ELSEVIER

Serotoninergic mechanisms and obesity

Richard J. Wurtman and Judith J. Wurtman

Department of Brain and Cognitive Sciences, and Clinical Research Center, Massachusetts Institute of Technology, Cambridge, MA USA

Brain serotonin appears to be an excellent target for designing drugs to treat obesity. The prototype drug dexfenfluramine accelerates the onset of satiety and suppresses "carbohydrate craving," the tendency to consume large quantities of snacks rich in carbohydrates and fats but not proteins. The drug works by blocking serotonin's reuptake into presynaptic terminals; its metabolite norfenfluramine also releases serotonin into synapses and activates certain postsynaptic serotonin receptors. Dopaminergic drugs such as amphetamine and phentermine suppress the appetite but apparently lack macronutrient specificity.

The special importance of serotoninergic neurons in feeding behavior derives in part from the fact that eating per se affects the production and release of serotonin. This is because dietary carbohydrates, acting via insulin—which lowers plasma concentrations of the large neutral amino acids (LNAA)—increase the uptake of tryptophan in the brain; this in turn increases the substrate saturation of tryptophan hydroxylase, the key enzyme that converts this amino acid to serotonin. Paradoxically, dietary proteins—which, unlike carbohydrates or fats, do contain tryptophan—decrease tryptophan's uptake in the brain (because they cause disproportionately great increases in blood levels of the other LNAA, which compete with tryptophan for brain uptake), and thus fail to increase brain tryptophan or serotonin levels. Brain serotonin also is critically involved in controling mood, and many patients learn that they can improve their mood by eating carbohydrate-rich, protein-poor foods, particularly as snacks. This carbohydrate craving transiently ameliorates their depressive symptoms, but predisposes to weight gain, a phenomenon readily observed in people with seasonal affective disorder syndrome, premenstrual syndrome, or nicotine withdrawal. (J. Nutr. Biochem. 9:511–515, 1998) *© Elsevier Science Inc. 1998*

Keywords: obesity; serotonin; tryptophan; carbohydrates; protein; carbohydrate craving

Obesity as the result of using foods as though they were drugs

Why does a larger and larger fraction of the American population become obese, and why do so many remain that way? The consensus view of most physicians and scientists probably has been that obesity reflects a failure of regulation; that is, somehow the body is "defending" an inappropriate but preordained weight and/or fat content and is doing so by causing the individual to consume the excessive number of calories required for that purpose.

An alternative view is that obesity is often the result of an appetite disturbance, which is rooted not in a misguided attempt to regulate body weight at a level that is too high, but in an equally misguided attempt to use certain foods as drugs. Because these foods, in the United States, are presented in ever larger portions and contain ever larger amounts of fat, more and more people become obese. According to this view, the obese overeat not because they are "defending" some "set-point", or even because they are particularly hungry, but because they do not feel well, and experience has taught them that eating certain foods can at least transiently make them feel better.[1–3] Such patients overeat episodically, usually snacking on sweet or starchy foods that also are rich in fat (e.g., potato chips, baked potatoes with butter and sour cream, or french fries dunked in mayonnaise). The carbohydrates in the food affect how they feel (less sad or tired or muddle-headed, etc.) but the fats affect their waist lines. The neurochemical basis for this

Address correspondence and reprint requests to Dr. Richard J. Wurtman, Cecil H. Green Distinguished Professor and Director, Clinical Research Center, M.I.T., 77 Mass. Ave., E25-604, Cambridge, MA 02139 USA.
This paper was delivered at the October 23–25, 1997, conference "The Determination, Treatment, and Prevention of Obesity," which was sponsored by the Institute of Nutrition, University of North Carolina at Chapel Hill; Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill; and the School of Medicine, East Carolina University, in cooperation with the North American Association for the Study of Obesity, the National Institutes of Health, the American Cancer Society, and Eli Lilly & Company.
Received November 3, 1997; accepted March 10, 1998.

© Elsevier Science Inc. 1998
655 Avenue of the Americas, New York, NY 10010
0955-2863/98/$19.00
PII S0955-2863(98)00029-1

behavior is the increase that the carbohydrates induce—such as that following the specific serotonin reputake inhibitors (SSRIs) Prozac, Paxil, or Zoloft—in serotonin levels within brain synapses, and thus, for depressive people, in mood. Regulatory mechanisms that maintain body weight or fat content may or may not exist, but in any case they are overridden in these people by the more pressing search for a way to increase brain serotonin.

The foods chosen by such "carbohydrate cravers" are rich in carbohydrates and poor in proteins.[1,4,5] The carbohydrates initiate their behavioral effects by releasing insulin. This hormone quickly depresses circulating levels of most of the large neutral amino acids (LNAA) by facilitating their uptake into skeletal muscle; however, it fails to cause a significant decrease in blood tryptophan. Hence, because the transport of these amino acids across the blood-brain barrier is competitive, more tryptophan enters the brain, and more of it is converted to its neurotransmitter product serotonin[6–8] and released into synapses.[9] Thus, dietary carbohydrates increase the release of serotonin by increasing its levels within presynaptic nerve terminals. The monoamine oxidase inhibitor antidepressants, which block serotonin's breakdown in the nerve terminals, act by a similar mechanism to enhance serotonin release. The SSRIs increase serotonin levels within synapses by blocking the neurotransmitter's reuptake into the neuron that released it. This action alone appears insufficient to allow them to suppress carbohydrate-craving behavior and reduce body weight. Dexfenfluramine, which does suppress carbohydrate snacking and cause weight loss, both blocks serotonin's reuptake and, through its metabolite dexnorfenfluramine, causes its release into synapses.[10] The metabolite also activates postsynaptic 5HT2A and 5HT2C receptors,[11] and the drug also decreases food intake by promoting feelings of satiety.

Whether the carbohydrates in a food are simple sugars or complex starches does not matter; what does matter is the food's glycemic index, or its relative ability to cause insulin secretion.[12] However, sweets are more often *perceived* as having the desired mood effects because they generally are consumed as desserts or snacks, in the absence of dietary proteins, whereas starchy foods are usually eaten during a meal, along with proteins, which block the increase that the carbohydrates would otherwise induce in the plasma tryptophan ratio (the ratio of the tryptophan concentration to the summed concentrations of the other LNAA) and thus on brain serotonin.[7,8] A snack or meal that contains approximately 8% protein or less and is rich in carbohydrates will increase brain serotonin production, whereas one containing protein-rich foods such as meats or eggs will have the opposite effect.[13] Indeed, it can be speculated that serotonin-releasing neurons evolved their peculiar nutrient dependence precisely to enable omnivorous species such as humans and laboratory rodents to keep the dietary carbohydrate:protein ratio within a narrow range (e.g., 4.5 to 5.0) and to keep protein intake (as a percentage of total calories) in humans at approximately $13 \pm 1\%$. What makes the bear stop eating honey and go catch a fish? Quite possibly it is the aversive effects of a prolonged rise in brain serotonin.

Food consumption, tryptophan availability, and brain serotonin synthesis

The initial observation that the physiologic changes in tryptophan availability that follow food consumption could affect serotonin synthesis was made in studies on rats performed in 1971.[6] Animals were allowed to eat a test diet that contained carbohydrates and fat but lacked protein. Soon after the start of the meal, brain levels of the essential (and scarce) amino acid tryptophan were found to have risen, thus increasing the substrate saturation of the enzyme tryptophan hydroxylase, which controls serotonin synthesis. The resulting increase in brain serotonin levels was associated with an increase in brain levels of serotonin's metabolite 5-hydroxyindoleacetic acid (5-HIAA), suggesting that serotonin release had also been enhanced. Direct evidence that physiologic variations in brain tryptophan concentrations affect serotonin release was not obtained until 1987, when studies on superfused rat brain slices established the relationship.[9]

The rise in brain tryptophan levels after consumption of this test diet was accompanied by a small increase (rats) or no change (humans) in plasma tryptophan levels. Both of these changes had been unanticipated, because the insulin secretion elicited by dietary carbohydrates was known to lower plasma levels of other LNAA. This unusual response of plasma tryptophan was soon recognized as resulting from the amino acid's unusual propensity to bind loosely to circulating albumin. Insulin causes nonesterified fatty acid (NEFA) molecules to dissociate from albumin and enter adipocytes. This dissociation increases the protein's capacity to bind circulating tryptophan; hence whatever reduction insulin causes in "free" plasma tryptophan levels is compensated by a rise in the amount of tryptophan bound to albumin, yielding, in humans, no net change in total plasma tryptophan levels.[14] Because this binding is of low affinity, the albumin-bound tryptophan is almost as able as free tryptophan to be taken up in the brain.

Considerably more difficult to explain were the data obtained subsequently on brain tryptophan and serotonin levels after rats consumed a meal rich in protein. Although plasma tryptophan levels rose, reflecting the contribution of some of the tryptophan molecules in the protein, brain tryptophan and serotonin levels either failed to increase or, if the meal contained sufficient protein, actually decreased.[7] The explanation for this paradox was found to lie in the transport systems that carry tryptophan across the blood-brain barrier[15] and into neurons. The endothelial cells that line central nervous system capillaries contain various macromolecules that shuttle specific nutrients or their metabolites between the blood and the brain's extracellular space. One such macromolecule mediates the transcapillary flux (by facilitated diffusion) of tryptophan and other LNAA; others move choline, basic or acidic amino acids, hexoses, monocarboxylic acids, adenosine, adenine, and various vitamins. The amount of any LNAA transported by the macromolecule depends on its ability to compete with the other circulating LNAA for binding sites. Thus, the ability of circulating tryptophan molecules to enter the brain is increased when plasma levels of the other LNAA decrease (as occurs when carbohydrate consumption causes

insulin to be secreted) and is diminished when the other LNAA increase (after protein consumption), even if plasma tryptophan levels remain unchanged. Because all dietary proteins are considerably richer in the other LNAA than in tryptophan (only 1.0–1.5% of most proteins), consumption of a protein-rich meal decreases the plasma tryptophan ratio. This, in turn, decreases tryptophan's transport into the brain and slows its conversion to serotonin. (Similar plasma ratios predict brain levels of each of the other LNAA, including drugs such as L-dopa, after meals or other treatments that modify plasma amino acid patterns.)

The fact that giving pure tryptophan could increase brain serotonin synthesis and could thereby affect various serotonin-dependent brain functions (e.g., sleepiness, mood) had been known at least since 1968. What was novel and perhaps surprising about the above findings was their demonstration that brain tryptophan levels and serotonin synthesis normally vary, depending, for example, on the decision to eat a carbohydrate-rich versus a protein-rich breakfast. However, it remained possible that mechanisms external to the serotonin-releasing neuron might exist that kept such food-induced increases in serotonin's synthesis from causing parallel changes in the amounts released into the synapses. Indeed, it was known that if rats were given very large doses of tryptophan that were sufficient to raise brain tryptophan levels well beyond their normal range, the firing frequencies of their serotonin-releasing raphe neurons decreased markedly; this was interpreted as reflecting the operation of a feedback system designed to keep serotonin release within a physiologic range. [Similar decreases in raphe firing had also been observed in animals given drugs such as monoamine oxidase (MAO) inhibitors or serotonin-reuptake blockers that cause persistent increases in intrasynaptic serotonin levels.] However, if rats were given small doses of tryptophan that were sufficient to raise brain tryptophan levels somewhat, but not beyond their normal peaks, or if they consumed a carbohydrate-rich meal, which raised brain tryptophan levels physiologically, no decreases in raphe firing occurred. Hence food-induced changes in serotonin synthesis *are* able to affect the amounts of serotonin released per firing without slowing the neuron's firing frequencies, and thus *are* "allowed" to modulate the net output of information from serotoninergic neurons.

Brain serotonin, nutrient choice, and carbohydrate craving

If rats are allowed to pick from foods in two pans that are presented concurrently and contain differing proportions of protein and carbohydrate, they choose among the two so as to obtain fairly constant (for each animal) amounts of these macronutrients. However, if before "dinner" they receive either a carbohydrate-based snack or a drug that facilitates serotoninergic neurotransmission, they quickly modify their food choice, selectively diminishing their intake of carbohydrates.[16,17] These observations support the hypothesis that the responses of serotoninergic neurons to food-induced changes in the relative concentrations of plasma amino acids allow these neurons to serve a special function as sensors in the brain's mechanisms governing nutrient choice.[2] Perhaps they participate in a feedback loop through which the composition of breakfast (that is, the proportions of protein and carbohydrates) can exert a small effect on the choice of lunch by increasing or decreasing brain serotonin levels.

A similar mechanism may operate in humans. Subjects housed in a research hospital were allowed to choose from six different isocaloric foods (containing varying proportions of protein and carbohydrate but constant amounts of fat) at each meal, taking as many small portions as they liked; they also had continuous access to a computer-driven vending machine, stocked with mixed carbohydrate-rich and protein-rich isocaloric snacks. It was observed that the basic parameters of each person's food intake (total number of calories, grams of carbohydrate and protein, number and composition of snacks) tended to vary only within a narrow range from day to day and to be unaffected by placebo administration.

To assay the involvement of brain serotonin in maintaining this constancy of nutrient intake, pharmacologic studies were undertaken in individuals in whom the feedback mechanism might be impaired. These were obese people who claimed to suffer from carbohydrate craving, manifested as their tendency to consume large quantities of carbohydrate-rich snacks, usually at characteristic times of day or evening. (Too few protein-rich snacks were consumed by such subjects to allow assessment of drug effects on this source of calories.) When such patients were treated with the serotoninergic drugs fenfluramine or dexfenfluramine, consumption of carbohydrates in meals or as snacks declined significantly, and fat intake also fell; however, mealtime protein intake was unaffected. Other drugs also thought to enhance serotonin-mediated neurotransmission selectively (e.g., the antidepressants zymelidine, fluvoxamine, and fluoxetine) also have been found to cause short-term weight loss; this contrasts with the weight gain (and carbohydrate craving) often associated with less chemically specific antidepressants, such as amitriptyline. It has not yet been determined whether these drugs also selectively suppress carbohydrate intake in humans.

The assessment of carbohydrate craving is best done by direct measurement of what and when people eat, and not, as is more often the case in nutritional studies, with a questionnaire. This is because the inappropriate intake of carbohydrate-rich (or carbohydrate- and fat-rich) foods tends to occur as snacks[1,2] and people seem to remember what they ate as snacks much less accurately than what they consumed at meals. A typical carbohydrate-craving obese woman may eat only 1900 calories per day at mealtimes, concurrently consuming quite normal amounts of carbohydrate and protein, but she may eat 1000 or more calories per day as snacks, usually late in the afternoon or perhaps during the evening.

In our initial studies, we hospitalized subjects in a clinical research center and measured snack intake using a vending machine with eight or ten slots, each containing carbohydrate-rich or protein-rich foods of similar calorie and fat contents, controlled by a computer into which the subject entered, at will, his or her access code and slot choice.[4] Mealtime food intake was measured using a variant of the Chinese *dim sum* lunch:[4] Subjects had access to as

many or as few small portions as they desired of six foods per meal. They placed the plates on their trays and consumed their food (all in the absence of dietitians or other staff) in the facility's dining room. When they left, the dietitians counted the plates (which had been coded by placing a label on their underside) and weighed any food remaining on the plates. We now use a simpler outpatient procedure for monitoring snack intake.[18]

Daily patterns of calorie and macronutrient intake for each subject were found to be highly characteristic and unaffected by placebo administration (just as sleep patterns reportedly tend to be). Carbohydrate craving was found to typify perhaps three-fourths or more of the approximately 2000 obese potential subjects who responded to our advertisements. However, this estimate is *only* an estimate: An acceptable epidemiologic study of the frequency of this phenomenon among obese subjects has not been done. Many nonobese people also exhibit carbohydrate craving, consuming carbohydrate snacks at times of day when they experience a decrease in mood; these people apparently avoid becoming obese by making sensible snack choices (high carbohydrate but little or no fat, such as dry popcorn instead of premium ice cream) and by using "life-style" maneuvers such as aerobic exercise to compensate for the extra calories.[3]

Excessive carbohydrate hunger, psychiatric syndromes, and weight regulation

With the collaboration of a number of gifted colleagues, principally Dermot O'Rourke, Amnon Brzezinski, and Bonnie Spring, we have identified or confirmed the association of carbohydrate craving (and weight gain) and mood disturbance (usually atypical depression) in three syndromes in addition to carbohydrate-craving obesity: seasonal affective disorder syndrome (SADS),[19] premenstrual syndrome,[18,20] and behavioral disturbances that often accompany smoking withdrawal.[21] In all of these situations, abnormal Hamilton Test scores[22] and scores obtained using comparable behavioral test instruments, such as the Profile of Mood States,[23] coincide with demonstrated excesses in snack carbohydrate intake.

Three of these four syndromes are cyclic: Carbohydrate-craving behavior occurs at a typical time of day in patients with carbohydrate-craving obesity,[4] at a particular time of the menstrual cycle in premenstrual syndrome,[18] and at a definite time of the year in SADS.[24] The fourth, nicotine withdrawal, is precipitated more or less on demand by the patient. All the syndromes apparently reflect some disturbance in serotonin-mediated neurotransmission, because the appetitive and affective manifestations of all four syndromes can be treated readily by administering dexfenfluramine, which amplifies this neurotransmission.[4,19–21] Whether certain people are intrinsically vulnerable to these syndromes (e.g., are born with too many or too few raphe neurons) cannot now be assessed. An equally tenable hypothesis is that increasing serotonin release by eating carbohydrate snacks or taking a serotoninergic drug exerts a truly pharmacologic effect on the patient's mood disturbance, enabling the patient to experience the short-term normalization of mood that a carbohydrate-mediated increase in brain serotonin might provide. However, it recently has been shown that brains of women—a subset of the population that is uniquely susceptible to premenstrual syndrome and especially prone to SADS and to recidivism after attempted smoking withdrawal—produce only approximately two-thirds as much serotonin as do those of men.[25]

Not *all* obese people tend to exhibit episodic carbohydrate craving and symptoms of depression: Some will eat anything they find in the refrigerator and may even strike the observer as jolly. Obesity is probably as etiologically heterogeneous a disease such as hypertension, with—at least for the carbohydrate cravers–an equally dreary likelihood of true cure. Just as only the minority of hypertensive patients are able to control their diseases without drugs over the long term, by making appropriate behavioral choices (e.g., by losing weight, diminishing salt intake, taking a less stressful job), many carbohydrate-craving obese patients are likely to need multiple courses of drugs that enhance serotonin-mediated neurotransmission or perhaps to need continuous treatment, even after they start to experience the virtues of exercising and avoiding high fat foods, because their brains make them vulnerable to periods of uncontrolable carbohydrate cravings. This is especially likely if they suffer from SADS or premenstrual syndrome, try to stop smoking, or confront severe emotional stresses. Understanding the biological processes that predispose these patients to obesity, and designing drugs, based on laboratory and clinical research, that diminish their proclivity for using carbohydrate-rich foods as mood altering drugs may help them to live longer and enjoy a better quality of life.

Acknowledgments

Some of the studies described in this report and performed in the authors' laboratories at MIT were supported by the Center for Brain Sciences and Metabolism Charitable Trust.

References

1 Wurtman, J.J. (1983). *The Carbohydrate Craver's Diet.* Houghton Mifflin, Boston, MA, USA
2 Wurtman, R.J. and Wurtman, J.J. (1989). Carbohydrates and depression. *Sci. Amer.* **260,** 68–75
3 Wurtman, J.J. and Suffes, S. (1996). *The Serotonin Solution.* Fawcett, NY, USA
4 Wurtman, J.J., Wurtman, R.J., Mark, S., Tsay, R., Gilbert W., and Growdon, J. (1985). D-fenfluramine selectively suppresses carbohydrate snacking by obese subjects. *Int. J. Eating Disord.* **4,** 89–99
5 Wurtman, J., Wurtman, R.J., Reynolds, S., Tsay, R., and Chew, B. (1987). D-fenfluramine suppresses snack intake among carbohydrate cravers but not among noncarbohydrate cravers. *Int. J. Eat. Disord.* **6,** 687–699
6 Fernstrom, J.D. and Wurtman, R.J. (1971). Brain serotonin content: Physiological dependence on plasma tryptophan levels. *Science* **173,** 149–152
7 Fernstrom, J.D. and Wurtman, R.J. (1972). Brain serotonin content: Physiological regulation by plasma neutral amino acids. *Science* **178,** 414–416
8 Fernstrom, J.D. and Wurtman, R.J. (1974). Nutrition and the brain. *Sci. Amer.* **230,** 84–91
9 Schaechter, J. and Wurtman, R.J. (1989). Tryptophan availability modulates serotonin release from rat hypothalamic slices. *J. Neurochem.* **53,** 1925–1933

10 Wurtman, R.J. (1996). Pharmacology of dexfenfluramine. In *Obesity Management and Redux* (S. Nicolaidis, ed.), pp. 13–16, Academic Press, New York, NY, USA

11 Spedding, M., Ouvry, V., Millan, M., DuHault, J., and Dacquet, C. (1996). Neural control of dieting. *Nature* **380,** 488

12 Lieberman, H.J., Caballero, B., and Finer, N. (1986). The composition of lunch determines afternoon plasma ratios in humans. *J. Neural Trans.* **65,** 211–217

13 Yokogoshi, H. and Wurtman, R.J. (1986). Meal composition and plasma amino acid ratios: Effects of various proteins or carbohydrates, and of various protein concentrations. *Metabolism* **35,** 837–842

14 Madras, B.K., Cohen, E.L., Messing, R., Munro, H.N., and Wurtman, R.J. (1974). Relevance of serum-free tryptophan to tissue tryptophan concentrations. *Metabolism* **23,** 1107–1116

15 Pardridge, W.M. (1977). Regulation of amino acid availability to the brain. In *Nutrition and the Brain*, Vol. 7, (R.J. Wurtman and J.J. Wurtman, eds.), pp. 141–204, Raven Press, New York, NY, USA

16 Wurtman, J.J. and Wurtman, R.J. (1979). Drugs that enhance central serotoninergic transmission diminish elective carbohydrate consumption by rats. *Life Sci.* **24,** 895–904

17 Wurtman, J.J., Moses, P.L., and Wurtman, R.J. (1983). Prior carbohydrate consumption affects the amount of carbohydrate that rats choose to eat. *J. Nutr.* **113,** 70–78

18 Wurtman, J.J., Brzezinski, A., Laferrere, B., and Wurtman, R.J. (1989). Effect of nutrient intake on premenstrual depression. *Am. J. Obstet. Gynecol.* **161(5),** 1228–1234

19 O'Rourke, D., Wurtman, J., Wurtman, R., Chebli, R., and Gleason R. (1989). Treatment of seasonal depression with d-fenfluramine. *J. Clin. Psychiatry* **50,** 343–347

20 Brzezinski, A.A., Wurtman, J.J., Wurtman, R.J., Gleason, R., Nader, T.A., and Laferrere, B. (1990). D-fenfluramine suppresses the increased calorie and carbohydrate intakes and improves the mood of women with premenstrual syndrome. *Obstet. Gynecol.* **76,** 206–301

21 Spring, B., Wurtman, J., Gleason, R., and Wurtman, R.J. (1991). Weight gain and withdrawal symptoms after smoking cessation: A preventive intervention using de-fenfluramine. *Health Psychol.* **10(3),** 216–223

22 Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *Br. J. Clin. Psychol.* **6,** 278–296

23 McNair, D.M., Lorr, M., and Droppleman, L.F. (1971). *Profile of Mood States Manual*. Educational and Industrial Testing Service, San Diego, CA, USA

24 Rosenthal, N.R., Genhart, M., Jacobson, F.M., Skwerer, R.G., and Wehr, T.A. (1987). Disturbances of appetite and weight regulation in seasonal affective disorder. *Ann. N.Y. Acad. Sci.* **499,** 216–230

25 Nishizawa, S., Benkelfat, C., Young, S.N., Leyton, M., Mzengeza, S., De Montigny, C., Blier, P., and Diksic, M. (1997). Differences between males and females in rates of serotonin synthesis in human brain. *Proc. Nat. Acad. Sci.* **94,** 5308–5313