Brain Serotonin, Carbohydrate-Craving, Obesity and Depression

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Abstract

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Serotonin-releasing brain neurons are unique in that the amount of neurotransmitter they release is normally controlled by food intake: Carbohydrate consumption - acting via insulin secretion and the "plasma tryptophan ratio" - increases serotonin release; protein intake lacks this effect. This ability of neurons to couple neuronal signaling properties to food consumption is a link in the feedback mechanism that normally keeps carbohydrate and protein intakes more or less constant. However, serotonin release is also involved in such functions as sleep onset, pain sensitivity, blood pressure regulation, and control of the mood. Hence many patients learn to overeat carbohydrates (particularly snack foods, like potato chips or pastries, which are rich in carbohydrates and fats) to make themselves feel better. This tendency to use certain foods as though they were drugs is a frequent cause of weight gain, and can also be seen in patients who become fat when exposed to stress, or in women with premenstrual syndrome, or in patients with "winter depression," or in people who are attempting to give up smoking. (Nicotine, like dietary carbohydrates, increases brain serotonin secretion; nicotine withdrawal has the opposite effect.) It also occurs in patients with normal-weight bulimia. Dexfenfluramine constitutes a highly effective treatment for such patients. In addition to producing its general satiety-promoting effect, it specifically reduces their overconsumption of carbohydrate-rich (or carbohydrate- and fat-rich) foods.

Key words: overweight, neurotransmitters, diet composition, affective disorders

Introduction

Serotonin in the brain, and perhaps elsewhere, is involved in mechanisms that 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 dexnorfenfluramine) or by activating serotoninergic neurons (e.g., nicotine), and those that prolong serotonin's existence within synapses by blocking its reuptake (e.g., dexfenfluramine; fluoxetine). Additional ways are known by which intrasynaptic serotonin can be increased, and it can be anticipated that drugs acting at these loci will also become candidates for treating obesity.

Serotoninergic drugs act in at least three ways to facilitate weight loss: They accelerate the onset of satiety (2) and enhance basal metabolic rate by about 100 calories per day (5). They also inhibit the "carbohydrate craving" manifested by many people who are overweight or are becoming so (c.f.,34), and there is reason to believe that this inappropriate eating behavior actually constitutes a "serotonin hunger" by the brain, in which case giving the serotoninergic drug might constitute a specific therapy for the etiologic process causing the obesity.

Since serotonin's involvement in satiety and metabolic rate are also discussed elsewhere in these proceedings, the following article concentrates on serotonin's role in the weight gain caused by carbohydrate craving.

An association between a mood disturbance (often an atypical depression characterized by sadness, lethargy, "muddle headedness," and social withdrawal), the inability to lose or to stop gaining weight, and a craving for carbohydrates, is observed in a number of syndromes which lead patients to solicit medical assistance (34). These include obesity per se (33); the premenstrual syndrome (or Late Luteal Phase Dysphoric Disorder) (3); Seasonal Affective Disorder (25,26); and the nicotine-abstinence syndrome in long-term smokers who try to abstain (29,32). Data from animal studies suggest that this association of affective and appetitive symptoms arises from the neurochemical effects of eating carbohydrate-rich, protein-poor foods: These foods act via the hormone insulin to increase brain tryptophan levels, thereby accelerating the production and release of the neurotransmitter serotonin (7). The resulting increase in serotonin levels within brain synapses (like the increase produced by administering most anti-depressant drugs) tends to ameliorate mood disturbances, albeit transiently.

Patients overeat high-carbohydrate foods particularly in the form of snacks, not because they are hungry or even because they like the taste, but for the psychopharmacologi-

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cal effects. Unfortunately, many carbohydrate-rich foods also contain fat (e.g., ice cream, cookies, potato chips, bread with butter) which leads to weight gain. Drugs that promote serotonin-mediated neurotransmission might be expected to benefit both the affective and the appetitive disturbances, and the clinical data currently available on two such drugs, dexfenfluramine and fluoxetine, indicate that this can, in fact, be the case.

A dietary carbohydrate's ability to modify the plasma amino acid pattern so as to enhance the uptake of circulating tryptophan into the brain depends on its glycemic index or its ability to promote the secretion of insulin; it is independent of whether the food happens to taste sweet (18). Insulin has little or no effect on plasma tryptophan levels [free or albumin-bound, both of which are accessible to the brain (22)], but it markedly lowers the plasma levels of the "large neutral amino acids" (LNAA), which compete with tryptophan for passage across the blood-brain barrier. This decrease allows more tryptophan to enter the brain and resolves the paradox of why dietary carbohydrates, which lack tryptophan, should increase brain levels of this amino acid while protein-rich foods, which do contain it, fail to do so: Dietary proteins do raise plasma tryptophan levels; however, since tryptophan tends to be the least abundant of the 22 amino acids in proteins, this rise is small relative to the increases in such other, more abundant LNAA as leucine, isoleucine, and valine.

The increase in brain serotonin synthesis - and levels - that accompanies the rise in tryptophan reflects an unusual property of the enzyme, tryptophan hydroxylase, which catalyzes the initial and rate-limiting step in this process (i.e., its low affinity for its substrate, tryptophan) (6). At normal levels of brain tryptophan, the enzyme is quite unsaturated with substrate, so that an increase in tryptophan levels (as might follow a carbohydrate-rich meal or snack) speedily increases the enzyme's saturation and accelerates serotonin synthesis. It is interesting to note that the components of the mechanism coupling food consumption to serotonin synthesis are all "open-loop," and lack tight homeostatic regulation. Plasma amino acid levels rise and fall, some over a six-fold range (8), depending on what is being digested; tryptophan's transport into the brain varies with food-induced changes in the plasma amino acid pattern, and a change in brain tryptophan levels modulates the rate of serotonin synthesis by changing the saturation of tryptophan hydroxylase. (Unlike carbohydrates and proteins, dietary fats are not known to have a major effect on the production of any brain neurotransmitter.)

An increase in brain tryptophan levels on the order of that produced by eating a carbohydrate-rich, protein-poor meal causes parallel increases in the amounts of serotonin released into synapses, basally and when the neurons fire (27). This change in amplitude of a neurochemical signal provides the brain with on-line information about the individual's nutritional state and, particularly, about the macronutrient composition of the last meal or snack. The brain can then use this information in deciding what should be eaten next. Although people tend to be unaware of the extent to which protein and carbohydrate intake is regulated, there is abundant evidence that this phenomenon occurs. Thus, in virtually all cultures where it has been measured, protein intake is found to constitute about $13 \pm 2\%$ of daily calorie consumption, and the ratio of carbohydrates to protein in the diet varies narrowly, around 4-5:1 (15). This regulation is not manifest at every meal or snack, nor even every day; however, it is demonstrable in patterns of food consumption over longer periods.

Of course, many factors affect what we choose to eat: culture, taste and smell, appearance, and, especially in the contemporary United States where fewer and fewer meals are taken at home, what happens to be on the menu. However, it is clear that one such factor is the composition of the food that has been eaten previously. If a laboratory rat is given a choice of two foods, one of which would tend to raise brain serotonin (because it is rich in carbohydrates and poor in protein) and one which would not, it will consume daily approximately equal amounts of each every day. However, if the animal is given a drug that selectively releases, acts like, or prolongs the intrasynaptic actions of serotonin, consumption of the carbohydrate-rich food is selectively suppressed (17,21). Why did the evolutionary process allow the production and release of an important neurotransmitter, serotonin, to rise or fall depending on what a person happens to choose for breakfast? Possibly so that he or she can make nutritionally wiser choices for lunch. Unfortunately, brain serotonin has additional functions, including the maintenance of a subjectively acceptable mood state. Thus, in certain syndromes, its role in macronutrient maintenance can become hostage to its effect on mood.

The hypothesis that there is a subset of obese patients whose weight problem is associated with uncontrolled carbohydrate intake and with symptoms of atypical depression is supported by the occurrence of this triad of symptoms in several other diseases. Two are cyclically symptomatic, in late fall and winter for patients with the Seasonal Affective Disorder and premenstrually in women with the Late Luteal Phase Dysphoric Disorder. Other patients inflict these symptoms on themselves by making the medically-essential decision to give up smoking. The hypothesis that these syndromes are all related to inadequate serotonin release in the brain is supported by numerous findings: 1) the unique ability of serotonin-producing neurons to make and release more of their neurotransmitter after carbohydrate-rich foods are eaten (7); 2) animal studies demonstrating that serotonin-like drugs given systemically (21) [or serotonin itself, placed within the hypothalamus (17)] can selectively suppress carbohydrate intake; 3) clinical studies showing that serotonin antagonists can cause weight gain (14); 4) the well-established generalization that drugs (such as the monoamine oxidase inhibitors and monoamine uptake blockers) which increase intrasynaptic serotonin levels tend to have antidepressant properties; 5) animal studies showing that systemic administration of nicotine increases serotonin release (24); and 6) studies on long-term smokers attempting to free themselves from nicotine addiction. Such people typically exhibit mood disturbances, weight gain, and carbohydrate craving, often to the point of causing them to resume smoking (32).

That the mechanism by which nicotine withdrawal produces this behavioral triad is associated with impaired serotonin release was initially suggested by the finding that serotonin neurons contain excitatory nicotinic cholinergic receptors, the apparent number of which changes after prolonged exposure to nicotine (1). We could postulate that exposure to nicotine initially fosters positive subjective responses, partly by enhancing serotonin release (24); however, habituation and tolerance might then occur, so that the nicotinic receptors on serotonin neurons could no longer be stimulated by the endogenous transmitter, acetylcholine, which normally activates them. Thereafter, the patient must smoke to maintain serotonin release even at pre-drug levels. Recovery from this adaptive response could take a long time; we observed that ex-smokers continued to snack excessively on carbohydrate-rich foods after 29 days of abstinence (29).

These hypotheses have been tested successfully by administering the serotoninergic drugs dexfenfluramine and fluoxetine to carbohydrate-craving obese patients and those with the other three syndromes. Dexfenfluramine is a serotonin uptake blocker; its chief metabolite, nordexfenfluramine, also releases serotonin directly into synapses. This process does not require that the neurons continue to fire; hence, unlike uptake blockers, which ultimately slow neuronal firing and suppress serotonin release, the drug apparently retains its clinical activity for at least a year (12). Dexfenfluramine is not available in the United States, although it has been marketed in Europe for about six years; the racemic mixture of dextro- and levo-fenfluramine (a dopamine-receptor antagonist) has been marketed in the United States for more than two decades. Fluoxetine, a widely-used antidepressant, has also been shown to cause useful weight loss in some obese people for several months (4).

In rats, megadoses of either dexfenfluramine or fluoxetine, well beyond the clinical range, can cause prolonged decreases in brain serotonin levels (9,31) and in the quantities of serotonin released into synapses upon depolarization (11,16). Some investigators have proposed that these changes reflect "neurotoxicity"(28): however, neither drug has been shown to produce any of the classic hallmarks of neurotoxicity (e.g., loss of cell bodies; axonal uptake of silver; "sprouting" of surviving neurons; or gliosis, identifiable histologically or by measuring characteristic glial proteins), nor any signs whatsoever of behavioral or neurological toxicity. In all probability, the megadose-induced reductions in serotonin levels (and their immunohistochemical equivalent of reduced numbers of neurons visibly staining for serotonin) (13,20) reflect exaggerations of the drugs' mechanisms of action, which cause serotonin to be lost from the neurons by releasing it and blocking its reuptake. Moreover, a prolonged massive increase in intrasynaptic serotonin levels, acting via presynaptic serotonin receptors, probably modifies the mechanisms that regulate serotonin levels, without affecting its release or the neuronal functions it mediates. Indeed, the prolonged serotonin depletion that megadoses of either drug induce can be blocked by serotonin receptor antagonists acting externally to the neuron (10).

Conclusion

Many other new drugs thought to selectively enhance serotonin-mediated neurotransmission have been developed in the past decade, and several of these compounds - originally conceptualized as antidepressants - are being evaluated for the management of obesity. Since serotoninergic mechanisms reduce body weight by accelerating the onset of satiety (2) and increasing the metabolic rate (5) besides suppressing excessive snacking of carbohydrate-rich foods, these drugs are more broadly useful in treating obesity or uncontrolled weight gain than their specific efficacy in carbohydrate-cravers might imply (30). Epidemiologic evidence accumulated during the past few years indicates that obesity can significantly enhance morbidity and mortality even among patients who weigh only 20 percent above normal and is thus important to treat (19,23). Obviously, patients whose obesity can be effectively treated using just such "life-style" manipulations as increased exercise and reduced calorie and fat intake should follow that course. However, treatment failures following such regimens abound. Hence, the availability of effective drugs which may be administered over and over again, when uncontrolled eating leads to weight gain, might have the same salutary effect on the natural history of obesity and its sequellae that the development of antihypertensive agents had on blood pressure and stroke three decades ago. And if, in the process, the drugs also ease the affective symptoms which afflict many of these patients, so much the better.

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