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Influence of Timed Nutrient Diet on Depression and Light Sensitivity in Seasonal Affective Disorder

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INFLUENCE OF TIMED NUTRIENT DIET ON DEPRESSION AND LIGHT SENSITIVITY IN SEASONAL AFFECTIVE DISORDER

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Seasonal Affective Disorder (SAD) patients crave and eat more carbohydrates (CHO) in fall-winter when depressed, especially in the evenings, and feel energetic thereafter. Evening CHO-rich meals can phase delay circadian rhythms, and glucose increases retinal response to light. We studied timed CHO- or protein-rich (PROT) diet as a putative therapy for SAD. Unmedicated, DSM-IV-diagnosed depressed women with SAD (n = 22, 19–63 yrs) in the follicular phase of the menstrual cycle (present in 19) were randomized to nine days of eating ~1600 kcal of either CHO before 12:00 h (n = 9), CHO after 18:00 h (n = 6), or PROT after 18:00 h (n = 7); only water was allowed for the rest of the day. Measurements included the depression questionnaire SIGH-SAD (with 21-item Hamilton depression subscale), Eating Behavior Questionnaire (DEBQ), percentage fat (by bioimpedancemetry), clinical biochemistry (glucose, cholesterol, triglycerides, TSH, T4, cortisol), and electroretinogram (ERG). No differential effects of diet were found on any of the studied parameters (except DEBQ). Clinically, participants improved slightly; the 21-HDRS score (mean ± SD) decreased from 19.6 ± 6.4 to 14.4 ± 7.4 ($p = .004$). Percent change correlated significantly with menstrual day at diet onset (mood improved the first week after menstruation onset), change in available sunshine (more sunlight, better mood), and initial

percentage fat (fatter patients improved more). Scotopic ERG amplitude was diminished after treatment ($p = .025$, three groups combined), probably due to greater exposure to sunshine in 14/22 subjects (partial correlation analysis significant). Keeping in mind the limitations of this ambulatory study (i.e., inability to control outdoor light exposure, small number of participants, and briefness of intervention), it is suggested that the 25% clinical improvement (of the order of magnitude of placebo) is not related to nutrient diet or its timing, but rather to natural changes during the menstrual cycle, available sunshine, and ease of dieting for fatter patients. (Author correspondence: dani@irs.ru)

INTRODUCTION

Seasonal Affective Disorder (SAD) patients crave and eat more carbohydrates (CHO) in fall-winter (Kräuchi & Wirz-Justice, 2000). Carbohydrate craving and weight gain may be a residual adaptive reaction in the annually "hibernating" SAD patients (Davis & Levitan, 2005). CHO intake may be not only be a symptom of the disorder, but also an attempt to self-treat. Similar ideas have been proposed for early morning awakening in major depression as a kind of (inadequate) sleep deprivation therapy. In contrast to controls, patients with SAD report activation following high carbohydrate meals (Rosenthal et al., 1989). Some patients do recognize that carbohydrates help them immediately overcome feelings of dissatisfaction and provide more energy (Kräuchi et al., 1997; Rosenthal et al., 1984). It may not be a coincidence, therefore, that both low mood/energy and CHO craving/consumption increase toward the evening (Kräuchi et al., 1990; Rosenthal et al., 1984).

One of the popular biochemical hypotheses explores whether carbohydrates stimulate the influx of tryptophan to the brain (relative to other amino acids; Wurtman & Wurtman, 1988). Tryptophan is synthesized into the brain neurotransmitter serotonin, the turnover of which is believed to be insufficient in SAD. Both tryptophan depletion diet and tryptophan pills influence the symptoms of SAD (Neumeister et al., 2001).

Glucose has been found to increase the retinal response to light (namely, from rods) in mammals, including humans (Ames et al., 1992; Macaluso et al., 1992; Skrandies & Heinrich, 1992). Though no change of the rod amplitude has been found during winter depression (but rather a shift of rod retinal sensitivity to a lower level; see Hébert et al., 2004; Lam et al., 1992), it has been not ruled out that glucose or carbohydrates may improve depression additionally via a change of retinal functionality.

Not only nutrient content but also nutrient timing may play a role in the putative antidepressant effect of food. Circadian rhythms in SAD

patients have higher day-to-day phase variability with a tendency to phase delay (summarized in Koorengevel et al., 2002). Some data (Lewy et al., 2006; Terman et al., 2001) support the hypothesis that a phase advance of circadian rhythms can improve mood in SAD patients. Evening carbohydrate intake can phase delay circadian rhythms in healthy individuals (Kräuchi et al., 2002). If so, morning but not evening CHO intake may be postulated to induce a therapeutic effect.

The present study tested whether a CHO-rich or protein-rich diet may influence depression in SAD. It is hypothesized that a morning CHO-rich diet is more effective than evening CHO-rich diet, and a protein-rich diet is not effective at all. Apart from psychometric and physical measurements, biochemistry and ocular light response (by electroretinogram) were analyzed. The study was controlled for menstrual cycle phase and available sunshine.

METHODS

Participants

The study was performed in Novosibirsk (55° N) during two consecutive winters (2001–2002 and 2002–2003). The experimental protocol conformed to international ethical standards (Touitou et al., 2006) and was approved by the local ethic committee. Recruitment was from a database of SAD patients and via advertisements in local newspapers. After a short inquiry by telephone, the applicants were invited for a personal interview with a clinician (DK). Inclusion criteria were: diagnosis of winter SAD based on DSM-IV criteria (American Psychiatric Association, 1994), women, age 18–65 yrs, currently depressed, free from antidepressant interventions, good physical health, sleep at normal night times, and willingness to participate. The qualified volunteers signed a consent form and were informed that the aim of the study was to test the influence of nutrients on depression. They were paid a small amount for their compliance to the dietary interventions.

Protocol and Interventions

This was an open, parallel-group, randomized clinical trial. Each SAD patient was randomly assigned to one of three nine-day diets: CHO-rich food in the morning (before 12:00 h), CHO-rich food in the evening (after 18:00 h), or protein-rich (PROT) food in the evening (after 18:00 h; see Figure 1). No other meals were allowed the rest of day, except for mineral water. PROT-rich food in the morning was not included in the design because compliance could be especially difficult for SAD patients who "treat" themselves preferentially with carbohydrates
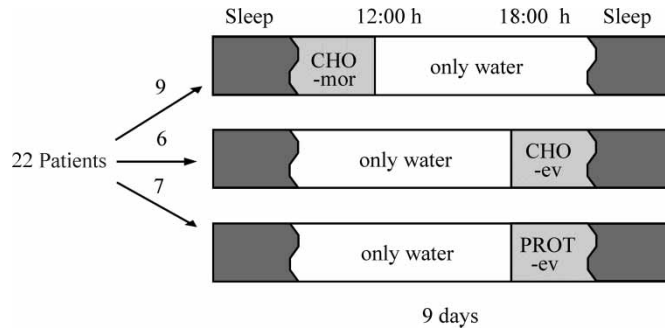
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FIGURE 1 A scheme of the diet study. Abbreviations: CHO-mor = carbohydrate-rich meals in the morning, CHO-ev = carbohydrate-rich meals in the evening, PROT-ev = protein-rich meals in the evening.

and eat mostly in the evenings; this diet was thus considered unethical. The study start day was assigned to the first half of the patient's menstrual cycle, if present. Patients came to the Eye clinic at 11:00 h to give a 10 ml of fasting blood sample and to carry out some measurements (i.e., the completion of depression and eating questionnaires, assessment of body weight and percentage fat, and performance of electroretinogram), which took 2–3 h. After giving blood, patients were allowed a snack with tea, and thereafter they immediately started the assigned diet. They received a list of prescribed or prohibited food to eat at home (see Table 1). The amount of daily food was defined as a large meal which corresponds to at least 1600 kcalories/day (a mild hypocaloric diet). During the nine days of dieting, patients filled out sleep and food intake diaries. On the day following the end of the diet, patients returned to the clinic for the follow-up investigation.

Outcomes

Depression score obtained with SIGH-SAD (Williams et al., 1994) was the primary outcome study measure. It includes the 21-item Hamilton scale ($HDRS_{21}$) and an eight-item addendum designed specifically to score the so-called "atypical" SAD symptoms. Because the diet may confound the score on four addendum items related to increased appetite, eating, weight, and carbohydrate craving, a truncated $SIGH\text{-}SAD_{25}$ version as well as $HDRS_{21}$ were analyzed separately from SIGH-SAD. The symptoms were estimated over the previous 3–4 days. The ratings were all done by a single investigator (DK).

Questionnaire approaches included also expectations toward depression outcome rated by patients at the initial visit on a Likert scale (from 1, no improvement, to 5, complete recovery). At the follow-up

TABLE 1 A List of Food for Patients to Use in Their Diet

CHO-rich food
- Pasta
- Cereals (semolina, rice, buckwheat, corn, etc.)
- Potatoes
- Farinaceous food (cakes - not fat)
- Sweets (sugar, jam, honey, candies, chocolate, etc.)
- Sweet dairy products (condensed milk with sugar, ice-cream, yogurt, etc.)
- Fruits (grapes, apples, oranges, etc.)
- Berries
- Juice, jelly, cocoa

PROT-rich food
- Meat (not fat)
- Fish (except herring and other fat fishes)
- Eggs
- Cheese, curds
- Nuts

Food that could be added to both CHO and PROT diet
- Vegetables (cabbages, beans, onions, etc.; except potatoes)
- Mushrooms
- Salads
- Seasonings (including broth cubes)
- Oil & butter (no more than 50 g a day)
- Milk, kefir (no more than 300 ml a day)
- Sour cream (10% fat, no more than 100 g a day)
- Coffee, tea*, cola
- Alcohol (beer, wine, etc.)

Prohibited
- Fat food (pork, sausages, herring, cakes with cream, fat sour cream, food canned with oil)
Volume of Basic Food Eaten/Day
- Minimum 1600 kcal, which corresponds to approximately 1 big plate of food (400 g and more)

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*To sweeten tea, diabetic sugar substitute pills are obtainable from investigator.

visit, subjects reported whether the dieting was rather easy or difficult for them. The Dutch Eating Behaviour Questionnaire (DEBQ; Van Strien et al., 1986) was filled in at both visits; it assesses a degree of drive to eat related to external, restraint, and emotional factors. For example, the emotional factor is constructed from 13 questions expressing desire to eat following (negative) emotions.

Weight, height, and percentage of fat were measured. The percentage of fat was measured by a bioimpedancemeter Omron BF 302 (Matsusaka Co, Ltd, Japan). Electroretinography (ERG) was performed by standard techniques with a DTL fiber as an active electrode positioned deeply in the conjunctival bag of both eyes (Hébert et al., 1996). First, rod sensitivity was measured after 30 min pre-adaptation in complete darkness (scotopic ERG); then, cone sensitivity was recorded after 10 min pre-adaptation in light of 100 lux intensity presented within a Ganzfeld globe (photopic

ERG). Sensitivity was measured by presenting light flashes of a definite number, interval, duration, intensity, and color (for the flash details, see Hébert et al., 1996). The evoked bio-potentials from the retina in each series of flashes were amplified, averaged, and presented graphically on the screen by the Medelec system (England, issue 1987). Amplitude and timing of the response were then analyzed by conventional methods (Brown, 1968).

Blood was centrifuged, and 4 ml of serum was frozen for later assay of glucose, cholesterol, triglycerides, thyroid-stimulating hormone (TSH), thyroxine (T_4), and cortisol. These indices were chosen to track possible metabolic and stress effects of the selected diets. Two serum samples from each person (baseline and follow-up) were assayed in the same run to avoid interassay variability. Glucose, cholesterol, and triglycerides were assayed by conventional clinical laboratory methods. TSH, T_4, and cortisol were measured by immunochemiluminometric assay (ILMA; reagent kits from Immunotech, Prague, Czech Republic; Alkor-Bio, Saint Petersburg, Russia). The sensitivity of the assay and maximal intra-assay variations within the normal range of the hormones were: 0.03 mU/l and 6.2% for TSH, 10 nmol/l and 4.9% for T_4, and 5 nmol/l and 8% for cortisol.

Daily hours of sunshine available over the duration of the study were provided by the local meteorologic station.

Statistics

The influence of diet on depression and other parameters of interest was tested by analysis of variance for repeated measures (rANOVA) with factors Group (diet type) and Time (before/after diet); Huynh-Feldt's corrected probabilities (P) are reported. Comparison between variables was made with Student's *t*-test and correlation with Pearson's test when not otherwise specified. Standard deviations from the mean ($\pm$ SD) accompany mean values in the text, whereas standard errors of the means (SEM) are presented in figures.

RESULTS

Baseline Data

Twenty-two SAD subjects aged 19–63 (37.8 $\pm$ 11.8) yrs started the study, and all completed it (11 in the first year and 11 in the second year). Seventeen of the 22 subjects had previously participated in clinical trials and showed good compliance. Women with menstrual cycles (n = 19) started the study within days 0–15 after menstruation onset (median = six days). Nine participants were randomized to a

CHO-morning diet, six to a CHO-evening diet, and seven to a PROT-evening diet. The groups did not differ by age, weight, body-mass index, percentage fat, or menstrual cycle day at dieting onset, and neither was there a significant difference in initial SIGH-SAD scores. Subject expectations were low (median rating "little improvement"), and happened to be lower in the CHO-evening group than in the two others combined (tied $p = .037$, Mann-Whitney test). The diets were evaluated between December 5 and February 22. The entry date was similar for subjects of all study groups; median: January 13 for CHO-morning, January 17 for CHO-evening, and January 11 for PROT-evening group ($p = 0.93$, Kruskal-Wallis test). According to individual diaries, the average sleep period during the diets ranged from 22:32–01:26 h to 07:15–09:42 h. Biochemical variables were not analyzed in two cases: one subject refused consent to venipuncture, and in another, the tube with collected blood broke during centrifuging. One subject could not undergo ERG because of glaucoma, a medical condition in which the mydriatic required for pupillary dilation in order to conduct the ERG is contraindicated.

Outcomes and Estimation

No differential effects of diet on depression were found. Overall, improvement was from SIGH-SAD score 30.7 ± 8.0 to 22.2 ± 11.1 ($p = .002$; see Figure 2), with four subjects classified as responders ($\geq 50\%$ score reduction) and one as remitted ($\geq 50\%$ improvement, final score ≤ 14 with ≤ 7 on $HDRS_{21}$ and ≤ 7 on addendum items). $SIGH\text{-}SAD_{25}$ and Hamilton subscale separately showed similar results. The decrease of the $HDRS_{21}$ score was from 19.6 ± 6.4 to 14.4 ± 7.4 ($p = .004$).

Weight decreased after the hypocaloric diet by 1.2 ± 1.3 kg ($p < .001$), and the percentage loss tended to be more pronounced with the CHO-morning diet compared to the evening diets ($p = .078$). Percentage fat also tended to decrease, from $26.4 \pm 9.5\%$ to $26.1 \pm 9.5\%$ ($p = .083$). Nine patients rated dieting as quite easy, and 13 as quite difficult, but this was independent of the type of diet (distribution across diets, χ^2 test $= .32$).

Neither clinical chemistry (i.e., glucose, cholesterol, triglycerides, TSH, T_4, and cortisol) nor sleep logs yielded differences between the diet groups. In particular, glucose levels were not significantly changed after any of the diets ($p > .60$), nor was there a significant interaction of the change between the diets (rANOVA, Group $\times$ Time, $p = .82$).

Subjects' ratings of the "emotional" factor on the Eating Behavior Questionnaire increased after the CHO-morning diet, decreased after the CHO-evening diet, and remained unchanged after the PROT-evening diet (see Figure 2). Ratings of "restrained" and "external" eating factors were similar before and after the diets.
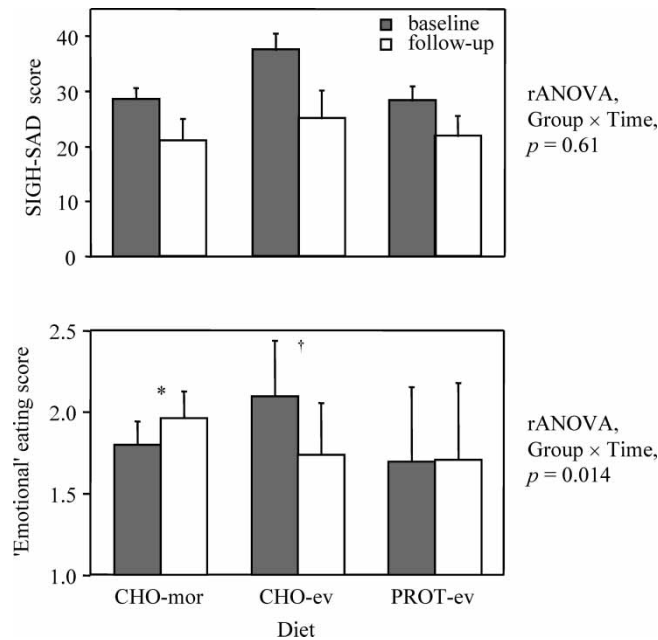
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FIGURE 2 Depression score (upper diagram) and self-ratings of "emotional" eating behavior (lower diagram) in three groups of SAD patients before and after nine days of timed nutrient diet. $^{*}p = 0.036$, $^{†}p = 0.059$, Wilcoxon tied p value.

No differential effects of diet were found on retinal sensitivity as measured with ERG (see Figure 3). However, the ERG revealed an overall decrease in the rod response (rANOVA, factor Time, $p = .025$). Specifically, the response was lower at flash intensity -1.3 log cd · sec/m^2: 193.3 ± 35.8 vs. 205.0 ± 39.0 μV ($p = .011$). The logK index (an approximated intensity at which half-maximum rod response was achieved) did not differ before and after diets: -3.06 ± 0.26 vs. -3.08 ± 0.26 log cd · sec/m^2 (rANOVA, factor Time, $p = .69$). Implicit times of the recorded ERG waves were also unchanged.

The hours of sunshine during four days preceding measurements (the recall period for patients for the depression rating) did not differ between initial and follow-up investigation: 9.9 ± 11.1 vs. 10.4 ± 6.5 h ($p = .88$), although it more often increased than decreased (in 14 vs. 8 cases, $p > .1$, sign criteria).

Ancillary Analyses

Score change (%) of the HDRS$_{21}$ was significantly correlated with menstrual day at diet onset (mood specifically improved the first week after menstruation onset), change in available sunshine (more sunlight, better mood), initial percentage fat (fatter patients improved more), age (older
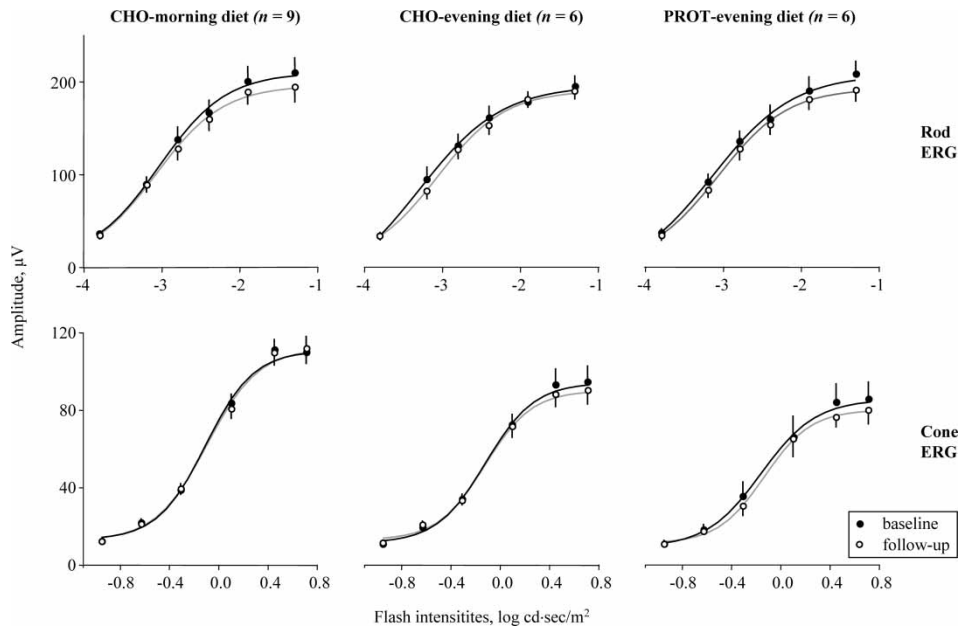
FIGURE 3 Amplitude of responses of rods and cones to light flashes of different intensities as measured by ERG (electroretinography) in three groups of SAD patients before and after nine days of timed nutrient diet. The plots are fitted with a sigmoidal function. rANOVA: group × time × intensity; rod ERG $p = 0.31$, cone ERG $p = 0.77$.

patients improved more), and ease of dieting (easy dieting associated with better improvement, Spearman's test). The change in available sunshine was calculated as the difference between hours of sunlight during the four days preceding the day of follow-up and the day of baseline investigation. This was best correlated with depression score improvement, compared with the change found for the other intervals explored (9, 8, 7, 6, 5, or 3, 2, 1 preceding days).

Because the above five factors that correlated with the $HDRS_{21}$ might be interrelated, a partial correlation analysis was performed to determine which of them are true or false predictors of the improvement. Two more potential factors were added in the analysis: diet type and expectations toward depression outcome. The analysis revealed the first three correlations remained significant (see regression plots in Figure 4), while correlations with age and ease of dieting turned out to be non-significant. The latter factors might be a reflection of stronger initial percentage fat as predictor (e.g., fatter women perhaps perceived dieting as easy, and the ease made for better improvement than in thin women).

No significant correlation between the change in rod ERG amplitude and either depression score or other variables (tested above) were
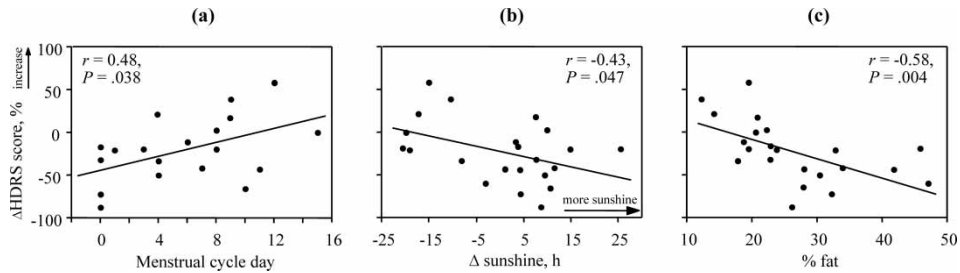
FIGURE 4 Correlation between change of 21-item Hamilton depression scale score (%) during the nine-day diet and (a) menstrual cycle day at diet onset, (b) a change in hours of sunshine during four days preceding the scorings, and (c) initial percentage fat in SAD patients.

found. However, an interesting finding of the partial correlation analysis was the detection of a significant relationship between change in rod ERG amplitude (%) and change in available sunshine (more sunlight, more decrease in amplitude; $p < .05$).

DISCUSSION

Depression

The study showed that none of the three nine-day diets (i.e., morning carbohydrate-rich diet, evening carbohydrate-rich diet, or evening protein-rich diet) had a selective mood-elevating effect upon winter depression. The 25% clinical improvement is characteristic for the placebo response rate in SAD, which is usually ~30% after one week placebo treatment (e.g., Eastman et al., 1998; Lam et al., 1995).

Because of the absence of differential effects of the diets, additional (post-hoc) analyses were completed, with significant results. These included significant correlations of the improvement with daily natural changes in sunshine availability (the relationship earlier described only in Avery et al., 2001; Molin et al., 1996), with the initial percentage of fat (suggesting the ease of dieting in fatter women did play a role), and with the menstrual cycle phase. The last relationship is well-known: depression level varies across the menstrual cycle (reviewed in Hendrick et al., 1996), and it has been previously shown that the SIGH-SAD score in SAD improved more when a one-week light therapy was initiated in the first-to-second than third or fourth quarter of the menstrual cycle (Danilenko & Putilov, 1994).

The above-listed correlations suggest that the type-II error (i.e., when the effect is in the general population but not found in a particular study) is not large. It is unlikely that there is an effect, at least not with the protocol used. However, under controlled laboratory conditions, an antidepressant

effect of diet may indeed be revealed. A phase advance of the circadian timing system is highly correlated with clinical improvement in SAD (Lewy et al., 2006; Terman et al., 2001) and CHO-rich morning meals have been shown to induce a phase advance under constant routine conditions (Kräuchi et al., 2002). However, the prerequisites for successful antidepressant response may be more complex than a simple phase advance and require a correction of internal phase misalignment between sleep and circadian rhythms, which demands measurement of melatonin at baseline and the administration of a stimulus at the appropriate time of day (Lewy et al., 2006).

Light Sensitivity

None of the diets affected the ERG in any specific way. It cannot be completely ruled out that the influence of the selected diets may be indeed evinced under laboratory conditions strictly controlled for nutrient intake and sunlight avoidance, and with an ERG system having better resolution of recordings. Serum glucose levels remained similar before and after the diets, and this was useful to interpret the lack of differential effect of diets on ERG (given the hypothesis that CHO, or glucose intake, may affect retinal response to light and depression level). However, an overall decrease in the rod ERG response after nine days was unexpected. This is unlikely to correspond to clinical improvement, as in other SAD studies no significant change in scotopic ERG amplitude has been found following clinical improvement, either in summer or after bright light therapy, but rather a lowering of the logK index (i.e., an increase of rod sensitivity; see Hébert et al., 2004; Lavoie et al., 2006). Therefore, the ERG amplitude decrease may represent a type-I error (i.e., effect not present in the general population but is found in a particular study), and it may be connected with factors other than diet, such as menstrual phase (Brûlé et al., 2007) or light exposure during the preceding days (Rufiange et al., 2007). Indications for the latter relationship were indeed found in the present study (i.e., more light during the preceding days, lower rod ERG response).

Eating Behavior

Despite the absence of a specific mood-elevating effect, the diets did influence some psychometric ratings (i.e., the Eating Behavior Questionnaire). It is known that eating style in SAD is emotional; many patients realize that and eat sweets and starches after emotional (negative) events, mostly in the evening (Kräuchi et al., 1997; Rosenthal et al., 1984). In the present study, the emotional eating score was increased with the morning carbohydrate-rich diet and decreased with the evening

carbohydrate-rich diet (and did not change with the evening protein-rich diet). This may be interpreted as a better realizing of the "food-mood" dependence when the subjects were CHO-deprived in the evening, and, in contrast, less realizing of such when they had sufficient CHO in the evening. Although emotional eating typology is a trait marker of SAD (Kräuchi et al., 1997), the present result suggest that DEBQ self-ratings may also vary depending on what and when subjects have eaten the preceding days.

Study Limitations

The limitations of the study include the uncontrolled lighting conditions of an ambulatory study and limited number of subjects, as well as the relatively short duration of the intervention (nine days) with only one follow-up, without direct control of compliance apart from log books (exact time, content, and calories of ingested meals). Also, the study design was necessarily open, as subjects were aware of what they ate. It should be noted, however, that many studies of light therapy in SAD have been of similar (1–2 week) duration with clear antidepressant effects emerging.

In conclusion, our outpatient parallel-group study did not demonstrate any clinical improvement of winter depressive state by timed nutrient CHO diet. Instead, a relationship was found between the (small) depression alleviation and day of the menstrual cycle day as well as natural changes in available sunshine.

ACKNOWLEDGMENTS

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