Eating behavior and adherence to dietary prescriptions in obese adult subjects treated with 5-hydroxytryptophan[1,2]

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ABSTRACT Previous observations have shown that oral administration of 5-hydroxytryptophan (5-HTP) without dietary prescriptions causes anorexia, decreased food intake, and weight loss in obese subjects. To confirm these data over a longer period of observation and to verify whether adherence to dietary restriction could be improved by 5-HTP, 20 obese patients were randomly assigned to receive either 5-HTP (900 mg/d) or a placebo. The study was double-blinded and was for two consecutive 6-wk periods. No diet was prescribed during the first period, a 5040-kJ/d diet was recommended for the second. Significant weight loss was observed in 5-HTP–treated patients during both periods. A reduction in carbohydrate intake and a consistent presence of early satiety were also found. These findings together with the good tolerance observed suggest that 5-HTP may be safely used to treat obesity. *Am J Clin Nutr* 1992;56:863–7.

KEY WORDS Eating behavior, anorexia, 5-hydroxytryptophan, serotonin, obesity, adherence to diet, appetite for carbohydrates, weight loss

Introduction

Pharmacological, biochemical, and behavioral evidence has accumulated in the last two decades, suggesting that brain serotonin has an inhibitory influence on eating behavior both in animals and in humans (1–4). Reported studies in favor of a possible role played by the serotoninergic system in the pathogenesis of anorexia present in different diseases further support this idea (5–7). Changes in the metabolism of brain serotonin in animals experiencing different nutritional states have been reported (8, 9). Food deprivation producing a marked increase in serotonin metabolism in the lateral hypothalamus may reflect changes in the availability of brain tryptophan; this in turn constitutes a potential mechanism by which behavioral responses are coordinated with nutritional inputs (10). A variety of different direct- and indirect-acting agonists at central serotonin synapses such as dexfenfluramine and fluoxetine have been shown to cause weight loss as well as a marked reduction in food intake in obese subjects (11–13). However, the administration of both drugs caused a high incidence of side effects (12, 13).

In a previous short-term (5 wk), double-blind, crossover study we observed that oral administration of the physiological serotonin precursor 5-hydroxytryptophan (5-HTP), without any specific dietary prescription, was followed by the onset of typical anorexia-related signs, eg, decreased food intake and weight loss in obese subjects (14). The present study attempted to confirm these data over a longer period of observation and to verify whether adherence to dietary restriction could be improved by administering 5-HTP to obese hyperphagic subjects.

Subjects and methods

Subjects

Twenty-eight obese, hyperphagic adult female subjects (mean age 43.2 y ± 1.7; SE) with body mass indexes between 30 and 40 were studied. Hyperphagia was defined as the excess of daily energy introduced with respect to the energy need calculated according to sex, age, and physical activity. Subjects with glucose intolerance, hyperlipidemia, or hyperuricemia were excluded from the study.

Study design

The research protocol was approved by the Faculty Ethics Committee of the University of Rome, La Sapienza. After giving informed consent, subjects were randomly assigned to receive either 5-HTP (900 mg/d) or a placebo composed of corn starch, mannitol, and magnesium stearate (both from Sigma-Tau Industries, Pomezia, Italy). The drug, which was in the form of capsules that do not dissolve until pH 8.6, was taken three times per day, 30 min before each meal. The 12-wk-study period was subdivided for each group of subjects into two consecutive 6-wk periods. During the first period there were no dietary restrictions, whereas a 5040-kJ/d diet was recommended to subjects during the second period of observation. The 5040 kJ were subdivided as follows: 53% from carbohydrates, 29% from lipids, and 18% from proteins. No carbohydrate-rich foods were allowed between meals. Subjects were examined every 2 wk to evaluate feeding behavior and body weight. Routine blood chemistry measurements were performed for each subject at the beginning

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Received January 22, 1991.

Accepted for publication May 25, 1992.

TABLE 1
Baseline characteristics of subjects*

	Body weight	Total energy	Proteins	Carbohydrates	Lipids
	kg	*kJ/d*	*g/d*	*g/d*	*g/d*
Placebo	94.3 ± 5.3	11 398 ± 1 020	104 ± 11.3	331 ± 29.1	120 ± 12.3
5-HTP	99.7 ± 5.9	13 528 ± 1 033	117 ± 8.8	349 ± 47.8	144 ± 12.6

* $\bar{x}$ ± SE; n = 10 for both groups.

and at the end of each period of observation. To test subjects' compliance to treatment, 24-h urinary excretion of 5-hydroxy-3-indoleacetic acid (5-HIAA) was also determined every 2 wk by the chromatographic-colorimetric method described by Udenfriend et al (15).

Daily total energy intake as well as single macronutrient selection, which may define a subject's eating behavior, were assessed every 2 wk by using a 3-d diet diary. Food diaries, including all beverages, were compiled by subjects for 3 consecutive working days. Each subject was instructed to carefully weigh food before meals and then reweigh any leftovers. All reports were validated by a next of kin's signature. To avoid reported interference due to premenstrual depression, food-intake measurements were not assigned to this time of the month (16).

To investigate anorexia, patients were invited to report the presence of a series of symptoms, namely meat aversion, taste and smell alteration, nausea and/or vomiting, and early satiety. All of these symptoms interfere with eating and are possibly related to a pathological modification of the central-nervous-system (CNS) regulation of feeding behavior (5, 6). Subjects were invited to report at the end of each period of study the presence of side effects, including weakness, myalgia, drowsiness, vertigo, diarrhea, and stipsis.

Statistical analysis

All data were subjected to standard statistical analysis including mean, standard error, and Student's t tests for both paired and unpaired data; modifications observed within each treatment group were compared or placebo and the 5-HTP groups were compared (17). The Chi-square test was used to compare the prevalence of both the anorexia-related symptoms and the side effects observed during placebo and 5-HTP treatments. (17). The minimum probability level considered for statistical significance was $P < 0.05$.

Results

Twenty of the 28 subjects included completed the study. The eight dropouts (three in the study group and five in the control group) did not complete the study for the following reasons: three had family problems, two self-prescribed a low-energy diet during the first study period, two self-administered other anorectic drugs, and one did not complete the follow-up. Two groups of 10 subjects each therefore were studied. As shown in **Table 1**, baseline characteristics were comparable for the two groups of subjects who did not differ in body weight, daily-total-energy intake, and specific-macronutrient selection.

Changes in body weight, expressed as percentage of basal values, are shown in **Figure 1**. subjects receiving the placebo did not show any significant change in their body weight during either study period (94.3 ± 5.6 vs 93.2 ± 5.3 kg, $\bar{x}$ ± SE, basal value vs end-of-study value). In contrast, subjects receiving 5-HTP showed a significant weight loss at the end of the first period

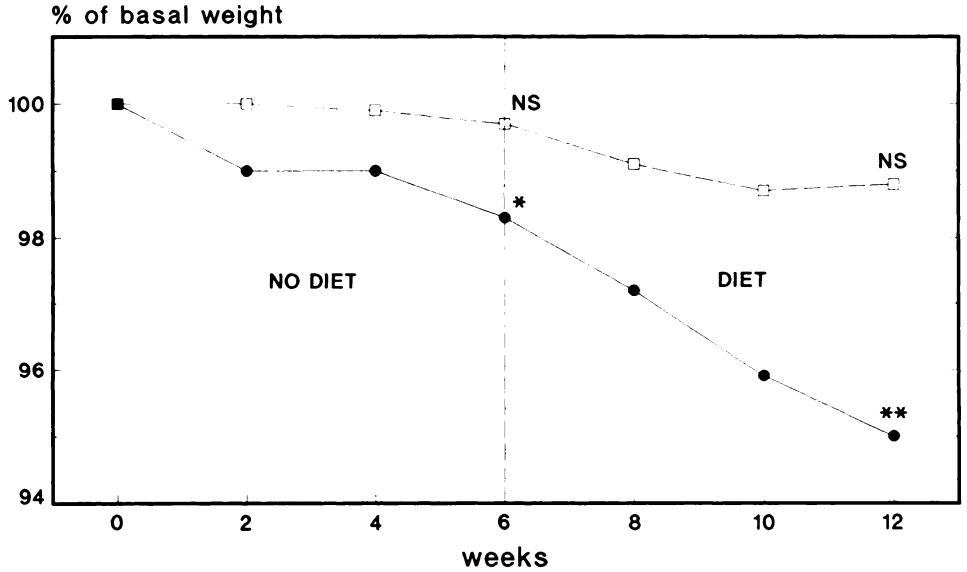

FIG 1. Mean body-weight modifications, expressed as percentage of the basal value, during both no-diet and diet periods of observation. □, placebo; ●, 5-hydroxytryptophan (5-HTP). *Significantly different from beginning of study, $P < 0.03$. **Significantly different from value at 6 wk for 5-HTP group. $P < 0.02$.

(99.7 ± 5.9 vs 98.0 ± 5.0 kg, $P < 0.03$) followed by a greater reduction of their body weight at the end of the second period of observation (98.0 ± 5.0 vs 94.7 ± 5.1, $P < 0.02$). In the group final weight loss was ≈5% of the basal body weight.

Analysis of the mean total energy intake, as calculated from subject's reports, showed no significant changes in the placebo group during either period (**Fig 2**). The spontaneous reduction of daily energy intake from 11399 ± 1021 to 9778 ± 907 kJ/d observed at the end of the first study period was not statistically significant, nor was the further negligible decrease to 8644 ± 1319 kJ/d observed during the diet period. There was a significant reduction of total energy intake in subjects receiving 5-HTP from 13528 ± 1033 to 7892 ± 773 kJ/d. In these subjects, total energy intake showed a further significant reduction to 5326 ± 647 kJ/d in the second study period.

A specific behavior was observed in macronutrient selections. The total protein intake remained unmodified in the control group during the study period. In the 5-HTP group, protein intake was progressively reduced during the first period to values that were not further modified during the second half of the study (Fig 2). The carbohydrate intake, though reduced, was not statistically different from the basal value for the control group (Fig 2). Conversely, subjects receiving 5-HTP showed a significant 50% reduction of their intake of carbohydrates at the end of the first study period. This was followed by a further significant reduction in the second study period during which the total carbohydrate intake was even lower than the quantities included in the dietary prescription. Finally, the lipid intake showed changes similar to those observed for carbohydrates although the quantities consumed during the second period in the 5-HTP–treated patients were always higher than those included in the prescribed diet (Fig 2).

The evaluation of anorexia showed different behavior in the two groups of subjects. Among the symptoms included in a questionnaire, early satiety was reported by 100% and 90% of subjects receiving 5-HTP during the first and second study periods, respectively. Reports of early satiety were always significantly higher for subjects receiving 5-HTP than for the control group. Reports of nausea, which was episodically reported by 80% of subjects on 5-HTP during the first study period, were significantly reduced during the last 6 wk of observation to 20%, suggesting that this symptom may be considered a transitory effect of 5-HTP administration. The other symptoms were not reported differently by the two groups of subjects (**Fig 3**).

The occurrence of side effects such as weakness, myalgia, drowsiness, vertigo, diarrhea, and stipsis were investigated. All of these symptoms were equally distributed in both groups of patients with no differences between the two periods of observation (**Fig 4**). The total urinary 5-HIAA excretion showed a 50-fold difference between the two groups and provided evidence for subject-compliance with treatment (**Fig 5**).

Discussion

The role of amino acids in the regulation of food intake has been supported by experimental data suggesting that changes in plasma amino acid concentrations may modify food intake by affecting the brain availability of neurotransmitter amino acid

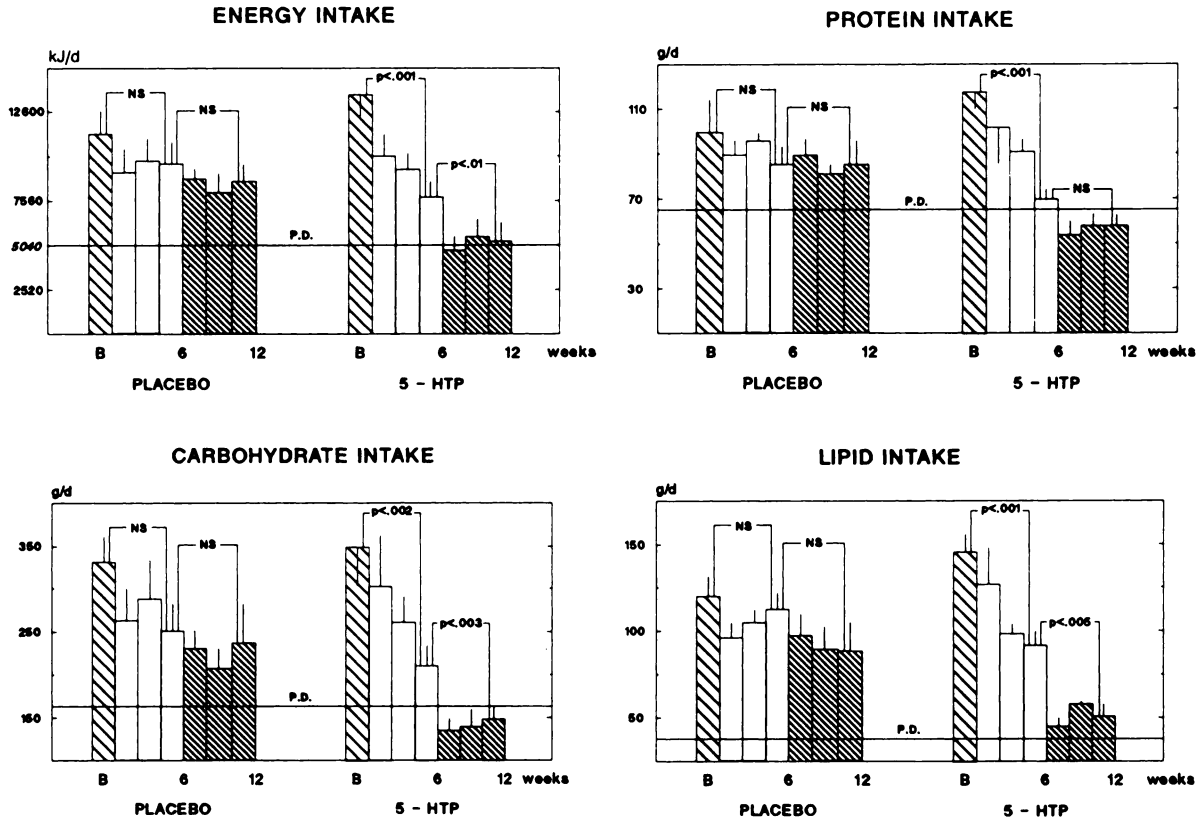

FIG 2. Mean ± SE modifications of total energy and single macronutrient intakes during both no-diet (□) and diet (▨) periods of observation in the two groups of subjects. B (▧) basal records; P.D., prescribed diet.

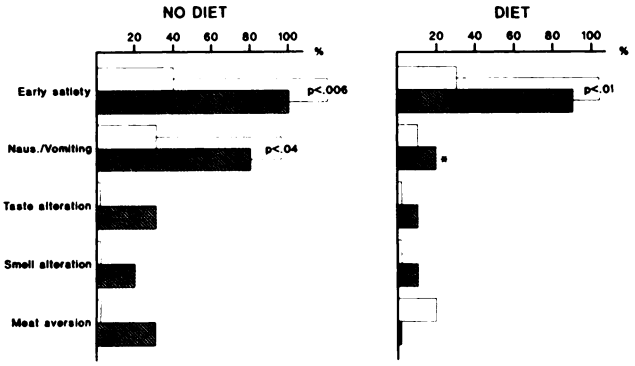

FIG 3. Prevalence of the symptoms used to evaluate anorexia in the two groups of subjects during no-diet and diet periods of observation. *Significantly different from no diet for 5-hydroxytryptophan (5-HTP) group, $P < 0.01$. □, placebo; ▨, 5-HTP.

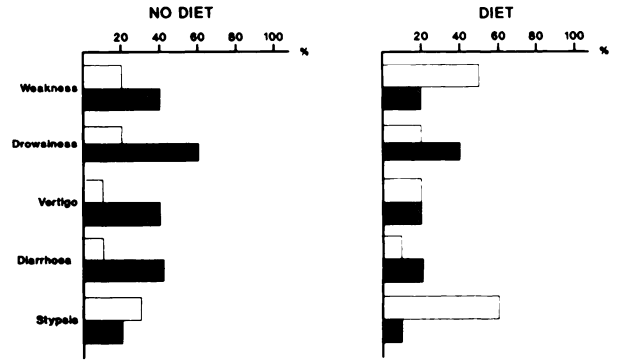

FIG 4. Prevalence of the side effects investigated in the two groups of subjects during no-diet or diet periods of observation. There were no statistically significant differences between groups or study periods. □, placebo; ▨, 5-hydroxytryptophan (5-HTP).

precursors (18). Of the two major neurotransmitter systems involved in the regulation of feeding, the serotoninergic system seems to play a specific role (19). A pharmacological study by Leibowitz et al (20), in fact, precisely characterized the brain sites and receptors involved as well as the possible physiological role of endogenous serotonin in controlling natural patterns of eating and nutrient selection. In particular, serotonin's action is believed to influence both the energy balance and the circadian patterns of eating by activating satiety neurons localized in the medial hypothalamus (19). In this process, serotonin seems to interact antagonistically with norepinephrine and its 2-noradrenergic receptors (21). Pharmacologically induced variations in brain serotonin concentrations or serotoninergic activity in experimental animals result in fluctuation of appetite (22, 23). In 1981, Wurtman et al (4) and more recently Hill and Blundell (24) have shown that the serotoninergic system also plays an important role in macronutrient selection especially in obese people consuming large amounts of carbohydrate-rich food. The same authors have also demonstrated that such behavior can be counteracted by pharmacologically enhancing brain serotonin synthesis. Pharmacological manipulation of brain serotonin concentrations with serotoninergic-active agents like dexfenfluramine and fluoxetine has been reported to control food intake and reduce body weight in obese patients (12, 13). Nevertheless, the incidence of side effects reported by subjects receiving both drugs was higher than that reported in the control groups (12, 13).

In a previous study we observed that oral administration of 5-HTP to adult obese subjects was followed by decreased food intake and weight loss without affecting the subjects' mood (14). The results of the present study seem to confirm those previously reported. In fact, during the diet-free, 6-wk period of observation, subjects receiving 5-HTP at doses similar to those prescribed in the previous study showed a significant reduction of both body weight and daily carbohydrate intake. Moreover, when subjects were given a low-energy diet a further significant reduction of both indices was observed. Because of the meal-structure characteristic of the Italian diet (ie, pasta first, protein and bread second at lunch or dinner), the early satiety referred to during the diet-free first period of the study may have altered the evaluation of total carbohydrate intake. However, a significant reduction in carbohydrate intake was also observed during the low-energy diet period, when the meal structure was subverted as past and other carbohydrate-rich food were allowed only in small amounts. In addition, the significant reduction in bread intake, which is usually eaten in combination with proteins, argues in favor of a specific effect of carbohydrates on appetite, exerted by 5-HTP. Thus, the optimal adherence to dietary prescription observed in subjects receiving 5-HTP may have been the consequence of a combination of both early satiety and low-carbohydrate intake.

The relatively high incidence of nausea during 5-HTP administration may raise the concern that it could, at least in part, have been responsible for the 5-HTP effects observed. However, note that for most subjects, nausea was reported episodically. Nausea was significantly less frequent during the second 6-wk period when the greater reduction in food intake and weight loss was observed. Finally, when present, nausea was of low intensity and never caused a subject to drop out of the study. We believe that the effect of nausea on weight loss was negligible. The lack of a significant reduction of body weight observed in the control group during both study periods (ie, both without and with the low-energy diet) was likely due to subjects' noncompliance with dietary prescriptions as demonstrated by diet reports.

In conclusion, the results of this study seem to confirm the specific role played by the serotoninergic system in the regulation

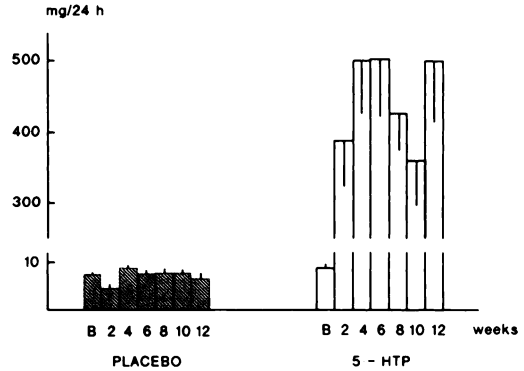

FIG 5. Mean total 5-hydroxy-3-indoleacetic acid (5-HIAA) excretion during the 12-wk study period in both groups of subjects.

of feeding behavior in humans. The administration of 5-HTP was in fact followed by a reduction of both daily total energy and carbohydrate intakes followed by a significant loss of body weight. The optimal adherence to dietary prescription as well as the good tolerance to 5-HTP treatment observed suggest that this substance may be safely used in the long-term treatment of obesity.

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