The Effect of a Carbohydrate-Rich Beverage on Mood, Appetite, and Cognitive Function in Women With Premenstrual Syndrome

RAJA SAYEGH, MD, ISAAC SCHIFF, MD, JUDITH WURTMAN, MD, PAUL SPIERS, PhD, JANINE McDERMOTT, BA, AND RICHARD WURTMAN, MD

Objective: **To test the efficacy of a specially-formulated, carbohydrate-rich beverage (one known to increase the serum ratio of tryptophan to other large neutral amino acids) on the mood, cognitive, and appetitive disturbances of premenstrual syndrome (PMS).**

Methods: **Twenty-four women with confirmed PMS were enrolled in a double-blind, crossover study to test the efficacy of the specially-formulated beverage compared with two other isocaloric products on PMS symptoms. The study was conducted over three menstrual cycles preceded by a 1-month placebo run-in. Patients were tested at home or work using an interactive computer-telephone system. Standardized measurements of mood, cognitive performance, and food cravings were made before and 30, 90, and 180 minutes after consumption of active and placebo beverages during the late luteal phase of the menstrual cycle.**

Results: **The experimental carbohydrate intervention significantly decreased self-reported depression, anger, confusion, and carbohydrate craving 90–180 minutes after intake. Memory word recognition was also improved significantly compared with scores obtained during the placebo run-in month ($P < .05$). The isocaloric placebo interventions had no significant effect on any of these measures.**

Conclusion: **The results suggest that the psychological and appetitive symptoms of PMS can be relieved after consuming a specially-formulated, carbohydrate-rich beverage known to increase serum tryptophan levels.** ***(Obstet Gynecol 1995;86:520–8)***

Premenstrual syndrome (PMS) describes a set of somatic, appetitive, behavioral, and cognitive changes that recur monthly during the late luteal phase of the menstrual cycle.[1] The etiology of PMS remains unknown, but deficiencies in serotonin-mediated brain neurotransmission are now considered responsible, in part, for the symptoms of dysphoria and increased consumption of carbohydrate-rich foods observed with this syndrome.[2–5] The evidence for that comes from studies in which drugs that increase synaptic serotonin levels ameliorate these symptoms. Dexfenfluramine, which releases brain serotonin and blocks its re-uptake, improves premenstrual dysphoria and normalizes calorie and carbohydrate consumption among women with moderate to severe PMS.[5,6] Similarly, fluoxetine, a selective serotonin re-uptake blocker, improves the psychological symptoms of women with severe PMS.[2,7–11]

Previous studies in the rat have demonstrated that dietary manipulations that increase the relative abundance of serum tryptophan compared with other amino acids are associated with an increase in brain tryptophan levels and serotonin synthesis. In one such manipulation, the intake of carbohydrates was found to increase brain serotonin synthesis by an insulin-mediated reduction in plasma levels of large neutral amino acids that naturally compete with tryptophan,

From the Division of Reproductive Endocrinology and Infertility, Vincent Memorial Obstetrics and Gynecology Service, Massachusetts General Hospital, Harvard Medical School, Boston; and the Department of Brain and Cognitive Science, Massachusetts Institute of Technology, Cambridge, Massachusetts.

This work was supported by a grant from Walden Laboratories, Sausalito, California.

We thank Dr. Ray Gleason of the Clinical Research Center at the Massachusetts Institute of Technology, Cambridge, Massachusetts, for serving as statistical consultant, and Dr. Mary Collins of McLean Hospital, Belmont, Massachusetts, for screening the subjects involved in this study for psychiatric disorders.

Financial Disclosure

The experiments described herein were funded by Walden Laboratories (Sausalito, California), a start-up company that is presently discontinuing operations relating to nutritional and pharmaceutical products. A patent based on data in this article has been applied for by Walden Laboratories. Dr. Judith Wurtman held equity in and has served as scientific adviser to Walden Laboratories. She no longer has any position with the company or any equity in it.

 0029-7844/95/$9.50
SSDI 0029-7844(95)00246-X

serotonin's precursor, for receptor-mediated transport across the blood-brain barrier.[12] In humans, clinical studies have shown that dietary modifications that cause a depletion of serum tryptophan levels have negative effects on mood and cognition,[13,14] suggesting that the mechanisms of tryptophan uptake and serotonin synthesis by the human brain may be similar to that of the rat. Women with PMS increase their consumption of carbohydrate-rich foods significantly, and some evidence suggests that this may induce a serotonin-mediated improvement in mood.[15,16] The hypothesis that the carbohydrate craving of women with PMS reflects an attempt at self-medication was examined in a previous study[15] by allowing subjects to consume a dinner of corn flakes and assessing their mood using self-reported psychological measures immediately before and after the meal. There was a significant improvement in mood 90 minutes after the meal, suggesting that carbohydrate intake can generate a response that is similar, albeit less robust, than that seen after treatment with serotoninergic drugs. However, this was not a double-blind study, which means that the observed improvement in symptoms may have been due to expectation effects. Furthermore, because the test meal was given at dinnertime, it is possible that food intake alone contributed to the observed improvement in mood. Moreover, conducting the study in the neutral setting of a clinical research center may in itself have contributed to a lessening of tension, anger, or depression.

With the shortcomings of the aforementioned study in mind, the current study was designed to examine the efficacy of a specially-formulated, carbohydrate-rich beverage in relieving premenstrual disturbances in mood, appetite, and cognitive performance. Women with PMS were tested in their home or work environment in a double-blind, placebo-controlled, crossover trial. This allowed the subjects to be tested whenever they were premenstrual, even if that occurred on weekends or holidays, and did not restrict testing to weekdays when the research facility was open. Our hypothesis was that the intake of appropriately designed, carbohydrate-rich foods alleviates the symptoms of PMS.

Materials and Methods

Subjects responded to newspaper advertisements inviting participation in a study on the effects of dietary interventions on premenstrual mood changes. The study protocol was approved by the Institutional Review Board of Massachusetts General Hospital, and all subjects gave informed consent before starting the study. To qualify, subjects had to meet established National Institute of Mental Health criteria for the diagnosis of PMS[17] as well as the criteria listed in the diagnostic and statistical manual for the diagnosis of late luteal-phase dysphoric disorder.[18] This meant a 1-year history of five or more symptoms attributable to the disorder, with at least one symptom being marked affective lability, irritability, tension, or depression. Symptoms had to be severe enough to impair daily activities and had to be present premenstrually and remit with the onset of menses. The subjects had to be in good health, nonsmokers, and not using oral contraceptives or any other medication. Women who were pregnant or lactating or had irregular menstrual cycles, gynecologic disorders, or psychiatric illness were not accepted. For 2 consecutive months, subjects had to prospectively rate daily changes in their mood, appetite, work and social impairment, and physical symptoms using a symptom rating scale. The items on the scale were based on those in the daily calendars used by Mortola et al[19] and Endicott and Halbreich[20] to track premenstrual symptomatology. In addition, the data form included questions on food cravings, health status, and daily incidence of stressful events and was completed each day for the first 2 weeks of each cycle. Psychiatric illness was excluded by independent interviews with a psychiatrist. Women with high scores on the mood and appetite scales in the early phase of the menstrual cycle (follicular phase) were asked to withdraw because they might have had a diagnosis other than PMS (eg, depression or premenstrual magnification syndrome). Patients were supplied with, and instructed in the use of, ovulation prediction kits (Clear Plan Easy; Whitehall Laboratories, Madison, NJ). As soon as the color change that indicates the preovulatory LH surge in urine was observed, patients were asked to report their symptoms each evening by telephone using a voice-mail system in addition to completing the daily calendar. Subjects with a 30% increase in the symptom severity during the postovulatory phase of two menstrual cycles as reported on the daily diary form qualified for the testing phase and were asked to continue tracking and reporting ovulation and symptoms in the same way over the next 4 months.

Three dietary interventions were tested. The experimental beverage, designated A, contained a mixture of simple and complex carbohydrates previously shown to raise the serum tryptophan to large neutral amino acid ratio significantly above fasting levels and hypothesized to be the most likely dietary intervention to alter premenstrual symptoms. Two other beverages, designated B and C, were also tested; these were similar in appearance and identical in calorie content to beverage A but contained mixtures of protein and carbohydrate (B) or carbohydrates (C) that left the serum tryptophan

to large neutral amino acid ratio unchanged. In an earlier pilot test on volunteers, consumption of drink A, which contained 47.5 g of a mixture of dextrose and maltodextrin, caused a 29% increase in the serum tryptophan to large neutral amino acid ratio at 90 minutes (mean [standard error of the mean] T0 = 0.168 [0.016], T90 = 0.217 [0.025], $P < .05$), and this increase was sustained 180 minutes after intake. Control drink B consisted of 15 g of casein and 32.5 g of dextrose; its consumption caused a slight and insignificant decrease in the plasma tryptophan to large neutral amino acid ratio (T0 = 0.088 [0.007], T90 = 0.086 [0.004]). Control drink C contained 47.5 g of a mixture of galactose and dextrose; this increased the serum tryptophan to large neutral amino acid ratio by less than 4% (T0 = 0.107 [0.004], T90 = 0.112 [0.004]). Based on these data, we assumed that using the three drinks in a randomized, blinded study would distinguish the effects of consuming calories per se (drink B) or carbohydrates per se (drink C) from the effects of consuming nutrients that presumably enhance serotonin-mediated neurotransmission (drink A). Drink B was also used as the placebo run-in product during the first month of testing. The three drinks were isocaloric and supplied slightly under 200 calories. They were manufactured by Shear-Kershman (St. Louis, MO), provided in individual containers as orange-flavored powders, and reconstituted in 7.5 ounces of water immediately before consumption.

The subjects consumed one of the test beverages during the late luteal phase of the menstrual cycle on a day when premenstrual symptomatology had significantly worsened from follicular levels. The testing day was determined by closely monitoring the severity of each subject's symptoms as reported on her daily chart and transmitted by telephone each evening. Symptoms were checked daily after ovulation, and when mood and appetite measurements indicated at least a 30% increase in severity over follicular levels, the subject was called and scheduled to be tested within the next 48 hours. Because premenstrual tension, anger, depression, and confusion scores obtained with the self-reported form have been shown previously to correlate significantly with scores on the Profile of Mood States (POMS),[19] it was assumed that the daily symptom report was predictive of the subject's pre-drink responses on the POMS. The three drinks were administered according to a Latin square crossover schedule, and the study was carried out double-blind. The 3-month testing period was preceded by a placebo run-in month during which all subjects ingested control beverage B. This testing period was used to decrease the possibility that participation in the study would in itself alleviate premenstrual symptomatology. Neither the subjects nor staff members in contact with the subjects knew that the first month intervention was a placebo; however, the subjects were told that they would receive the same drink again during one of the 3 subsequent test months. Subjects were told to eat lunch no later than 11:45 AM on each test day so as not to consume the test beverage soon after the meal. Specific guidelines as to the size and content of the lunch meal were provided before testing to minimize possible effects of the meal itself on hunger, appetite and food cravings, and variations in the digestion and absorption of the test beverages. Subjects were not allowed to consume any food or beverage except water during the testing period. If a woman's menstrual period happened to start before the designated test day, she was tested on that beverage during her next menstrual cycle. Testing usually started around 2 PM.

Mood and appetite scores were obtained during a 3-hour period that presumably overlapped with the period of sustained increase in the serum tryptophan to large neutral amino acid ratio after ingestion of drink A. Subjects were tested immediately before consuming the test beverage (T0) and 30 (T30), 90 (T90), and 180 (T180) minutes thereafter. Mood was measured using an abbreviated questionnaire modeled on the POMS.[21] Subjective ratings of tension, depression, anger, and confusion were obtained using a five-point scale in which 0 was "not at all" and 4 was "very much." Cravings for protein-rich foods (eg, fish or chicken), carbohydrate-rich foods (eg, cookies or chips), fat-rich foods (eg, cheese or peanut butter), and fruits and vegetables as well as appetite in general were assessed with a ten-point scale in which 1 was "not at all" and 10 was "very much."

The mood and appetite assessments were carried out using a computerized telephone system. The subject called a toll-free number, entered an identity code using the number pad of the telephone, and was then asked to respond to questions on the mood and appetite scales. The computer asked the subject to respond to questions about how she felt and also to rate her cravings and appetite at that moment. She was asked to use the numbers on the telephone keypad to quantify her responses. After each response, the computer stated a verbal equivalent of the number response; ie, if the subject pressed "1" in response to a query on confusion, the computer stated, "You are a little confused." If the computer statement did not conform to the patient's subjective state, she was given the opportunity to change her answer. The instructions were repeated several times during the testing process, and subjects were taught how to interact with the computer before the initiation of the actual testing process. Use of this telephone-dependent testing system enabled testing to be carried out on weekends and holidays as well as

during the work week in the subject's own environment. In many cases, the testing began while the subjects were at work and was completed after they had returned home.

The cognitive tests were administered by an investigator over the telephone because the verbal responses to two of the three tests could not be quantified on a scale of 1–10. Repetitive administration of cognitive tests is known to improve performance. To minimize such practice effects, subjects were not tested before consuming the test drink, but were tested only once during the 3-hour period after its consumption. Moreover, different forms of each test were used when the effects of the other two drinks were examined. T90 was chosen as the test time for cognitive function because we believed that T30 testing would precede the expected changes in brain serotonin levels and T180 testing might affect responses because of testing fatigue. Responses were compared with those obtained during the follicular phases of the first two cycles and to responses obtained during the late luteal phase of the placebo run-in cycle. The follicular-phase testing was carried out between days 7 and 8 of the menstrual cycle and at the same time of day that luteal-phase testing was done. The follicular scores obtained from the first 2 months of testing were summed to obtain a mean follicular rating for each of the cognitive measurements.

Three cognitive tests were administered at T90: the Paced Auditory Serial Addition Test (PASAT), the Auditory Consonant Trigrams Recognition (ACT-R) and the Controlled Oral Word Association Test (COWAT). In the PASAT, the subject must add 60 pairs of randomized digits so that each digit is added to the digit immediately preceding it, but not to the sum of the two digits preceding it.[22] Each sum is stated aloud by the subject before the next digit is spoken by the investigator, and the entire test is timed and presented rapidly at a fixed rate. The ACT-R measures verbal recognition and memory by asking the subject to recall six sets of three consonants previously spoken by the investigator and repeated by the subject.[23] The consonants that must be recognized are interspersed among consonant sets that the subject has not heard previously. The COWAT, which assesses word finding and verbal retrieval, asks the subject to say as many words during 1 minute as she can think of that begin with a particular letter of the alphabet.[24] Different letters with similar word frequencies are used during each testing period.

A repeated measures Latin squares design was used in analyzing the data in order to adjust for anticipated order effects. For variables showing a significant interaction effect (product versus time), single-factor analyses of variance (ANOVA) by time were done using Newman-Kuels pairwise comparisons to test for significant differences between products. The pre-drink T0 mood and carbohydrate craving scores showed large inter-subject variability from cycle to cycle. To adjust for this, statistical analyses were performed using the T0 scores as the covariate. Repeated measures of covariance were used to assess effects of the dietary interventions on mood. Before analyzing the data for the mood scores, we decided to focus on the change in mood 90–180 minutes after intake. This time period was selected as the most likely to reveal changes in mood, appetite, and cognitive measures; it coincided with the period of expected increase in the serum tryptophan to large neutral amino acid ratios found in our pilot study as well as in other studies in both men and women.[25,26] However, because T180 often coincided with subjects' dinnertime and complaints of hunger, it was difficult to distinguish between self-reported cravings for specific foods and generalized hunger cravings. Accordingly, we decided a priori to focus on appetite ratings at T90. To prevent practice effects from altering cognitive performance, no pre-drink measurements were made during the 3 test months. Instead, the cognitive score obtained during the placebo run-in month was used as the baseline score. This baseline score was then compared with the mean score from 2 months of follicular-phase testing to determine whether cognitive performance worsened during the luteal phase of the menstrual cycle. A paired t test was used for this comparison. Subsequently, T90 luteal-phase scores from the 4 test months (including the placebo test month) were analyzed using a single-factor repeated measures ANOVA with planned comparisons (probable least squares difference).

Over 500 women claiming to have PMS inquired about participating in the study in response to the advertisement. Ninety-nine subjects qualified for the testing phase of the study, but the final study sample consisted of 24 subjects. Of the 75 subjects who dropped out, 30% were asked to terminate their participation because of very mild mood and appetite disturbances, onset of menstrual irregularities, or pregnancy. Another 50% were asked to withdraw because of breach of protocol, either failed compliance with the rigorous testing schedule or the inability to track and report their daily premenstrual symptomatology. The remaining 20% of the 75 dropouts elected to switch to a concurrent drug study for PMS. The final study sample of 24 women had a mean age of 37 years (standard deviation [SD] 1.2); the mean height was 64 inches (SD 0.5) and the mean weight was 134 lb (SD 4.7). All 24 subjects completing the study demonstrated at least a 30% increase in premenstrual symptom scores above follicular values on their daily ratings of symptomatology.

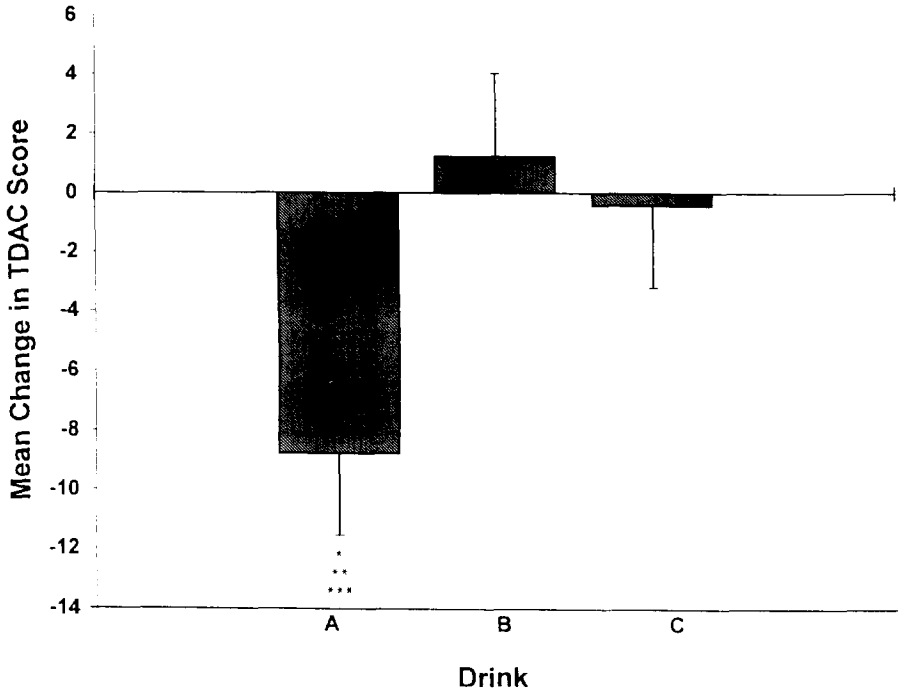

Figure 1. Changes in total mood score (summed tension, anger, depression, and confusion) (TDAC) at T180. To adjust for large intersubject variability between cycles in pre-drink mood, statistical adjustments were made using the T0 score as the covariate. *$P < .04$ treatment effect of drink A; **$P < .02$ compared with drink B; ***$P < .04$ compared with drink C.

Moreover, when their mean follicular scores on the mood and appetite scales were compared with their baseline scores on each test day (T0), there was a significant increase in depression, anger, tension, and confusion on the POMS scale and in self-assessed appetite ($P < .01$).

Results

No order effects were found on any of the outcome measures. Moreover, the effects of placebo drink B were no different between the first month during which all subjects consumed it and later months. Drink A, the experimental beverage containing the mixture of dextrose and maltodextrin designed to elevate the serum tryptophan to large neutral amino acid ratio, proved most effective in improving mood scores at T180. At that time, there was a significant treatment effect of drink A on the summed scores of four factors on the POMS, depression, tension, anger and confusion, ($F = 3.74$, $P < .04$) (Figure 1). Comparisons with the other drinks showed that the improvement in self-reported mood after consumption of drink A was significantly greater than that reported after consumption of drinks B ($P < .02$) and C ($P < .04$). The two factors on the POMS that showed the most robust improvements were anger and depression. Drink A was significantly more effective than B ($P < .05$) and C ($P < .01$) in reducing anger (Figure 2) and more effective than drink B ($P < .05$) in reducing depression scores (Figure 3). No effects and no differences between the three drinks were noted in the T30 or T90 mood scores. Drink A also showed a significant treatment effect on suppressing cravings for sweet and starchy carbohydrates 90 minutes after consumption ($F = 4.34$, $P < .03$) and was significantly more effective than drinks B ($P < .04$) and C ($P < .01$) in that regard (Figure 4). Total appetite and desire for protein-rich foods, fat-rich foods, and fruits and vegetables were unaffected by any of the treatments. No effect of any drink on appetite or food cravings was seen at T30 or T180.

During the premenstrual testing phase, no measurements of cognitive performance could be made immediately before the consumption of the test beverages because of the need to minimize practice effects. To establish that the subjects' cognitive performances had indeed deteriorated premenstrually, their performance on the cognitive tests obtained during the placebo run-in month were compared with their performance during the two follicular test sessions. No difference in performance on the COWAT or PASAT were found during the placebo run-in month compared with scores obtained during the follicular phase. However recognition memory assessed with the ACT-R declined significantly ($P < .02$). None of the drinks affected performance on the verbal retrieval test, COWAT, or the serial addition test, PASAT. However, drink A significantly improved scores on the recognition memory measure, ACT-R, compared with scores obtained during the

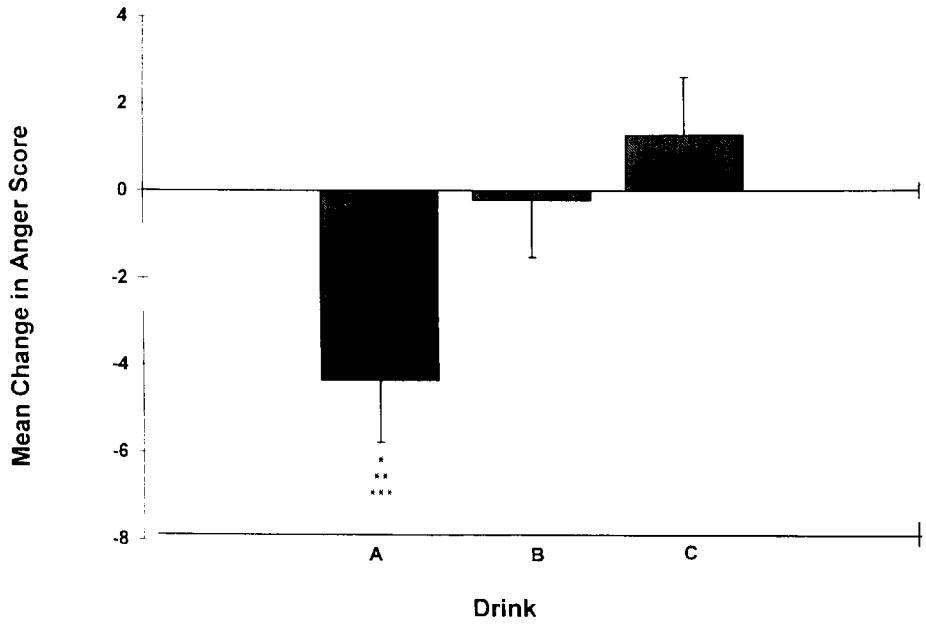

Figure 2. Change in anger scores at T180. To adjust for large inter-subject variability between cycles in pre-drink anger, statistical adjustments were made using the T0 score as the covariate. *$P < .02$ treatment effect of drink A; **$P < .05$ compared with drink B; ***$P < .01$ compared with drink C.

placebo run-in ($P < .04$), whereas drinks B and C did not show any improvement (Figure 5).

Discussion

Our data show that consumption of a carbohydrate beverage designed to increase the serum tryptophan to large neutral amino acid ratio relieves premenstrual mood and appetite disturbances and improves certain aspects of memory. These findings confirm those obtained in an earlier unblinded study and show that the improvement caused by ingesting an appropriate carbohydrate beverage is not due to a placebo response or to the ingestion of calories or carbohydrates per se. Moreover, improvement in premenstrual symptomatology occurred even though subjects remained exposed to the daily stresses of their work or home environments. The treatment effects of drink A and the differences seen between drink A and the control drinks were

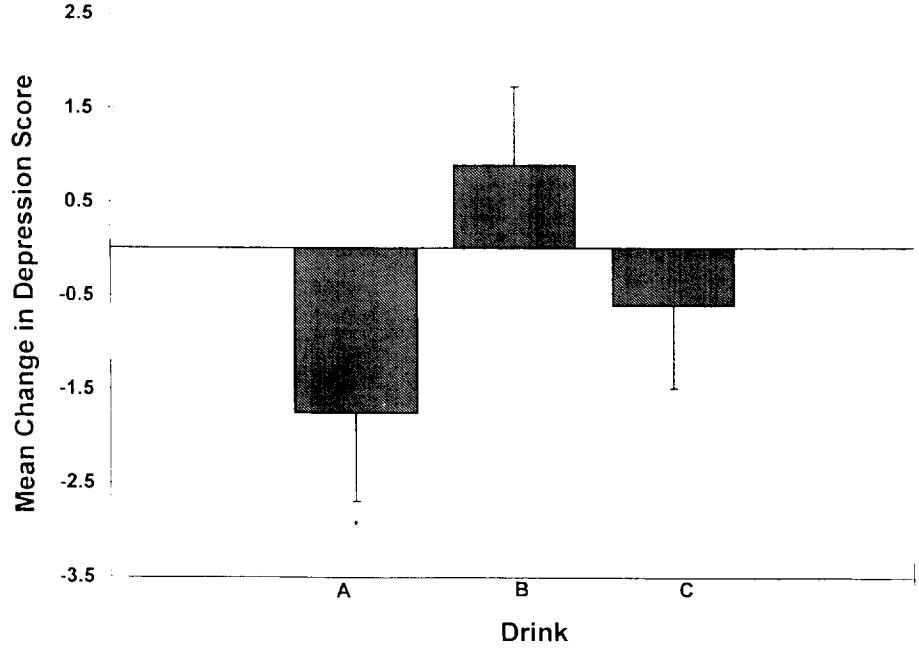

Figure 3. Changes in depression scores at T180. To adjust for large inter-subject variability between cycles in pre-drink depression, statistical adjustments were made using the T0 score as the covariate. *$P < .05$ compared with drink B.

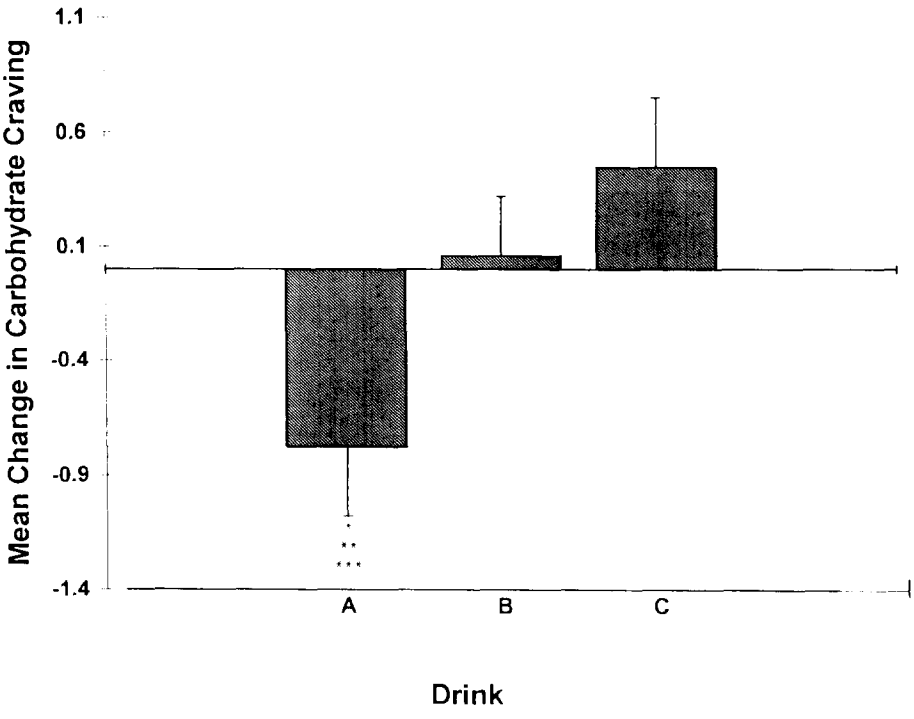

Figure 4. Changes in carbohydrate craving at T90. To adjust for large inter-subject variability between cycles in pre-drink carbohydrate-craving scores, statistical adjustments were made using the T0 score as the covariate. *$P < .03$ treatment effect of drink A; **$P < .04$ compared with drink B; ***$P < .01$ compared with drink C.

significant 180 minutes after intake, and this is consistent with the time course of sustained serum elevation of the tryptophan to large neutral amino acid ratio. Unlike the effects on mood, which peaked at T180, drink A seemed to exert its most significant effects on carbohydrate craving at T90; this is also consistent with the time course of the rise in the serum tryptophan to large neutral amino acid ratio. As mentioned earlier, the T180 appetite measurements frequently overlapped with dinnertime for many subjects. We speculate that the T180 appetite and craving scores for drink A did not show a significant improvement because they were

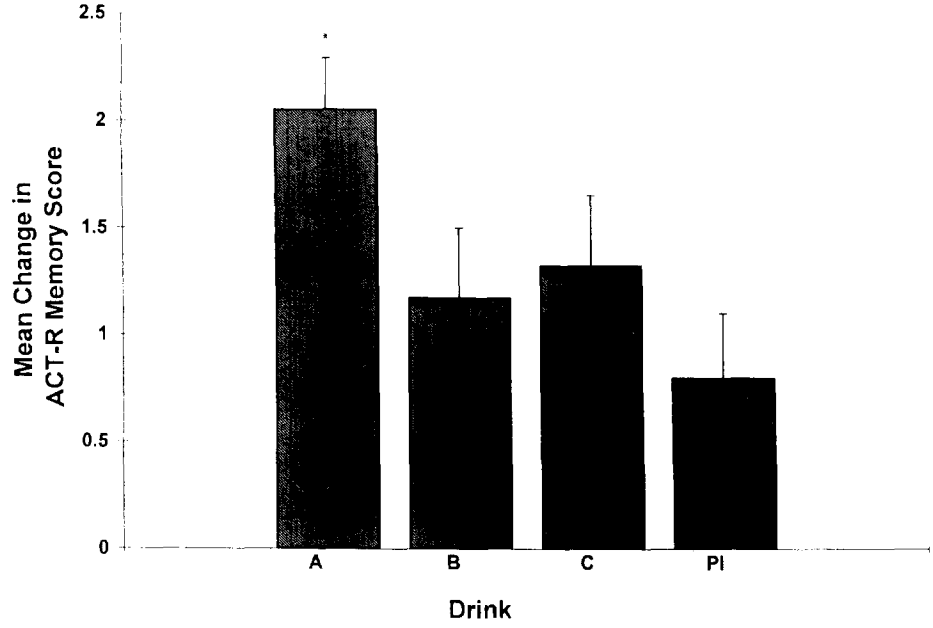

Figure 5. Changes in recognition memory score (Auditory Consonant Trigrams Recognition [ACT-R]) at T90. Measurements after consumption of the three test drinks were compared with those obtained during the placebo run-in month. Drink A improved recognition memory scores compared with placebo (Pl). *$P < .04$.

confounded by the fact that subjects were simply hungry and had not eaten for 6 hours (except for the test drink). Finally, no changes in any outcome measures were detected at T30, which precedes the expected rise in the serum tryptophan to large neutral amino acid ratio. The absence of effects at T30 suggests that consumption of the test drinks per se was not responsible for the subsequent alterations in mood, appetite, and cognitive performance.

In this study, none of the interventions restored premenstrual cognitive performance to follicular levels. However, drink A did significantly improve recognition memory compared with that observed during the placebo run-in period. The time course of this improvement at 90 minutes after intake is consistent with the time course of the expected biochemical changes in serum. However, we could not determine whether the observed improvement in memory after beverage consumption was specific and not a consequence of the overall improvement in mood because tests that might have aided in making this distinction could not be administered over the phone. It is interesting to note a recent study that suggested that late luteal-phase decrements in cognitive performance are independent of mood.[27] The study found that women with PMS performed less well on tests of learning during both phases of their cycle compared with women without PMS. This is in contrast to frontal lobe functions, in which a significant association was found between impairment of function and severity of premenstrual symptoms.[28] Moreover, our findings are consistent with a recent report in which dietary manipulations that caused tryptophan depletion produced selective impairments in learning and memory in normal volunteers.[13] It would be complementary to determine whether our dietary intervention, designed to enhance tryptophan availability, would improve cognitive functions among normal volunteers.

The ability of carbohydrate intake to improve mood among women with PMS has been observed in other populations who describe increased carbohydrate intake associated with depressed, anxious, or irritable mood states. Obese carbohydrate cravers who periodically increase their intake of carbohydrate-rich snacks[29] and individuals suffering from seasonal affective disorder who eat excessive amounts of carbohydrate-rich foods during the late fall and winter are thought to seek carbohydrate-rich foods as a form of self-medication.[30] Consumption of carbohydrate-rich test foods has been shown to improve depressed and anxious mood in such populations,[29,31] as has the administration of dexfenfluramine, a drug that selectively enhances serotoninergic-mediated neurotransmission by both releasing the amine and blocking its re-uptake.[30] However, consumption of particular carbohydrate-rich foods may not always improve the mood of such individuals if the composition of the food or quantity consumed precludes a sufficient elevation in the serum tryptophan to large neutral amino acid ratio to affect brain tryptophan uptake. This may explain why drink C, whose carbohydrate composition failed to elevate the tryptophan to large neutral amino acid ratio, was ineffective in improving premenstrual symptomatology.

The efficacy of drink A in relieving psychological and appetitive symptoms of PMS provides additional evidence that serotonin-mediated brain neurotransmission is involved in the late luteal-phase changes in mood and eating behavior. Our results are also consistent with a recent study that showed that dietary manipulations reducing the tryptophan to large neutral amino acid ratio exacerbate premenstrual symptoms.[32] Treatment of PMS with pharmacologic agents that increase intrasynaptic serotonin levels has been shown previously to reduce premenstrual behavioral disturbances[2,10,33] and to normalize carbohydrate intake.[15] Admittedly, the improvement in premenstrual mood and carbohydrate cravings observed in this study is considerably smaller than that observed after drug treatment, but so are the risks and side effects, which were nonexistent.

Although the results of PMS studies are often confounded by the number of placebo responders,[34] this was not the case in our study. There was no effect of treatment order on subjects' responses, and perhaps our use of computerized testing diminished placebo responses. Subjects were tested in their own surroundings, thereby removing possible effects of a neutral testing site on mood. Furthermore, subjects had no significant interactions with staff members during any but the cognitive tests, so unconscious tester bias was removed and subjects could not anticipate empathetic responses during testing. Indeed, use of the naturalistic environment may have reduced the robustness of improvement because there was no way of controlling for the stresses of the workplace, home, commuting, and fortuitous annoyances during the 3-hour test period. We conclude that the ingestion of appropriately designed carbohydrate-rich preparations during the late luteal phase of the menstrual cycle may relieve some of the premenstrual disturbances of mood and appetite and possibly cognition, thus providing a benign intervention for women with moderate to severe PMS. It is hoped that larger studies will confirm the usefulness of this intervention.

References

1. Steiner M. Female-specific mood disorders. Clin Obstet Gynecol 1992;35:599–611.

2. Wood S, Mortola J, Chan Y-F, Moossazadeh F, Yen S. Treatment of premenstrual syndrome and fluoxetine: A double-blind, placebo-controlled, crossover study. Obstet Gynecol 1992;80:339–44.
3. Bancroft J, Cook A, Williamson L. Food craving, mood, and the menstrual cycle. Psychol Med 1988;18:855–60.
4. Smith S, Schiff I. Modern management of premenstrual syndrome. New York: Norton Medical Books, 1993.
5. Brzezinski A, Wurtman J, Wurtman R, Gleason R, Nader T, Laferrere B. D-fenfluramine suppresses the increased calorie and carbohydrate intakes and improves the mood of women with premenstrual syndrome. Obstet Gynecol 1990;76:206–301.
6. Elia D, Auclair J, Rey C. Etude de l'efficacite et de l'acceptabilite d'Isomeride chez des femmes consultant en gynecologie. Rev Fr Gynecol Obstet 1992;87:361–9.
7. Elkin M. Open trial of fluoxetine therapy for premenstrual syndrome. South Med J 1993;86:503–7.
8. Stone A, Pearlstein T, Brown W. Fluoxetine in the treatment of premenstrual syndrome. Psychopharmacol Bull 1990;26:331–5.
9. Stone A, Pearlstein T, Brown W. Fluoxetine in the treatment of premenstrual syndrome. J Clin Psychiatry 1991;52:290–3.
10. Menkes DB, Taghavi E, Mason PA, Spears GFS, Howard RC. Fluoxetine treatment of severe premenstrual syndrome. BMJ 1992; 305:346–7.
11. Steiner M, Steinberg S, Stewart D, et al. Fluoxitine in the treatment of premenstrual dysphoria. N Engl J Med 1995;332:1529–34.
12. Fernstrom J, Wurtman R. Brain serotonin content: Physiological regulation by plasma neutral amino acids. Science 1971;178:414–6.
13. Park SB, Coull JT, McShane RH, et al. Tryptophan depletion in normal volunteers produces selective impairments in learning and memory. Neuropharmacology 1994;33:575–88.
14. Young SN, Smith SE, Pihl RO, Ervin FR. Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology 1985;87:173–7.
15. Wurtman J, Brzezinski A, Laferrere B, Wurtman R. Effect of nutrient intake on premenstrual depression. Am J Obstet Gynecol 1989;161:1228–34.
16. Bancroft J, Williamson L, Warner P, Rennie D, Smith S. Perimenstrual complaints in women complaining of PMS, menorrhagia and dysmenorrhea: Toward a dismantling of the premenstrual syndrome. Psychosocial Med 1993;55:133–45.
17. Rubinow DR, Roy-Byrne P. Premenstrual syndrome. Overview from a methodologic perspective. Am J Psychiatry 1984;141:163–72.
18. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed, revised. Washington, DC: American Psychiatric Association, 1987.
19. Mortola J, Girton L, Beck L, Yen S. Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: The calendar of premenstrual experiences. Obstet Gynecol 1990;76: 302–7.
20. Endicott J, Halbreich U. Retrospective report of premenstrual depressive changes: Factors affecting confirmation by daily ratings. Psychopharmacol Bull 1982;18:109–22.
21. McNair DM, Lorr M, Droppleman LS. EITS manual for the Profile of Mood States. San Diego: Educational and Industrial Testing Service, 1971.
22. Cronwall D, Wrightson P. Memory and information processing cavity after closed head injury. J Neurol Neurosurg Psychiatry 1981;44:889–95.
23. Milner B. Memory and the medial temporal regions of the brain. In: Pribam KH, Broadbent DE, eds. Biology of memory. San Diego: Academic Press, 1970.
24. Benton AL, Hamsher K, Des S, Varney NR, Spreen O. Contributions to neuropsychological assessment. New York: Oxford University Press, 1983.
25. Lieberman H, Caballero B, Finer N. The composition of lunch determines afternoon plasma tryptophan ratios in humans. J Neural Transm 1986;65:211–7.
26. Moller S. Neural amino acid plasma levels in healthy subjects: Effects of complex carbohydrate consumed along with protein. J Neural Transm 1989;76:55–63.
27. Keenan PA, Stern RA, Janowsky DS, Pedersen CA. Psychological aspects of premenstrual syndrome. I: Cognition and memory. Psychoneuroendocrinology 1992;17:179–87.
28. Brugger P, Milicevic A, Regard M, Cook N. Random-number generation and the menstrual cycle: Preliminary evidence for a premenstrual alteration of frontal lobe functioning. Percept Mot Skills 1993;77:915–21.
29. Lieberman H, Wurtman J, Chew B. Changes in mood after carbohydrate consumption among obese individuals. Am J Clin Nutr 1986;44:772–8.
30. O'Rourke D, Wurtman J, Wurtman R, Chebli R, Gleason R. Treatment of seasonal depression with d-fenfluramine. J Clin Psychiatry 1989;50:343–7.
31. Rosenthal N, Genhart M, Caballero B, Jacabsen J, Skwerer R. Psychobiological effects of carbohydrate- and protein-rich meals in patients with seasonal affective disorder. Biol Psychiatry 1989;25: 1029–40.
32. Menkes D, Coates D, Fawcett J. Acute tryptophan depletion aggravates premenstrual syndrome. J Affect Disord 1994;20:1–7.
33. Boyer W. Potential indications for the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 1992;6:5–12.
34. Reid R. Premenstrual syndrome. Curr Probl Obstet Gynecol Fertil 1985;8:1–5.

Address reprint requests to:
Raja Sayegh, MD
Vincent Memorial Obstetrics & Gynecology Service
Massachusetts General Hospital
Fruit Street
Boston, MA 02114

Received April 11, 1995.
Received in revised form June 15, 1995.
Accepted June 21, 1995.