BRAIN SEROTONIN, CARBOHYDRATE-CRAVING, OBESITY AND DEPRESSION*

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1. ABSTRACT

Serotonin in the brain, and perhaps elsewhere, is involved in mechanisms that affect macronutrient selection, generate feelings of satiety, and, if malfunctioning, predispose to obesity. Drugs which increase the quantities of serotonin present within synapses can cause weight reduction. Such drugs presently include those that release the neurotransmitter by a direct action on nerve terminals (e.g., dexfenfluramine’s metabolite dextrofenfluramine) or by activating serotonergic neurons (e.g., nicotine); by activating post-synaptic serotonin receptors (e.g., dextrofenfluramine); or by prolonging serotonin’s existence within synapses by blocking its reuptake (e.g., dextrofenfluramine; fluoxetine, sertraline, paroxetine). Additional ways are known by which intrasynaptic serotonin levels can be augmented (e.g. increasing its synthesis with tryptophan; inhibiting its destruction by monoamine oxidase), and it can be anticipated that drugs acting at these loci will also become candidates for treating obesity.

Serotonergic drugs act in at least three ways to facilitate weight loss: They accelerate the onset of satiety (Blundell, 1986), and enhance basal metabolic rate by about 100 calories per day (Fernstrom, 1989). They also inhibit the “carbohydrate craving” manifested by many people who are overweight or are becoming so (c.f., Wurtman and Wurtman, 1989). There is reason to believe that this inappropriate eating behavior actually constitutes a “serotonin hunger” by the brain, perhaps related to the number or activity of raphe neurons, in which case giving the serotonergic drug might constitute a specific therapy for the etiologic process causing the obesity.

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Two composite case reports are presented which typify syndromes that patients can present.

Laura, a 33 year old administrator, has suffered from severe premenstrual swings in appetite and mood for a decade. During the first 21 days of her menstrual cycle, her mood is normal and her food intake well balanced; 6 or 7 days past mid-cycle, however, she finds herself becoming irritable, anxious, angry, confused and clumsy. Although she pushes herself to continue daily aerobic exercise (indoors on an exercycle or outdoors), her fatigue level rises and she becomes more sluggish when she exercises. Her appetite also changes so that the foods she consumes are largely those rich in carbohydrates. She stops eating fruits and vegetables, limits her protein intake to dairy products such as sweetened yogurt and cheese, and eats only muffins, doughnuts, bagels, or frozen yogurt during the day. As she approaches the end of her cycle, she especially craves chocolate and often eats a pint of chocolate ice cream or bag of chocolate chip cookies for supper. She also desires salty snacks such as potato chips but tries to avoid them because she thinks they make her retain water. When her food intake was examined, Laura was found to consume about 2200 calories per day during the early part of her menstrual cycle, but almost 3000 calories during the latter half: these consisted primarily of starchy carbohydrates at meals, and cookies and chocolate between meals. During the follicular phase of the menstrual cycle, her mood (as assessed by the Hamilton Rating Scale of Depressed Mood) was normal; during the luteal phase, however, this score rose from 3 to 26 (an abnormal value) and measurements of menstrual symptomatology using the Menstrual Distress questionnaire also showed significant increases in self-reported anger, confusion, irritability, carbohydrate craving, fatigue and anxiety.

Laura claimed that she was unable to lose weight because her eating was out of control for much of each month and she could not keep from overeating carbohydrates, no matter how hard she tried. She had been able to stay on a low carbohydrate diet only once, and her mood and subjective fatigue became worse as a result.

As a subject in a placebo-controlled study on the ability of dexfenfluramine to suppress premenstrual carbohydrate craving, weight gain, and mood disturbances, Laura happened to receive the drug (15 mg p.o., b.i.d.) for the 15 days of each month’s luteal phase, over a period of three months. It completely suppressed her carbohydrate craving and premenstrual weight gain, as well as the abnormal test scores on the Hamilton Rating Scale and the Menstrual Distress questionnaire. During three additional months of the study, when she received placebo instead of drug, there was no beneficial effect.

Phyllis, a 55 year old housewife who is 45 lbs. over ideal body weight, has been unable to lose weight on conventional diets; although they work for a few weeks, she becomes agitated and anxious. She then reverts to her pre-diet intake and stops losing weight. She is sedentary except during spring and summer when she occasionally takes walks.

Phyllis usually starts each day with a low-calorie breakfast and a small lunch. By mid-afternoon, she feels her mood worsening, experiencing boredom, loneliness, frustration and often severe anxiety over unimportant problems. She starts to nibble on crackers, bread, cookies, cereal and ice cream. Dinner is a small meal, consisting of chicken or fish and vegetables. Later in the evening, however, she eats bread and cheese, ice cream, or a handful of cookies. This need to eat in the evening is again accompanied by feelings of loneliness or anxiety.

When asked about her eating pattern, Phyllis claims that she eats to feel better and that even though she feels guilty at the quantity of food she consumes and at its lack of nutrients, she is unable to stop herself. When studied in our research facility, she was found to consume 2100 calories per day at meals and 800 more as snacks, with these providing more than half of her total carbohydrate intake.

Like Laura, Phyllis received dexfenfluramine (15 mg p.o., b.i.d.) as part of a placebo-controlled, double-blind study on the use of this drug or of fluoxetine in treating