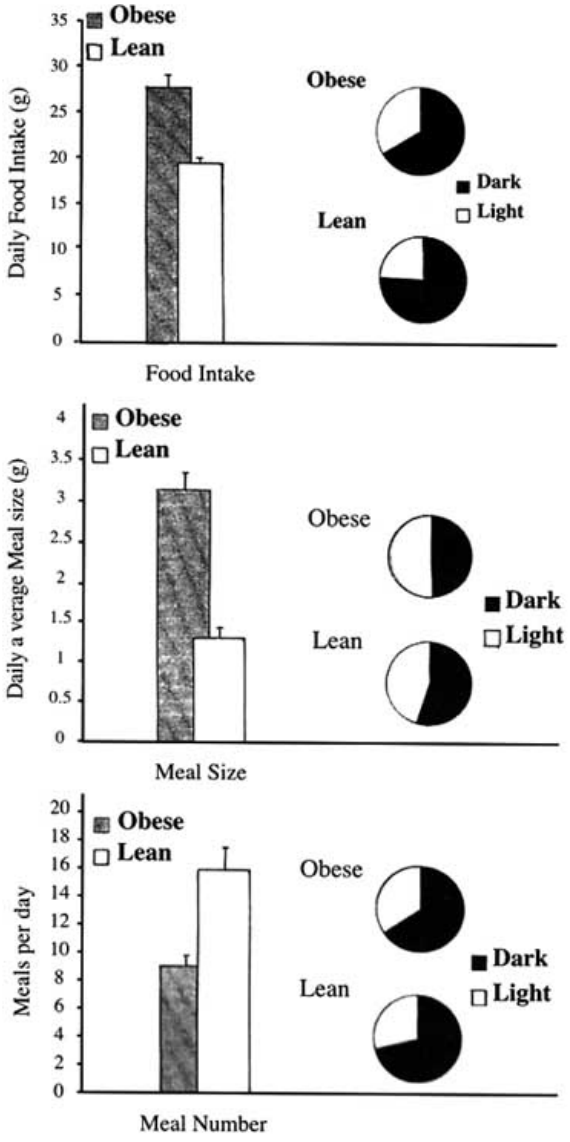

Fig. (4). Comparison of food intake, meal size, and meal number between lean and obese Zucker rats (from ref. 9)

changes after food deprivation and refeeding suggest that serotonin release could be also related to leptin secretion. Hence, low leptin secretion during food deprivation [27] can be associated with low serotonin release in the VMN. Moreover, a stimulatory effect of leptin on serotonin turnover has been reported, although indirectly via the inhibition of nitric oxide [32].

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 [10]. 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 an impaired function of monoamines may include their altered function on a postsynaptic level, where they play a role as neuromodulators of food intake related peptidergic motoneurons.

Since obese Zucker rats consume larger meals than controls and LHA dopamine levels are related to meal size, we investigated LHA dopaminergic activity using in-vivo microdialysis [30]. Studying the male Zucker rat, data showed that basal dopamine level was significantly higher in obese than in lean rats, and dopamine release during eating was greater in obese than in lean rats [30]. Thus, it appears that LHA in obese Zucker rats is set at a higher dopamine "threshold" level when compared with lean controls, and that larger meals are needed to reach that level and thus stop eating. If this thesis holds true, by "flooding" the LHA of obese Zucker rats with exogenous dopamine, the obese Zucker rats should eat smaller meals and thus reduce its food intake. We therefore tested this intriguing therapeutic strategy, potentially exploitable in humans, by continuously and bilaterally infusing dopamine for 13 days into the LHA of obese Zucker rats, using two osmotic mini-pumps [33]. We observed that intra-LHA dopamine infusion significantly depresses food intake, in agreement with data showing decreased food intake after acute injection of dopamine into the LHA [34]. This was solely caused by a significant and profound reduction in meal size. Interestingly, there was a compensatory rise in meal number that gradually increased food intake so that it eventually reached control level. However, the resulting feeding pattern did not normalize until dopamine infusion ceased. These data are consistent with our hypothesis that LHA-dopamine reflects and influences meal size, and further demonstrate that meal size and meal number are regulated in a reciprocal manner to compensate for each other, even when grossly manipulated by pharmacological agents.

To further explore and support the role of hypothalamic serotonin and dopamine in the regulation of feeding pattern during obesity, we grafted dopaminergic and serotonergic neurons into the LHA of obese Zucker rats. Our aim was to create an experimental model of chronic physiological over-release of dopamine or serotonin in the LHA, while studying feeding pattern before and after the transplant [35]. Compared to the pregrafting period, a smaller increase in meal size occurred in both serotonin-grafted and dopamine-grafted rats vs control rats (Fig. **5**). There was also a smaller decrease in meal number in both serotonin-grafted and dopamine-grafted rats vs control animals (Fig. **5**). Although the changes in feeding pattern resulted in a decrease in total food intake in serotonin-grafted rats vs control rats, no differences in body weight gain were observed in grafted vs control rats for the duration of the study.

Of particular interest in this study is the change in the dynamics of feeding pattern occurring in LHA-grafted rats [35]. Both dopamine and serotonin grafts reduced the increase of meal size by 20% and 42% respectively; both grafts stimulated an increase of meal number by 5% and 25%

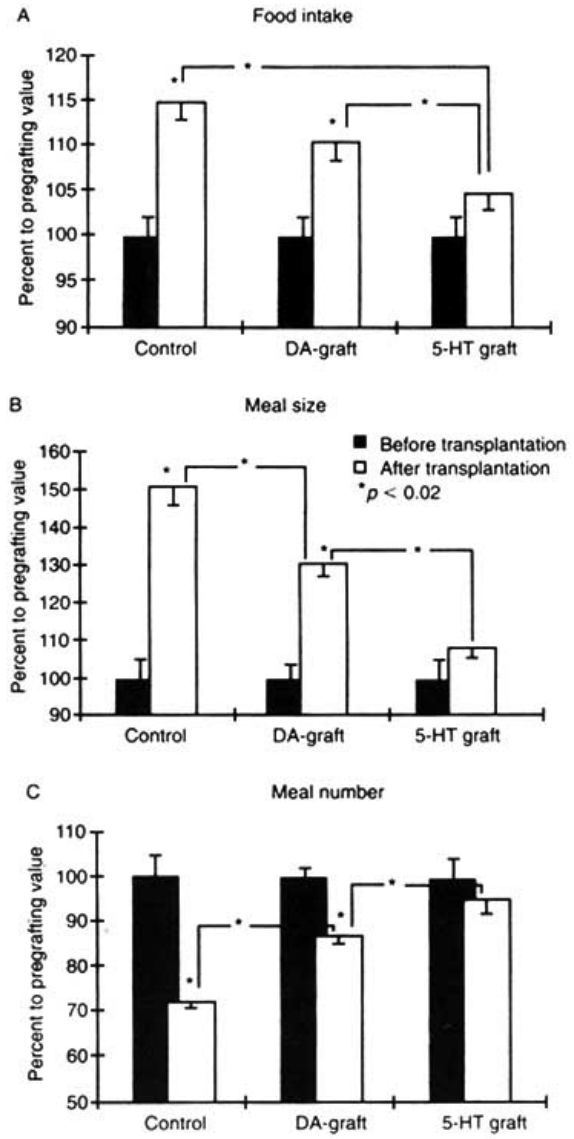

Fig. (5). Feeding pattern in control rats and in obese Zucker rats grafted with dopaminergic or serotonergic neurons in the LHA. (A): total daily food intake; (B): meal size; (C): meal number (from ref. 35)

vs control, respectively, which appeared to be compensatory for the decreased meal size. It was reported that concentrations of monoamines in the hypothalamus of obese Zucker rats are different from that of lean littermates [22, 23]. Moreover, meal ingestion in obese Zucker rats is accompanied by a greater increase of dopamine in the LHA compared with lean Zucker rats [30]. The changes in feeding pattern with age in the Zucker rat are accompanied by changes in the dynamics of dopamine and serotonin concentrations in the paraventricular nucleus of the hypothalamus (PVN) as they relate to meal ingestion [36]. These findings suggest that hypothalamic dopamine and serotonin reflect changes in the feeding pattern during obesity. These data suggest that dopamine and serotonin in the LHA can also modulate feeding pattern and hence can contribute in the formation of feeding patterns in the obese Zucker rat. Our data are in agreement with previously reported suppressive effects of pharmacological doses of dopamine on food intake and meal size after its administration into the LHA [33, 34] and the suppressive effect of serotonin on food intake after its injection into the medial hypothalamus [37].

The role of LHA dopamine in the regulation of feeding pattern can be related to meal size because a proportional increase between dopamine concentration in the LHA and its decrease in the VMN in relation to meal size has been shown in the Fischer rat [9]. In a related experiment, we found that LHA nicotine administration inhibits both meal size and number in rats and stimulates an increase of dopamine and serotonin in the LHA, suggesting that serotonin can also be involved in the regulation of feeding pattern [38] (Fig. **6** and Fig. **7**).

The pathway by which LHA dopamine and serotonin influence feeding pattern can be explained by recently reported data, which provided the putative neurochemical basis for food intake control. Two neuronal populations in the LHA, which express melanin-concentrating hormone [39] and hypocretin/orexin [40, 41], were discovered; both neuropeptides strongly stimulate food intake. Although so far there are no data exploring the relationships between LHA monoaminergic and the newly discovered peptidergic systems, it is possible that they involve a single regulatory pathway as it relates to food intake and body weight control.

It has been demonstrated that an increase of food intake is not essential for the development of obesity in Zucker rats [42], indicating that this obesity is due to abnormal regulation of metabolism and not to food intake *per se.* These data explain our findings as to why a decrease of total food intake in serotonin-grafted rats did not affect body weight gain. These data further suggest that relatively small changes in LHA monoamine concentrations produced by the graft is sufficient to affect the feeding pattern controlling mechanism, but is not sufficient to affect the body weight set-point. Particularly interesting is the observation that axons of dopaminergic neurons of the graft grew in the direction of the supraoptic nucleus [35]. This observation reinforced our postulate that magnocellular neurons of the supraoptic nucleus, and probably of the PVN, are also involved in the regulation of feeding pattern via catecholaminergic inputs; although the hierarchical function is in need of study.

Beside its role in influencing food intake, hypothalamic serotonin appears to impact also energy expenditure. In a recent report, Ohliger-Frerking *et al.* studied dorsal raphe nucleus serotonergic neurons, projecting to the VMN to influence feeding [43]. They showed that the neurons from obese Zucker rats exhibit both 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-

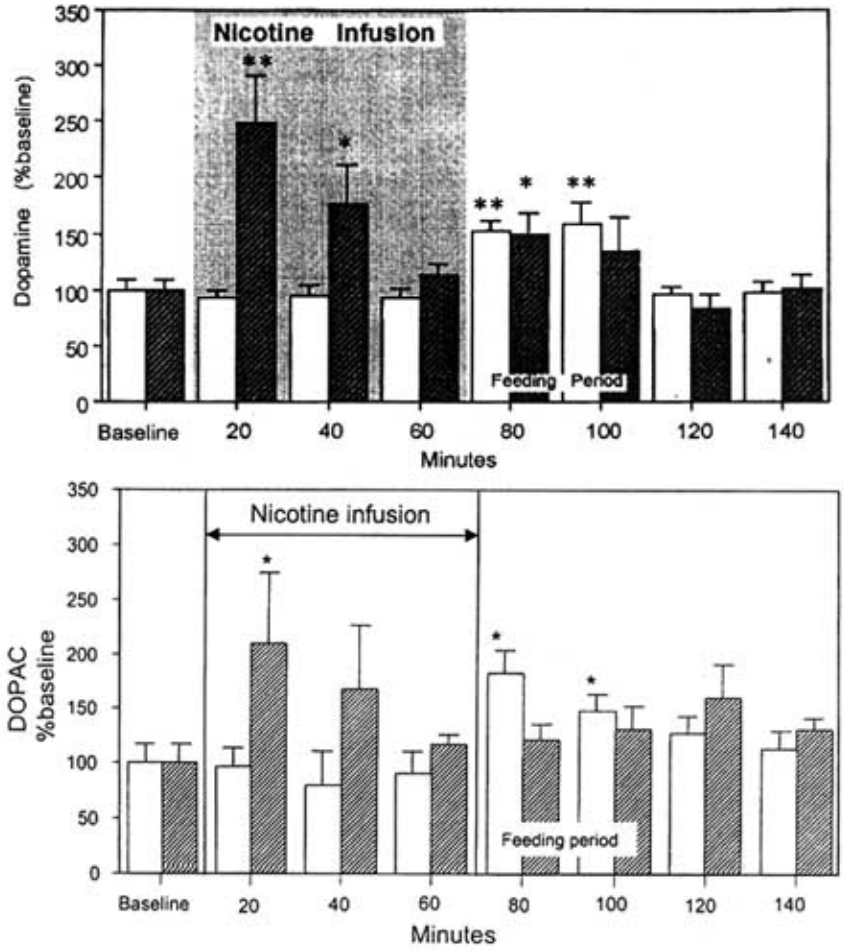

Fig. (6). Dopamine and its metabolite DOPAC levels in the LHA before, during, and after the nicotine administration and eating. Data are presented as percent baseline and expressed as mean ± SE (from ref. 38).

$HT_{1B/2C}$ receptors, reduces food intake and augment sympathetic activity, thus promoting weight loss [44].

These data obtained in the leptin signaling deficient model, indicate 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 influence energy expenditure via the sympathetic nervous system, 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, which show that dietary habits and nutrients may influence the monoaminergic system**.** As an example, (Table **I**) shows the expression of genes involved in monoaminergic activity in diet induced obese rats as seen in the arcuate nucleus and in peripheral fat relative to rats fed a normal diet. These data emphasize the up- and down-regulation of the various compounds in their respective pathway in obesity, underscoring the importance of these monoamines in the metabolic process.

II – The Diet-Induced Model of Obesity

When three-week old Sprague-Dawley pups are placed on a diet relatively high in fat and calories, approximately two thirds 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 the 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 become obese when

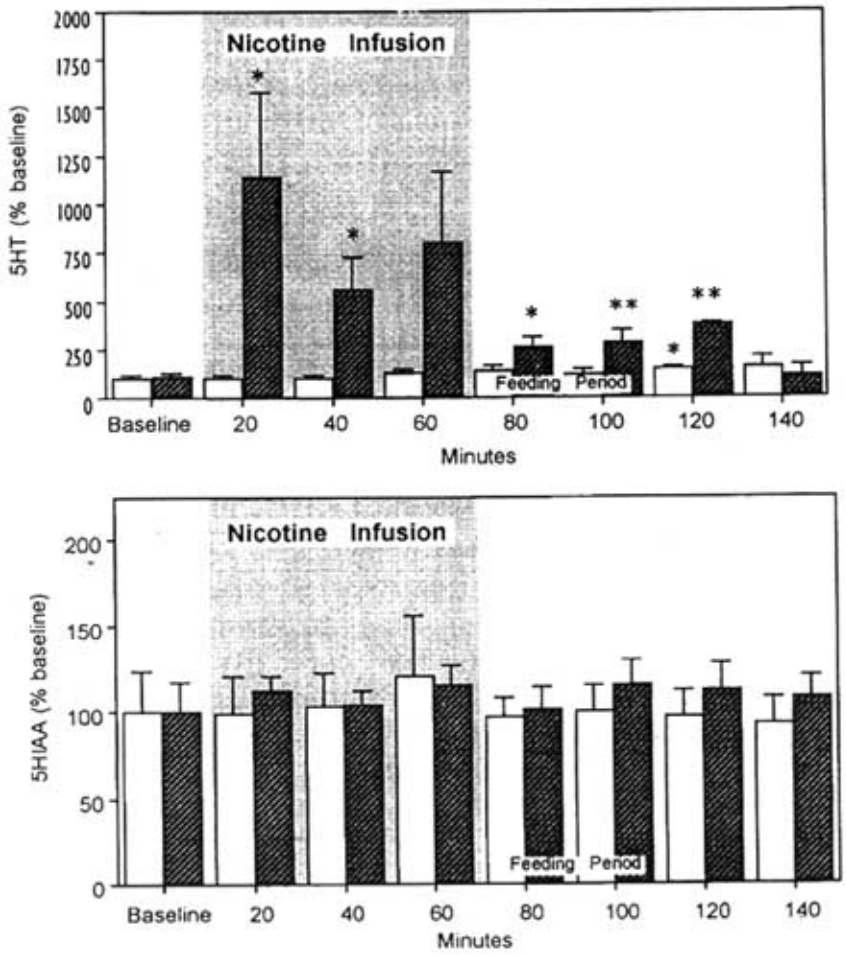

Fig. (7). Serotonin and its metabolite 5-HIAA levels in the LHA before, during, and after the nicotine administration and eating. Data are presented as percent baseline and expressed as mean ± SE (from ref. 38).

Table I. Expression of Serotonin- and Dopamine-related Genes in Diet induced Obese Rats

	Trp	TrpOH	DopaβOH	5HTTrans	DopaTrans	$5HT_{1c}$	DA1	$5HT_{1b}$	DA2
Arcuate Nucleus	**-2.5**	**2.1**	**5.6**	**1.1**	**14.8**	**1.6**	**8.0**	**-4.4**	**1.2**
Subcutaneous Fat	**1.1**	**1.8**	**-15.0**	**-1.5**	**-1.1**	**1.3**	**-3.0**	**-4.5**	**1.3**

Genes are expressed as fold change vs. normal diet. Trp: tryptophan; TrpOH: tryptophan hydroxylase; DopaβOH: Dopa-β-hydroxylase; $5HT_{1c}$: serotonin receptor, type1c; DA1: dopamine receptor, type 1; $5HT_{1b}$: serotonin receptor, type1b; DA2: dopamine receptor, type 2

dietary fat and caloric density are increased [45]. 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 contributory factors that the DIO model gave to our understanding of the mechanisms regulating food intake in obese rats is the demonstration that changes in the diet modulate gene expression. In a recent study, Schaffauser *et al*. studied rats fed a low- or a high-fat diet for 14 days [46]. Then, the mRNAs for $5\text{-}HT_{2C}$ receptor and NPY receptor was measured. The results showed that serotonin receptor expression was reduced, while NPY mRNA was increased. Hence dietary fat may modulate serotonergic activity by influencing the expression of serotonin receptor genes, and thus possibly 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 close link between serotonin and gene expression regulation is also supported by evidence suggesting that the transcription factor *tubby*, whose loss results in the development of obesity, is controlled by 5-HT_{2C} receptor *in vivo* [47].

The DIO model data 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. 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 hypothesised that most of the abnormality existing in the cascade of signaling pathways of the obese rat results in a disturbed hypothalamic monoaminergic neurotransmission.

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 [48] may be exploited to reduce food intake and achieve weight loss in hyperphagic obese patients. We recognise that serotonergic agents have been used in the treatment of hyperphagia, but it must be emphasised that their side effects may limit their use [49]. The recent development of sibutramine, a molecule that enhances serotonergic and dopaminergic activities, raises new enthusiasm and prospects for a pharmacologic therapeutic approach to the treatment of hyperphagia and obesity because its effects on food intake do not appear to be diminished by severe side effects [50].

A more physiologic 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

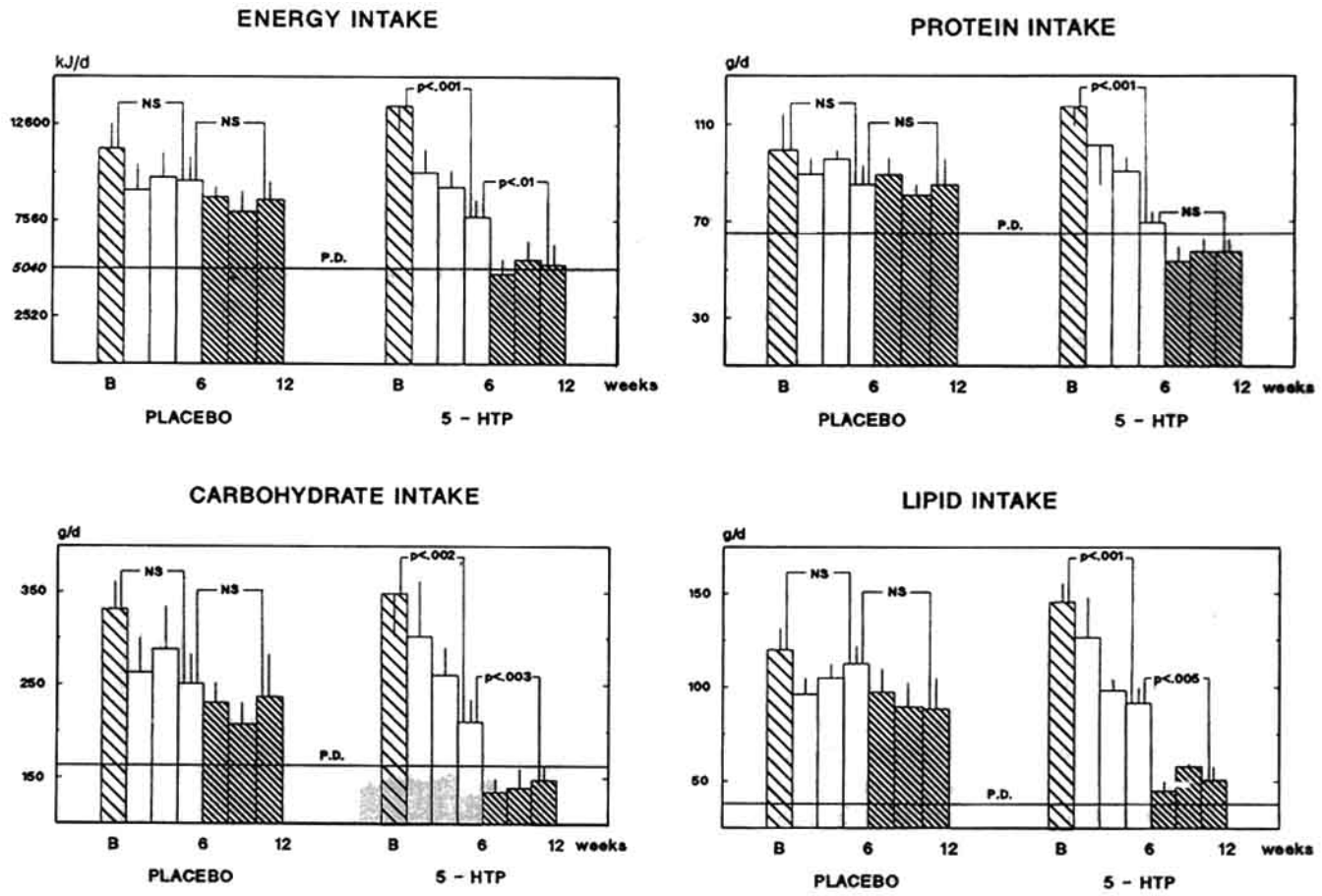

Fig. (8). Mean ± SE modifications of total energy and single macronutrient intakes during no-diet (white bars) and diet (shaded bars) periods of observation in the two groups of subjects B: baseline; P.D.: prescribed diet (from ref. 54)

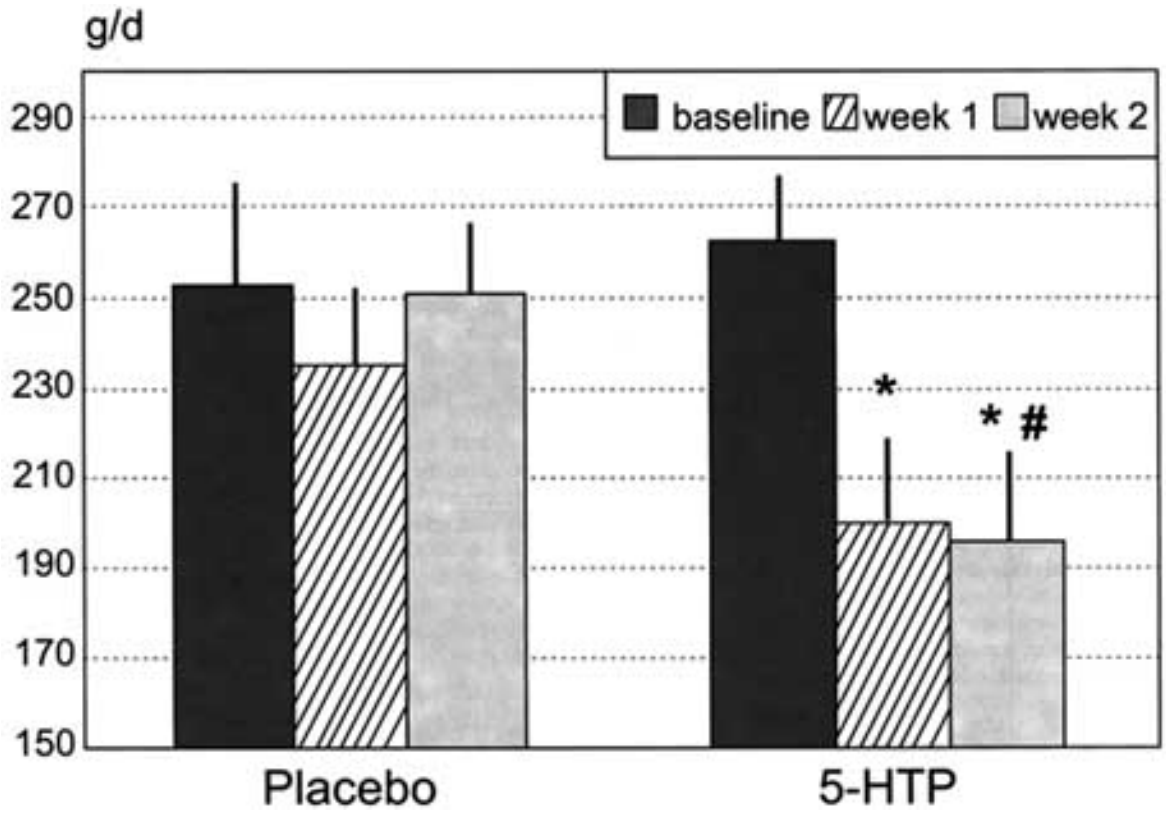

Fig. (9). Mean ± SE carbohydrate intake in the two groups studied. The oral administration of 5-hydroxytryptophan (5-HTP) significantly reduced carbohydrate intake when compared to baseline period and the Placebo group; *p<0.01 vs baseline, same group; #p<0.05 vs Placebo, same week (from ref. 55)

concentrations do not limit the enzyme activity; consequently, the more tryptophan that reaches the brain, the more serotonin is produced [51]. Thus, by providing the brain with pharmacologic doses of the precursor tryptophan, more serotonin should be produced, including 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, to avoid the possible occurrence of the eosinophilia-myalgia syndrome associated with the use of L-tryptophan [52]. In a series of 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/d reduces food intake in dietary-unrestricted obese patients [53]. This enhances the adherence to a hypocaloric dietary regimen [54] (Fig. **8**) and reduces carbohydrate craving in non-insulin-dependent diabetic patients [55] (Fig. **9**), supporting the proposed role of brain serotonin in determining macronutrient selection [48]. The clinical relevance of brain-neurotransmission modulation is also emphasised by the promising results obtained in the opposite clinical syndrome, i.e., 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 [56]. The sum total of these data support the hypothesis that brain monoaminergic neurotransmission may represent a common step on which different appetite-related messengers converge.

REFERENCES

[1] Kopelman, P.G. *Nature*, **2000**, *404*, 635.

[2] Lowell, B.B.; Spiegelman, B.M. *Nature*, **2000**, *404*, 652.

[3] Schwartz, M.W.; Woods, S.C.; Porte, D. Jr.; Seeley, R.J.; Baskin, D.G. *Nature*, **2000**, *404*, 661.

[4] Meguid, M.M.; Laviano, A.; Rossi Fanelli, F. *Appetite* **1998**, *31*, 404.

[5] Becker, E.E.; Kissileff, H.R. *Am. J. Physiol.*, **1974**, *226*, 383.

[6] Meguid, M.M.; Yang, Z.-J.; Gleason, J.R. *Nutrition*, **1996**, *12*, S57.

[7] Makarenko, I.G.; Meguid, M.M.; Ugrumov, M.V. *Neuroscience Letts.*, **2002**, *328*, 155.

[8] Makarenko, I.G.; Meguid, M.M.; Gatto, L.; Chen, C.; Ugrumov, M.V. *Brain Res.*, **2003**, *961*, 100.

[9] Meguid, M.M.; Fetissov, S.O.; Varma, M.; Sato, T.; Zhang, L.; Laviano, A.; Rossi-Fanelli, F. *Nutrition*, **2000**, *16*, 843

[10] Havel, P.J.; Larsen, P.J.; Cameron, J.L. In *Neuroendocrinology in Physiology and Medicine*; Conn, P.M.; Freeman, M.E., Eds.; Humana Press: Totowa, NJ, **2000**; pp. 335-352.

[11] Heisler, L.K.; Cowley, M.A.; Tecott, L.H.; Fan, W.; Low, M.J.; Smart, J.L.; Rubinstein, M.; Tatro, J.B.; Marcus, J.N.; Holstege, H.; Lee, C.E.; Cone, R.D.; Elmquist, J.K. *Science*, **2002**, *297*, 609.

[12] Nonogaki, K.; Strack, A.M.; Dallman, M.F.; Tecott, L.H. *Nature Med.*, **1998**, *4*, 1152.

[13] Zhou, Q.-Y. ; Palmiter, R.D. *Cell*, **1995**, *83*, 1197.

[14] Szczypka, M.S. ; Mandel, R.J. ; Donahue, B.A. ; Snyder, R.O.; Leff, S.E.; Palmiter, R.D. *Neuron*, **1999**, *22*, 167.

[15] Meguid, M.M.; Yang, Z.-J.; Koseki, M. *Brain Res. Bull.*, **1995**, *36*, 487.

[16] Meguid, M.M.; Yang, Z.-J.; Laviano, A. *Am. J. Physiol.*, **1997**, *272*, R1925.

[17] Smialowska, M.; Bajkowska, M.; Heilig, M.; Obuchowicz, E.; Turchan, J.; Maj, M.; Przewlocki, R. *Neuropeptides*, **2001**, *35*, 82.

[18] Schwartz, D.H.; Hernandez, L.; Hoebel, B.G. *Brain Res. Bull.*, **1990**, *25*, 797.

[19] Rouch, C.; Nicolaidis, S.; Orosco, M. *Physiol. Behav.*, **1999**, *65*, 653.

[20] Esler, M.; Rumantir, M.; Wiesner, G.; Kaye, D.; Hastings, J.; Lambert, G. *Am. J. Hypertens.*, **2001**, *14*, 304S.

[21] McLaughlin, C.L.; Baile, C.A.; *Physiol. Behav.*, **1981**, *26*, 607.

[22] Levin, B.E.; Sullivan, A.C. *Pharmacol. Biochem. Behav.*, **1979**, *11*, 77.

[23] Orosco, M.; Trouvin, J.H.; Cohen, Y.; Jaquot, C. *Physiol. Behav.*, **1986**, *36*, 853.

[24] Meguid, M.M.; Fetissov, S.O.; Blaha, V.; Yang, Z.-J. *NeuroReport*, **2000**, *11*, 2069.

[25] Glaum, S.R.; Hara, M.; Bindokas, V.P.; Lee, C.C.; Polonsky, K.S.; Bell, G.I.; Miller, R.J. *Mol. Pharm.*, **1996**, *50*, 230.

[26] Brunetti, L.; Michelotto, B.; Orlando, G.; Vacca, M. *Eur. J. Pharmacol.*, **1999**, *372*, 237.

[27] Trayhurn, P.; Thomas, M.E.; Duncan, J.S.; Rayner, D.V. *FEBS Lett.*, **1995**, *368*, 488.

[28] Saladin, R.; De Vos, P.; Guerre-Millo, M.; Leturque, A.; Girard, J.; Staels, B.; Auwerx, J. *Nature*, **1995**, *377*, 527.

[29] Yamashita, T.; Murakami, T.; Iida, M.; Kuwajima, M.; Shima, K. *Diabetes*, **1997**, *46*, 1077.

[30] Yang, Z.-J.; Meguid, M.M. *NeuroReport*, **1995**, *6*, 1191.

[31] Routh, V.H.; Stern, J.S.; Horwitz, B.A. *Am. J. Physiol.*, **1994**, *267*, R712.

[32] Calapai, G.; Corica, F.; Corsonello, A.; Sautebin, L.; Di Rosa, M.; Campo, G.M.; Buerni, M.; Mauro, V.N.; Caputi, A.P. *J. Clin. Invest.*, **1999**, *104*, 975.

[33] Yang, Z.-J.; Meguid, M.M.; Chai, J.K.; Chen, C.; Oler, A. *Pharmacol. Biochem. Behav.*, **1997**, *58*, 631.

[34] Leibowitz, S.F.; Rossakis, C. *Brain Res.*, **1979**, *172*, 101.

[35] Meguid, M.M.; Fetissov, S.O.; Miyata, G.; Torelli, G.F. *NeuroReport*, **1999**, *10*, 1049.

[36] Lemierre, S.; Rouch, C.; Nicolaidis, S. ; Orosco, M. *Int. J. Obesity*, **1998**, *22*, 993.

[37] Leibowitz, S.F.; Weiss, G.F.; Suh, J.S. *Pharmacol. Biochem. Behav.*, **1990**, *37*, 735.

[38] Yang, Z.-J.; Blaha, V.; Meguid, M.M.; Oler, A.; Miyata, G. *Pharmacol. Biochem. Behav.*, **1999**, *64*, 155.

[39] Qu, D.; Ludwig, D.S.; Gammeltoft, S.; Piper, M.; Pelleymounter, M.A., Cullen, M.J.; Mathes, W.F.; Przypek, R.; Kanarek, K.; Maratos-Flier, E. *Nature*, **1996**, *380*, 243.

[40] de Lecea, L.; Kilduff, T.S.; Peyron, C.; Gao, X.; Foye, P.E.; Danielson, P.E.; Fukuhara, C.; Battenberg, E.L.; Gautvik, V.T.; Bartlett, F.S. 2nd.; Frankel, W.M.; van den Pol, A.N.; Bloom, F.E.; Gautvik, K.M.; Sutcliffe, J.G. *Proc. Natl. Acad. Sci. USA*, **1998**, *95*, 322.

[41] Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R.M.; Tanaka, H.; Williams, S.C.; Richardson, J.A.; Kozlowski, G.P.; Wilson, S.; Arch, J.R.; Buckingham, R.E.; Haynes, A.C.; Carr, S.A.; Annan, R.S.; McNulty, D.E.; Liu, W.S.; Terrett, J.A.; Elshourbagy, N.A.; Bergsma, D.J.; Yanagisawa, M. *Cell*, **1998**, *92*, 573.

[42] Cleary, M.P.; Vasseli, J.R.; Greenwood, M.R.C. *Am. J. Physiol.*, **1980**, *238*, E284.

[43] Ohliger-Frerking, P.; Horowitz, J.M.; Horwitz, B.A. *Neurosci. Lett.*, **2002**, *332*, 107.

[44] Bray, G.A. *Int. J. Obes. Relat. Metab. Disord.*, **2000**, *24 (suppl. 2)*, S8.

[45] Hassanain, M.; Levin, B.E. *Brain Res.*, **2002**, *929*, 175.

[46] Schaffauser, A.; Madiche, A.M.; Braymer, H.D.; Bray, G.A.; York, D.A. *Obes. Res.*, **2002**, *10*, 1188.

[47] Santagata, S.; Boggon, T.J.; Baird, C.L.; Gomez, C.A.; Zhao, J.; Shan, W.S.; Myszka, D.G.; Shapiro, L. *Science*, **2001**, *292*, 2041.

[48] Leibowitz, S.F. *Drugs*, **1990**, *39 (suppl. 3)*, 33.

[49] Jung, R.T. In *Clinical Obesity*; Kopelman, P.G.; Stock, M.J., Eds.; Blackwell Science: London, **1998**; pp. 469-480.

[50] Bray, G.A.; Tartaglia, L.A. *Nature*, **2000**, *404*, 672.

[51] Tagliamonte, A.; Biggio, G.; Vargiu, L.; Gessa, G.L. *Life Sci.*, **1973**, *12*, 277.

[52] Duffy, J. *Hosp. Pract.*, **1992**, *30*, 65.

[53] Ceci, F.; Cangiano, C.; Cairella, M.; Cascino, A.; Del Ben, M.; Muscaritoli, M.; Sibilia, L.; Rossi-Fanelli, F. *J. Neural Transm.*, **1989**, *76*, 109.

[54] Cangiano, C.; Ceci, F.; Cascino, A.; Del Ben, M.; Laviano, A.; Muscaritoli, M.; Antonucci, F.; Rossi-Fanelli, F. *Am. J. Clin. Nutr.*, **1992**, *56*, 86.

[55] Cangiano, C.; Laviano, A.; Del Ben, M.; Preziosa, I.; Angelico, F.; Cascino, A.; Rossi-Fanelli, F. *Int. J. Obes. Relat. Metab. Disord.*, **1998**, *22*, 648.

[56] Cangiano, C.; Laviano, A.; Meguid, M.M.; Mulieri, M.; Conversano, L.; Preziosa, I.; Rossi-Fanelli, F. *J. Natl. Cancer Inst.*, **1996**, *88*, 550.