Tryptophan Administration may Enhance Weight Loss by Some Moderately Obese Patients on a Protein-Sparing Modified Fast (PSMF) Diet

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Drugs thought to enhance serotonin-mediated neurotransmission have been shown to diminish appetite for carbohydrates. Therefore, we examined the ability of tryptophan (TRP), serotonin's amino acid precursor, or a placebo to influence weight loss among 62 obese Swiss outpatients who were on a reducing diet [the Protein-Sparing Modified Fast (PSMF) Diet] which can be associated with severe carbohydrate craving. This diet provides relatively large amounts of protein (1.2–1.4 g/kg ideal body weight/day) but little carbohydrate (40 g/day or less), thus stimulating ketone body production. Its consumption also reduces the ratio of plasma TRP to the summed concentrations of the other large neutral amino acids, thereby probably diminishing brain TRP and serotonin levels. During the initial month of the PSMF diet all patients received the placebo; thereafter 30 received TRP (750 mg, twice daily, orally, for 3 months) and 32 the placebo, according to a double-blind protocol.

Among moderately obese patients (140–159% of ideal weight; N = 25), the TRP significantly enhanced weight loss ($p < .05$), especially during the first treatment month (3.4 ± 2.8 vs 1.7 ± 1.7 kg lost; means ± standard de-

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viation) but also during the total 3-month test period (2.6 ± 2.3 vs 1.5 ± 1.6 kg lost/month). The TRP didn't modify the reported adherence to the PSMF diet. The partial efficacy of TRP among our moderately obese subjects does not presently justify its routine use as an adjunct to a PSMF diet. However, greater efficacy may be obtained with better patient selection and under metabolic conditions designed to amplify the uptake of TRP into the brain (i.e., administration along with a carbohydrate).

INTRODUCTION

Success in the long-term management of obesity requires both that the patient lose weight during the period of active treatment and that he or she develop patterns of eating which allow maintenance of this weight loss thereafter. Both phases are rendered more difficult if the patient suffers from inappropriate craving for foods rich in carbohydrates. A history of such cravings can, in our experience, be elicited from most obese subjects presenting themselves for treatment at an obesity clinic (Wurtman & Wurtman, 1981; Wurtman et al., 1981); moreover the tendency to undergo such cravings (and to snack excessively on carbohydrates) may be exacerbated if the subject is placed on a weight-reducing or weight-maintenance diet that severely restricts carbohydrates (Wurtman, Moses, & Wurtman, 1983). One such reducing diet is the Protein-Sparing Modified Fast (PSMF) Diet (Burckhardt et al., 1980; Flatt & Blackburn, 1974), which allows the subject relatively large quantities of protein [1.2–1.4 g/kg of ideal body weight (IBW)/day] in order to sustain body muscle mass, but which limits dietary carbohydrates to 40 g/day (by restricting or proscribing certain foods). The carbohydrate cravings may, in these patients, be mediated by diet-induced changes in the plasma amino acid pattern, which secondarily diminish the synthesis and release of serotonin within the brain. Consuption of protein-rich, carbohydrate-poor meals lowers the "plasma/tryptophan (TRP) ratio" [the ratio of the TRP concentration to the summed concentration of other circulating large neutral amino acids (LNAA) which compete with TRP for passage across the blood-brain barrier (Crandall & Fernstrom, 1980; Fernstrom and Wurtman, 1971; Fernstrom, Larin, & Wurtman, 1973; Fernstrom et al., 1979; Wurtman, 1982)] well beyond its normal range (Heraief, Burckhardt, Mauron, Wurtman, & Wurtman, 1983), thereby diminishing the amounts of TRP available within brain neurons for conversion to serotonin. In our experience, the carbohydrate craving associated with the PSMF diet restricts this diets's overall success.

The present study was designed to examine the possibility that giving obese patients supplemental TRP while they are following the PSMF diet might enhance their weight loss, possibly by reducing their intake of

proscribed carbohydrate-rich foods. Presumably the supplemental TRP would enhance the release of serotonin from brain neurons, a process which has been shown, in experimental animals (Wurtman & Wurtman, 1977, 1979a,b) and in human subjects (Wurtman, 1983; Wurtman & Wurtman, 1981; Wurtman et al., 1981) to diminish appetite for carbohydrates, selectively (that is, to reduce the ratio of carbohydrate to protein in the foods chosen for consumption). That TRP administration can, indeed, enhance serotonin release within the human brain has been deduced from indirect studies showing elevated levels of serotonin's metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (Gilman, Bartlett, Bridges, Kantameni, & Curzen, 1980), and changes in sleep onset (Hartmann, 1977; Hartmann & Spinnweber, 1979; Wyatt et al., 1970), sleepiness (Lieberman, Corkin, Spring, Growdon, & Wurtman, 1982), and mood (Coppen, Herzberg, & Magga, 1967; Fernstrom et al., 1979; Lieberman et al., 1982).

Dl-fenfluramine (Wurtman & Wurtman, 1981; J. Wurtman et al., 1981) and d-fenfluramine (Hirsch et al., 1982; R. Wurtman, 1983; J. Wurtman, et al., 1985), drugs that release serotonin into brain synapses, have been found to be highly effective in diminishing carbohydrate snacking among inpatients receiving them for 2 weeks. Since the present study used outpatients who came to the clinic only at intervals of 2 or 4 weeks, it was not possible for us to measure directly the effects of the TRP on the selection of particular foods or nutrients; hence our study focused on the associated changes in body weight. The obese subjects were classified into three groups, according to their degree of obesity, since patients with an initial weight of 150% or more of ideal body weight (IBW) exhibit a tendency to adhere to the PSMF diet with a better compliance, and subsequently to lose more weight (Heraief & Burckhardt, 1982; Iselin & Burckhardt, 1982).

MATERIALS AND METHODS

Subjects and Diet

Subjects were obese Swiss outpatients treated at the Obesity Clinic of the Hospital of the University of Lausanne; they either came to the clinic spontaneously or were referred by their physician. They weighed more than 120% of the IBW (New York Metropolitan Life Insurance Co., 1959). All were asked to adhere to a PSMF diet (Burckhardt et al., 1980), by consuming relatively large quantities of lean meat, fish, fowl, and eggs (or restricted amounts of low-fat dairy products) and restricting their carbohydrate intake to selected vegetables and salads. [This diet provides 1.2 g protein/kg of IBW/day for women and 1.4 g/kg of IBW/day for men, along with less than 40 g/ day of carbohydrate and 10–20 g/day of fat. Sub-

jects also take 12–24 mmol of potassium chloride per day and multivitamin preparations three times per week. The present of ketonuria is confirmed three times weekly (Ketostix, Ames).] Subjects also agreed to participate in a prospective study on the weight-reducing effect of a concentrated nutrient, normally present in the diet (i.e., TRP), that might suppress their craving for carbohydrates. (They were not told that they would be receiving a placebo for part or all of the study.) Subjects were screened for metabolic or endocrine disease before being admitted to the study. Of the 103 who were allowed to enroll (91 women and 12 men), 41 were withdrawn before its conclusion; three included 24 who failed to keep clinic appointments, 11 for whom there was evidence of erratic dosing with TRP or with placebo, and 6 who had been consuming a PSMF diet immediately before the time that they would have entered the study.

Subjects were questioned about their tendency to experience a need to snack on carbohydrate-rich foods, at particular times of day. Most acknowledged this propensity. Thereafter they were asked to take a commercial instant coffee mix (Nescafe Gold, Nestle Co., Vevey, Switzerland), to which TRP (750 mg) or a placebo had been added. The test coffee drink was to be consumed twice daily, 30–60 min before their characteristic time of carbohydrate craving. (If this time could not be identified, the subject was instructed to take the beverage at least 60 min after lunch and after dinner.) Quinine (15 mg) was added to the placebo coffee preparation in order to mimic the slightly bitter taste of the preparation that contained TRP. Patients were allowed to add artificial sweeteners and/or 1–2 teaspoons of low fat milk to the coffee. Three of the patients who refused to take a coffee-containing preparation were allowed to receive the TRP or its placebo (diatomaceous earth) in capsules (three each, twice daily). The protocol was approved by the ethical committee of the hospital.

Subjects returned to the clinic at least once each month, to be weighed and questioned about their compliance with the diet and experimental protocol. Compliance was rated subjectively (by the dietician and/or physician), and by the presence or absence of ketonuria on a scale of 0 (poor), 1 (moderate), or 2 (good): in the poor compliance group (0), patients followed any diet; with moderate compliance (1), patients ate too much carbohydrate to sustain ketosis. Only patients who strictly adhered to the PSMF diet received the rating score of 2. During the first month of dieting, a period during which subjects generally tend to lose weight most rapidly, all consumed the placebo preparations. Thereafter, following a double-blind protocol, half received the TRP and half the placebo. Attending physicians and dieticians were not informed about the identities of the preparations being taken; however, an external physician who had access to the treatment code assigned subjects to placebo or TRP between three groups so as to equalize their distributions on the basis of their degree of obesity: mild (less than 139% of IBW), moderate (140–159%), and

severe (more than 160%). Thirty patients receiving TRP (23 females and 7 males) and 32 receiving placebo (30 females and 2 males) remained in the study long enough to allow use of data on their weight loss.

Unless otherwise indicated all data are given as means ± standard deviations. Mean values are compared using paired or unpaired Student's *t* tests; proportions of responding subjects in TRP and placebo groups are compared using chi-square analysis.

RESULTS

The TRP and placebo groups did not differ in sex distribution, in mean age, nor in initial weight expressed as percent of IBW (taken from the tables of the Metropolitan Life Insurance Co., 1959) (Table 1). [The absolute initial weight of the placebo group was less than that of the subjects receiving TRP ($p = .02$).] The mean duration of treatment (2.4 months) also did not differ between placebo and TRP groups. After the third month of the double-blind trial (i.e., the fourth month of the study) too few patients remained in each group to allow statistical analysis, hence data are presented only for the initial placebo month and the subsequent 3 months of TRP or placebo (Fig. 1).

Each patient's weight loss was examined as a function of month of treatment, nature of treatment (placebo vs TRP), and degree of compliance and obesity. As anticipated (Heraief & Burckhardt, 1982), the greatest weight loss was observed during the first month (4.1 ± 1.9 g kg in the placebo group and 3.8 ± 1.7 kg in the group subsequently receiving TRP), when all subjects were receiving placebos. During the second month (the first actual treatment month), weight loss averaged 2.5 ± 2.1 kg for subjects taking the placebo and 2.9 ± 2.3 kg for those receiving TRP. During the next 2 months, weight losses were 2.4 ± 1.6 and 1.6 ±

Table 1. Characteristics of placebo and tryptophan groups.[a]

		Placebo	TRP
Sex distribution	Female	30	23
	Male	2	7
Age (years)		40.2 ± 14.8	41.9 ± 11.3
Initial weight) (kg)		83.9 ± 11.9	90.9 ± 14.7[c]
(% IBW[b])		148.2 ± 15.3	152.2 ± 18.4
Reported CHO craving (Yes/No)		30/2	25/5

[a] *Data in all tables are expressed as means ± standard deviations.*
[b] *Actual weight/Ideal weight × 100. Ideal body weight is taken from tables of the Metropolitan Life Insurance Co., 1959.*
[c] *$p < .02$ differs from placebo group.*

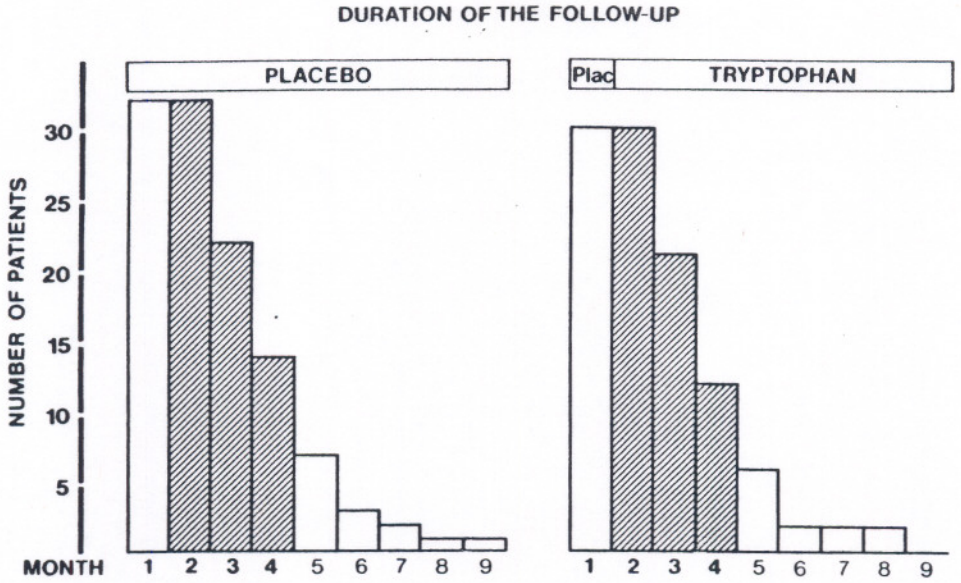

Figure 1. Duration of followup for placebo and tryptophan group. Open bars indicate numbers of subjects in each group during the initial placebo month (Month 1); shaded bars indicate number of subjects remaining within each group at the end of the treatment month indicated, during the 3 months of the treatment period.

1.9 kg, respectively, in the placebo group and 2.0 ± 1.8 and 2.0 ± 1.2 kg in the TRP group. Thus analysis of data for the entire subject population (including subjects whose compliance was so poor that they *gained* weight during the study) failed to display treatment effects. In general, the extent of each subject's compliance tended to parallel his or her weight loss.

We reanalyzed our data by determining whether TRP was more likely to be effective in (a) those with more or less severe obesity and (b) subjects with moderate or good compliance.

Although the extent of compliance correlated with weight loss during the initial treatment month, both among subjects receiving placebo and those taking TRP (Table 2), TRP did not produce significantly more weight loss than its placebo in any patient group segregated according to its degree of compliance.

In contrast, segregation of subjects by severity of obesity did allow demonstration of a significant TRP effect among the moderately obese group (Table 3). The initial weights of our subjects varied between 123 and 196% of IBW. For assessing possible relationships between the extent of the initial obesity and the subject's responsiveness to TRP, we classified each patient as mildly obese (less than 140% of IBW; $N = 18$); moderately obese (between 140 and 159% of IBW; $N = 25$); or severely obese (more than 159% of IBW; $N = 19$). The *moderately obese* subjects

Table 2. Relation between subject compliance and weight loss after placebo or TRP.

Group	Compliance 1[a]		Compliance 2[b]	
	Placebo	TRP	Placebo	TRP
Age (years)	39.6 ± 13.3	41.8 ± 13.5	42.7 ± 15.8	43.3 ± 8.8
Initial Weight (kg)	82.6 ± 8.9	86.9 ± 12.1	85.1 ± 17.6	98.5 ± 16.9
(% IBW)	147 ± 13	152 ± 18	152 ± 19	156 ± 19
Weight loss (kg)				
Month 1 (placebo)	(20)3.6 ± 1.7	(16)3.4 ± 1.9	(10)5.4 ± 1.7[c]	(11)4.7 ± 1.5[d]
Month 2	(20)2.0 ± 1.0	(16)2.4 ± 1.5	(10)4.2 ± 2.4[c]	(11)4.7 ± 2.4[d]
Month 3	(12)1.7 ± 1.4	(9)1.7 ± 1.3	(8)3.7 ± 1.0[d]	(10)2.4 ± 2.0
Month 4	(7)1.2 ± 1.2	(6)2.0 ± 1.5	(5)2.4 ± 1.0	(6)2.4 ± 0.9
Mean (Months 2–4)	1.8 ± 1.2	1.9 ± 1.4	3.6 ± 1.8[c]	3.5 ± 2.2[d]

[a]*Compliance 1: Mild adherence to the PSMF diet (patients followed a hypocaloric diet but consumed some disallowed foods).*
[b]*Compliance 2: Strict adherence to the PSMF diet, prescribed. Numbers in parentheses indicate group size.*
[c]$p < .001$ *differs from corresponding compliance 1 group for placebo treatment.*
[d]$p < .001$ *differs from corresponding compliance 1 group for TRP treatment.*

showed equivalent weight losses during the initial placebo month. However, during the second month they lost significantly more weight ($p < .05$) on TRP than on the placebo (Table 3). This tendency was sustained, but differences were not statistically significant beyond the second month, possibly because of the small size of the groups by this time. Overall weight loss for the 3-month treatment period was significantly greater among patients receiving TRP (2.6 ± 2.3 kg; range, 1.6–13.3 kg) than among those on the placebo (1.5 ± 1.6 kg; $p = .04$; range, 0.3–4 kg).

The *severely obese* patients who subsequently took placebo tended to lose more weight during the initial placebo month than those who subsequently took TRP, largely because of two particular patients who complied with the diet especially well, losing 17 and 25 kg, respectively, from the time they started the PSMF diet. During the third month the average weight loss of the placebo group was again significantly greater than that for the TRP group, again because of the contribution of these two patients. However, overall weight loss during the 3-month treatment period did not differ significantly between severely obese patients on the placebo (2.9 ± 1.9 kg; range, 1.4–10.3 kg) and those on TRP (2.4 ± 1.7 kg; range, 0.5–9.7 kg). The *mildly obese* patients tended to drop out of the study before sufficient data could be collected to evaluate TRP's effect. No significant differences were observed between the placebo- and TRP-treated groups.

Since so large a proportion of our patients claimed a tendency to carbohydrate craving (94% of the placebo group and 83% of the TRP group; Table 1), we were unable to use this characteristic as a means for sepa-

Table 3. Relation between severity of obesity and weight loss after placebo or TRP.

	Mild[b]		Moderate[b]		Severe[b]	
Obesity[a] Group	Placebo	TRP	Placebo	TRP	Placebo	TRP
Age (years)	31.5 ± 13.8	39.8 ± 11.3	42.6 ± 13.0	40.0 ± 12.0	46.5 ± 13.0	50.0 ± 10.3
Initial weight (kg)	73.7 ± 6.0	78.6 ± 8.3	83.0 ± 7.5	91.4 ± 14.5	96.3 ± 11.7	100.4 ± 12.2
Weight loss (kg/month)						
Month 1 (Placebo)	(10)3.9 ± 1.7	(8)3.5 ± 1.7	(13)3.5 ± 1.8	(12)3.6 ± 1.7	(9)5.2 ± 1.8	(10) ± 2.0
Month 2	(10)3.1 ± 1.7	(8)1.8 ± 1.8	(13)1.7 ± 1.7	(12)3.4 ± 2.8[3]	(9)3.2 ± 2.6	(10)3.3 ± 1.8
Month 3	—	—	(10)1.7 ± 1.7	(9)1.8 ± 1.7	(7)3.4 ± 1.0	(9)2.0 ± 1.4[c]
Month 4	—	—	(7)0.9 ± 1.4	(6)2.1 ± 1.4	(6)2.0 ± 1.3	(4)2.3 ± 1.7
Mean (Months 2–4)	—	—	1.5 ± 1.6	2.6 ± 2.3[3]	2.6 ± 1.9	2.4 ± 1.7

[a]Obesity is classified according to initial weight as percent of IBW. "Mild" obesity is between 120 and 139% of IBW; "moderate" obesity is between 140 and 159%; "severe" obesity is 160% or over.

[b]Parentheses indicate numbers of subjects remaining in study.

[c]$p < .05$ differs from corresponding placebo group.

rating those who might or might not respond to TRP. Among the group as a whole, 55% described a decrease in their carbohydrate craving during the initial month of the study when *all* were receiving the placebo.

DISCUSSION

These data show that, in a heterogeneous group of obese outpatients, supplemental oral TRP, studied in a double-blind protocol, could enhance weight loss in some patients, and that potential responders could be identified, prospectively, based on the degree of initial obesity ("moderate"; 140–159% of IBW). Patients may have been especially responsive to TRP because they were concurrently on a reducing diet (PSMF) that can cause carbohydrate craving and that produces changes in the plasma amino acid pattern indicative of diminished brain serotonin synthesis (Heraief et al., 1983; Wurtman, 1982). However obesity per se apparently also reduces the "plasma TRP ratio" (Heraief et al., 1983), probably by increasing basal plasma levels of the branched-chain amino acids (Heraief et al., 1983) and decreasing their decline in response to insulin. Hence obese patients as a group might tend to have lower brain TRP and serotonin levels than the nonobese.

In our study, as in previous studies using TRP to suppress food intake (Wurtman & Wurtman, 1981; Wurtman et al., 1981), only about 35–45% of the total population appeared to respond to the amino acid. A somewhat larger proportion (60–65%) tends to respond to fenfluramine, a drug that acts presynaptically to release brain serotonin into synapses (Garattini, Jori, Buczko, & Samamin, 1975). A prior study on outpatients consuming unit-sized portions of carbohydrate-rich snacks ad libitum had shown that 4 of 11 such subjects (36%) reduced snack intake significantly when receiving TRP (Wurtman & Wurtman, 1981); in another study using inpatients allowed to choose carbohydrate-rich or protein-rich snacks ad libitum from a vending machine, three of eight patients (38%) were "TRP-responders" (Wurtman et al., 1981). In contrast, 64 and 67%, respectively, of fenfluramine-treated subjects showed significant decreases in carbohydrate snacking in these two studies (Wurtman & Wurtman, 1981; Wurtman et al., 1981). The mechanisms that cause some obese patients *not* to respond to therapies directed at releasing more brain serotonin, and those that caused the drug to be more effective than the nutrient amino acid, have not been clarified. The lower response rate to TRP than to fenfluramine may reflect the etiologic heterogeneity of obesity, some patients perhaps having deficient serotonin-mediated neurotransmission, possibly with carbohydrate-craving, and some not. It may also be, in part, a motivational artefact, the mildly obese lacking sufficient incentive to remain on a restrictive diet, and the severely obese

needing no additional drug or "TRP effect" to commit themselves to that diet.

The response rate that we observed could reflect special problems associated with the design of our study, e.g., the fact that we saw our patients only once each 2 or 4 weeks; that we had no direct observations of what and how much they ate and whether they actually complied with the diet or the TRP regimen most of the time, and that, as discussed below, we were unable to give the TRP along with some carbohydrate, which would be expected to *enhance* its brain uptake by lowering plasma levels of its competitors (Crandell & Fernstrom, 1980). Instead, we gave the TRP after meals which were rich in these competing amino acids. Conceivably an obesity-management program in which each patient's TRP intake is individualized and in which patients are accepted only if their obesity is "moderate" and their apparent motivation good, but in need of buttressing, may show a greater degree of TRP responsiveness.

The TRP dose that we administered (750 mg p.o. twice daily) was lower than that generally used to induce sleep (Wyatt et al., 1970) or to treat depression (Coppen et al., 1967; Moller, Kirk, & Freming, 1976). A 1-g dose, given at the same time as in the present study (1 hour after a meal), increased plasma TRP levels and the plasma TRP/LNAA ratio by 150–200% after 2 hours among subjects consuming a PSMF diet; however, the plasma TRP/LNAA ratio was not significantly elevated beyond that seen in the same subjects after an overnight fast while on a normal diet (Heraief et al., 1983). Most likely, much greater increases in the plasma TRP ratio would have been produced had we been able to give the TRP along with an insulin-releasing carbohydrate; the protocol of the PSMF diet precluded administering this combination. We elected to use a relatively small TRP dose in order to minimize such reported TRP side-effects as sleepiness and because higher doses can, by diminishing the plasma *tyrosine* ratio, impair brain catecholamine synthesis (Wurtman, Larin, Mostafapour, & Fernstrom, 1974). We also included caffeine in our TRP and placebo preparations in order to reduce whatever mid-day sleepiness the TRP might produce; none of our patients complained of sleepiness or fatigue as a side effect of the amino acid, nor were there any other reported side effects.

In conclusion, a moderate dose of TRP significantly enhanced weight loss among some moderately obese patients on a PSMF diet. The effect was not sufficiently consistent to justify routine TRP supplementation with this diet. Nevertheless, the partial efficacy observed in this study suggests that TRP might be more effective when given to selected populations of obese people, perhaps along with carbohydrates.

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