Effects of normal meals rich in carbohydrates or proteins on plasma tryptophan and tyrosine ratios[1–3]

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ABSTRACT

Background: The delivery of circulating tryptophan to the brain and its conversion to serotonin vary directly with plasma concentrations of tryptophan and inversely with those of other large neutral amino acids (LNAAs). Although carbohydrate-rich, protein-free formula diets have been shown to elevate, and high-protein diets to depress, the tryptophan-LNAA ratio, few data are available about this ratio's responses to actual meals.

Objective: We determined whether carbohydrate-rich or protein-rich breakfasts, such as those Americans normally eat, produce substantial differences in the plasma tryptophan-LNAA ratio and in the corresponding ratio for tyrosine, the precursor of brain dopamine and norepinephrine.

Design: Nine overnight-fasted subjects consumed, 3–7 d apart, a carbohydrate-rich (69.9 g carbohydrate and 5.2 g protein) and a protein-rich (15.4 g carbohydrate and 46.8 g protein) breakfast. Blood samples collected at baseline and after 40, 80, 120, and 240 min were assayed for tryptophan, tyrosine, the 5 other LNAAs, and insulin.

Results: The carbohydrate-rich and protein-rich breakfasts had significantly different effects on both the plasma tryptophan-LNAA and tyrosine-LNAA ratios (each $P < 0.01$). Among the 8 subjects who consumed both breakfasts, the median difference for tryptophan:LNAA was 54% (range: 36–88%) and for tyrosine:LNAA was 28% (range: 10–64%). Insulin concentrations rose significantly after the carbohydrate but not after the protein meal.

Conclusions: High-carbohydrate and high-protein breakfasts similar to those Americans normally eat can cause substantial differences in the plasma tryptophan ratio and thus, probably, in brain tryptophan concentrations and serotonin synthesis. Such meals also change the plasma tyrosine ratio and may thereby modify catecholamine synthesis. *Am J Clin Nutr* 2003;77:128–32.

KEY WORDS Tryptophan, serotonin, tyrosine, dopamine, norepinephrine, insulin, dietary carbohydrates, dietary proteins, breakfast, plasma amino acids

INTRODUCTION

The rate of brain serotonin synthesis normally depends on its concentration of tryptophan, serotonin's essential amino acid precursor (1–4). This is because tryptophan hydroxylase (EC 1.13.99.3), the enzyme that catalyzes the initial and rate-limiting step, has a very low affinity for tryptophan and is thus highly unsaturated at physiologic brain tryptophan concentrations (5). Brain tryptophan concentrations and the flux of tryptophan from blood to brain, depend, in turn, partly on plasma tryptophan and partly on plasma concentrations of ≥6 other large neutral amino acids (LNAAs): tyrosine, phenylalanine, leucine, isoleucine, valine, and methionine (2, 6, 7), which compete with tryptophan for blood-brain barrier transport (8).

Because dietary carbohydrates and proteins affect plasma concentrations of tryptophan and the other LNAAs (9, 10), these macronutrients also affect brain tryptophan concentrations and, thereby, serotonin synthesis and release (11, 12). Dietary carbohydrates produce major, insulin-mediated decreases in the branched-chain amino acids but lesser reductions in plasma tryptophan, thus raising the plasma tryptophan ratio (6, 9, 10) and facilitating tryptophan's entry into the brain (13). Proteins, in contrast, lower the plasma tryptophan ratio because they contribute less tryptophan than do other LNAAs to the circulation.

The changes in brain serotonin caused by these macronutrients have been proposed as underlying the "carbohydrate craving" seen in disorders characterized by affective and appetitive symptoms (14), eg, seasonal depression (15), the premenstrual syndrome (16), smoking withdrawal (17), and obesity associated with carbohydrate snacking (18, 19). Conversely, the decreases in brain tryptophan and serotonin caused by low-carbohydrate weight-loss diets might underlie the associated binge eating sometimes seen in female dieters (20). It has also been speculated, but not shown for humans consuming real foods, that variations in the carbohydrate and protein contents of meals and snacks can cause sufficient changes in brain tryptophan to provide the brain with neurochemical signals, on the basis of neurotransmitter release, about the composition of the foods currently being digested and absorbed (21).

Although abundant evidence exists that synthetic-formula meals can affect the plasma tryptophan ratio (9, 10, 22), producing ≤2-fold differences, depending on their proportions of carbohydrates and proteins (22), few data are available on the changes

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TABLE 1
Macronutrient contents of breakfast meals

Food item	Amount	Energy	Protein	Carbohydrates	Fat
		kcal	*g*	*g*	*g*
High carbohydrate					
Waffles	2 each, 70 g	175.70	4.13	27.02	5.46
Maple syrup	30 g	78.60	0	20.16	0.06
Orange juice	0.12 L	56.03	0.85	13.45	0.07
Brewed coffee	0.24 L	4.74	0.24	0.95	0
Granulated sugar	10 mL	32.25	0	8.33	0
Total		347.32	5.21	69.90	5.59
High protein					
Turkey ham	30 g	34.29	5.46	0.21	1.29
Egg Beaters[1]	0.36 L	180.00	36.00	6.00	0
Grapefruit sections	0.12 L	34.50	0.63	8.83	0.11
American processed cheese	1 piece, 21 g	78.75	4.66	0.34	6.57
Butter, salted	5 mL	33.91	0.04	0.00	3.84
Total		361.44	46.80	15.39	11.81

[1] Beatrice Foods, Inc, Waukesha, WI.

in this ratio produced by the kinds of meals or snacks that Americans normally eat. Hence, we examined the changes in the plasma tryptophan ratio that result from consuming 2 relatively typical breakfasts (**Table 1**), one rich in carbohydrates (69.9 g) but containing little protein (5.2 g; carbohydrate:protein = 13.4) and one containing less carbohydrate (15.4 g) and more protein (46.8 g; carbohydrate:protein = 0.3). Because neuronal tyrosine concentrations can also influence the synthesis of brain dopamine and norepinephrine in physiologically active neurons (3, 23–25), we also measured the effects of the 2 breakfast meals on the plasma tyrosine-LNAA ratio, which determines postprandial brain tyrosine concentrations (7).

SUBJECTS AND METHODS

Subjects

Nine normal weight-for-height men and women were entered into the protocol, and 8 (6 women and 2 men) completed the study. The mean (± SEM) age for all subjects was 24.2 ± 1.3 y (range: 20–30 y), and their mean (± SEM) body mass index (in kg/m^2) was 24.8 ± 1.4 (range: 19.8–29.6). The protocol was approved by the Massachusetts Institute of Technology's Institutional Review Board and by its Clinical Research Center's Scientific Advisory Committee, and each subject signed a consent form that stated the purpose of the study, the nature of the experiment, and the sampling to be done. The subjects were asked to give a medical history and to undergo a physical examination, a complete blood count, and a pregnancy test when appropriate.

Experimental procedure

The subjects were outpatients at the Massachusetts Institute of Technology Clinical Research Center. Eight of the 9 consumed both of the breakfasts, 3–7 d apart, at 0700 after an overnight fast; subject 5 consumed only the carbohydrate-rich diet. The components of the 2 breakfasts are described in Table 1. The order of breakfasts consumed was randomized. Blood samples were taken before starting breakfast consumption and at intervals (40, 80, 120, and 240 min) after completion of the breakfast (which took ≈18 min). These were collected into heparinized tubes and immediately centrifuged at 1500 × *g* for 15 min at 4 °C; plasma was frozen until assayed. The subjects consumed a light lunch after the last blood sample was collected.

Analytic methods

Tryptophan was assayed by the method of Berardino et al (26) with the use of HPLC separation and quantification by fluorescence detection. Blood collected in heparinized tubes was centrifuged at 4 °C at 1500 × *g* for 15 min, and plasmas were separated. After deproteinization of 200-μL samples with perchloric acid (7.5 N; 10 μL) and centrifugation at 14 930 × *g* for 10 min at room temperature, 25-μL aliquots were automatically injected into an HPLC reversed-phase column and their fluorescence emissions quantitated. The fluorescence detector was set at wavelengths of 225 nm excitation and 350 nm emission.

The other principal LNAAs were separated by ion-exchange HPLC, subjected to postcolumn reaction with ninhydrin, and quantified with a Beckman amino acid autoanalyzer (Beckman Coulter, Inc, Fullerton, CA) by measuring absorbence at 570 nm (27). Insulin was assayed radioimmunologically (28) to confirm for each subject that the carbohydrate meal enhanced insulin secretion and the protein meal had little or no effect on insulin concentrations.

Statistical analyses

The primary outcomes of this study were the percentage changes from baseline in the tryptophan-LNAA and tyrosine-LNAA ratios over time. For each ratio, LNAA is the sum of tryptophan, tyrosine, phenylalanine, leucine, isoleucine, valine, and methionine minus the amino acid in the numerator. Data were plotted separately by subject and summarized as means ± SEMs over time and by breakfast. The percentage change from baseline in each ratio was modeled by using mixed-models analysis of variance; effects of the order of interventions, breakfast (carbohydrate rich and protein rich), time, and the breakfast-by-time interaction. Post hoc comparisons of each time point compared with baseline, and each time point between breakfasts, were quantified by using model contrasts. All reported *P* values are two-sided; post hoc tests were adjusted for multiple comparisons. Peak percentage change from baseline on carbohydrate-rich breakfast,

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TABLE 2
Effects of consuming a high-carbohydrate or high-protein breakfast on the plasma tryptophan–large neutral amino acid (LNAA) and plasma tyrosine-LNAA ratios[1]

	Breakfast	
	High carbohydrate (n = 9)	High protein (n = 8)
Baseline plasma tryptophan-LNAAs	0.099 ± 0.019	0.084 ± 0.027
Percentage change in plasma tryptophan-LNAAs from baseline values[2]		
40 min	−5.3 ± 5.8	−17.1 ± 6.1[3]
80 min	6.8 ± 5.2	−23.0 ± 5.5[3]
120 min	14.4 ± 5.6	−27.7 ± 5.9[3]
240 min	10.2 ± 5.9	−34.8 ± 6.2[3]
Baseline plasma tyrosine-LNAAs	0.100 ± 0.017	0.119 ± 0.020
Percentage change in plasma tyrosine-LNAAs from zero-time values[4]		
40 min	0.4 ± 3.0	−9.1 ± 3.2[3]
80 min	3.5 ± 2.9	−15.3 ± 3.0[3]
120 min	4.6 ± 3.3	−19.8 ± 3.5[3]
240 min	−4.7 ± 3.8	−21.9 ± 4.1[3]

[1] $\bar{x}$ ± SEM. LNAAs = tryptophan + tyrosine + leucine + isoleucine + valine + phenylalanine + methionine minus the amino acid in the numerator.
[2] Statistically significant interaction between breakfast and time, $P < 0.0001$ (mixed-models ANOVA).
[3] Statistically significant change from baseline value, $P < 0.05$ (mixed-models ANOVA and Bonferroni corrected model contrasts).
[4] Statistically significant interaction between breakfast and time, $P = 0.004$ (mixed-models ANOVA).

nadir percentage change from baseline on protein-rich breakfast, and the difference (peak − nadir) were calculated; the times of peak and nadir were also noted. The peak insulin concentrations on each breakfast were calculated and summarized as medians and ranges of values. Analyses used SAS version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Percentage change in tryptophan-LNAA ratios

There was a statistically significant interaction between breakfast and time ($P < 0.0001$), indicating that there are different effects of carbohydrate-rich and protein-rich breakfasts on plasma tryptophan-LNAA ratios (**Table 2**). With the carbohydrate-rich breakfast, tryptophan:LNAA was observed to decrease ≈5% below baseline at 40 min, then rise ≈7%, 14%, and 10% above baseline at 80, 120, and 240 min, respectively. These differences from baseline were not statistically significant.

In contrast, after consumption of the protein-rich breakfast, tryptophan:LNAA decreased ≈17%, 23%, 28%, and 35% below baseline at 40, 80, 120, and 240 min, and each of these decreases was statistically different from zero (each $P < 0.05$). Hence the changes from baseline produced by the 2 breakfasts did not differ significantly after 40 min but did so after 80, 120, and 240 min (each $P \leq 0.05$).

In the 8 subjects who completed both breakfasts, the median increase from baseline after carbohydrate was 11%, and the median nadir after protein was −37%. The median difference between the percentage changes after carbohydrate and protein was 54%; the range was 36–88%. In 5 subjects the carbohydrate-induced rise in tryptophan:LNAA peaked at 120 min after baseline, and in 5 subjects the protein-induced decrease was greatest 240 min after baseline.

Percentage change in tyrosine-LNAA ratios

There was a statistically significant interaction between breakfast and time ($P = 0.004$), indicating that there are different effects of protein-rich and carbohydrate-rich breakfasts on plasma tyrosine-LNAA ratios (Table 2). With the carbohydrate-rich breakfast, tyrosine:LNAA increased to < 1%, 3%, and 5% above baseline at 40, 80, and 120 min, respectively, and fell (5% from baseline) after 240 min. These changes from baseline were not statistically significant. With the protein-rich breakfast, tyrosine:LNAA decreased 9%, 15%, 20%, and 22% from baseline at 40, 80, 120, and 240 min, respectively; each such decrease was statistically different from zero (each $P < 0.05$). Hence the changes from baseline were statistically significantly different between breakfasts at each time point (each $P < 0.05$).

In the 8 subjects who completed both breakfasts, the median increase from baseline after carbohydrate was 7%, and the median nadir after protein −23%. The median difference between the percentage changes after carbohydrate and protein was 28%; the range was 10–64%.

Insulin

All subjects except one had undetectable basal plasma insulin concentrations (< 3 μIU/mL). After the carbohydrate breakfast, 8 of 9 subjects had clinically significant increases in insulin concentrations (ie, peak insulin ≥ 12.1 μIU/mL); the median peak was 20.1 μIU/mL, and peak concentrations ranged from 5.5 to 38 μIU/mL. After the protein breakfast, only 4 of 8 subjects had any increase in insulin concentrations, and none of these was clinically significant; the median peak was 3.2 μIU/mL, and peak concentrations ranged from undetectable (< 3 μIU/mL) to 9.5 μIU/mL.

Among the 4 subjects who did exhibit increased insulin secretion after the protein breakfast, the peak insulin concentration after the carbohydrate breakfast was ≥ 2.5-fold higher (2.6-, 3.0-, 4.7-, and 11-fold higher) than that after the protein breakfast. The subject with the peak insulin of 5.5 μIL/mL after the carbohydrate breakfast (subject 5) was not tested on the protein breakfast.

DISCUSSION

These data show that breakfast meals typical of those consumed in the United States can cause substantial variations in the plasma tryptophan-LNAA and tyrosine-LNAA ratios, depending on the proportions of carbohydrates and protein in the meal. Moreover, the differences between the ratios generated by a high-carbohydrate, low-protein breakfast and a breakfast rich in protein can be > 50% for tryptophan:LNAA and 30% for tyrosine:LNAA. For tryptophan:LNAA this mean difference is less than the 100% differences observed elsewhere (22) when subjects ate synthetic mixtures containing either sucrose or starch, or fat plus protein; for tyrosine:LNAA, the difference was greater than that observed after subjects consumed either a protein-free or a 50-g protein breakfast (9).

A 50% variation in the plasma tryptophan ratio is probably sufficient, in rats, to increase or decrease significantly the quantities

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of serotonin released by brain neurons. This is suggested by the following observations (2, 6, 7, 11, 12): Consumption of 2 test meals that caused the plasma tryptophan ratio to equal 0.10 or 0.15 produced brain tryptophan concentrations that differed by 39% (ie, 2.70 compared with 3.75 μg/g). But in another study, when the tryptophan concentrations in 2 sets of brain slices were decreased or increased by 40% (by adding more or less tryptophan to the media) the amounts of serotonin released from the slices spontaneously, or after electric depolarization, differed significantly, by 28% and 14%, respectively. (Data are lacking on which to base similar estimates of the effects of food on serotonin or catecholamine release in human brain.)

A 30% variation in the plasma tyrosine ratio would also be sufficient to produce major changes in brain tyrosine concentrations (7). But whether or not such changes would also affect brain dopamine or norepinephrine synthesis probably depends on the kinetic properties of the enzyme tyrosine hydroxylase (1.14.16.2) in particular sets of neurons. Some dopaminergic neurons, ie, those terminating in the prefrontal and cingulate cortices (29), apparently always respond to changes in local tyrosine concentrations, just as serotoninergic neurons throughout the brain and spinal cord (30) always respond to changes in tryptophan concentrations; this may be related to these neurons' high firing frequencies (29). But in most catecholaminergic neurons the enzyme's catalytic activity is limited, basally, not by its unsaturation with tyrosine, but by its much greater unsaturation with its cofactor tetrahydrobiopterin (25). When these neurons become physiologically active and undergo sustained periods of frequent depolarization, the enzyme protein becomes phosphorylated, dramatically increasing its affinity for tetrahydrobiopterin and allowing its net activity to depend on the tyrosine concentrations. Hence a food-induced increase in brain tyrosine might be expected to enhance dopamine or norepinephrine release from some catecholaminergic neurons but not from others. A food-induced decrease in brain tyrosine, if sufficient, might diminish catecholamine release to the point of activating a compensatory increase in the neuron's firing frequency, which might then amplify its sensitivity to tyrosine concentrations.

The magnitude of change in the plasma tryptophan ratio after, for example, consumption of a carbohydrate-rich snack probably depends on the individual's recent nutritional history: if the most recent meal consumed was like the protein-rich breakfast in this study—eliciting little insulin secretion, raising plasma LNAA concentrations, and decreasing the tryptophan-LNAA ratio—the effect of that snack on the ratio may be more robust than if the most recent meal was poor in protein. [The effect of the snack will also depend on the glycemic indexes of its carbohydrates (22).] The largest variation in the ratio will occur if a person is faced with choosing between 2 meals or snacks like the breakfasts provided in this study: if the carbohydrate-rich foods are chosen, the subsequent output of serotonin from brain neurons will probably be considerably different than it would have been had this choice instead been the protein-rich foods. Hence the "carbohydrate craving" exhibited by subjects with seasonal depression (14, 15), the premenstrual syndrome (16), and other serotonin-related disorders may reflect both the wish to consume carbohydrate-rich snacks and the wish to avoid those rich in proteins.

The proportion of high–glycemic index carbohydrate to protein that will neither raise nor lower plasma LNAAs (ie, because the direct contribution to the blood of the LNAAs in the protein is matched by the LNAA-lowering effect of the insulin secreted by the carbohydrate) is ≈5–6:1 for humans (31). Many supermarket items (eg, cookies, some breakfast cereals) contain carbohydrate and protein in ratios of 10:1 or greater, whereas meats, dairy products, and soy products provide substantially lower ratios. Hence the capacity of meal or snack foods to increase or decrease brain serotonin synthesis is considerable. These effects tend to be buffered at meals, when several different food items, or even courses, are chosen. In contrast, snacks may contain a single food item, and if that item is very rich—or poor—in protein, its effect on brain serotonin is largely unbuffered.

Although the macronutrient-induced changes in the plasma tyrosine ratio are in the same direction as those in the tryptophan ratio, the amplitudes of these changes are only approximately half those for the tryptophan ratio. This may provide the brain with an additional mechanism for distinguishing the effects of a high-carbohydrate from a high-protein meal. The high-carbohydrate food would be expected to cause considerably greater amplification of serotonin than of catecholamine release, and the high-protein item would reduce catecholamine output less than it reduces that of serotonin. Apparently no data are available on the concurrent effects of specific macronutrients on serotonin and catecholamine release in the brains of experimental animals.

RJ W and JJW designed the study, RHT designed the specific components of the 2 test breakfast meals, JMM managed the implementation of the study protocol, JJB performed the biochemical assays, MMR did the statistical analysis of the data and the power calculations that determined the number of subjects studied, and RJW oversaw the writing of the manuscript. No author had any financial interest in the organizations sponsoring this research (ie, the National Institutes of Health and the Center for Brain Sciences and Metabolism Charitable Trust). RJW is the Program Director of the MIT Clinical Research Center, which is funded by the NIH, and the Scientific Director of the Center for Brain Sciences and Metabolism Charitable Trust; and JJW is a Trustee of that Trust.

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