

Disturbed eating pattern, body weight and dexfenfluramine*

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ABSTRACT Recent findings suggest that the consumption of carbohydrate and protein can be regulated independently of caloric intake, and that a dysregulation in the control of carbohydrate intake may contribute to overeating and obesity in some individuals. The consumption of a carbohydrate-rich, protein-poor food can increase the synthesis of the brain neurotransmitter, serotonin, by elevating the plasma tryptophan ratio, which ratio predicts brain tryptophan influx and serotonin synthesis. Excess carbohydrate snacking has been reported in several clinical syndromes. Consumption of carbohydrates is anecdotally reported to be triggered by dysphoric mood and to improve mood, suggesting that eating carbohydrate may compensate for a functional deficiency of serotonin. Four syndromes, Carbohydrate-Craving Obesity, Premenstrual Distress Syndrome, Seasonal Affective Disorder, and Withdrawal from Cigarette Smoking, are characterized with regard to (1) whether macronutrient preference is selectively biased to favor carbohydrate *versus* protein or fat; (2) whether macronutrient bias emerges selectively at snacks *versus* meals; (3) affective response to ingestion of carbohydrate-rich food; and (4) effects of the serotonin-releasing agent, dexfenfluramine, on mood, caloric and macronutrient intake. Findings suggest that dexfenfluramine selectively suppresses carbohydrate intake in individuals and at times when that intake is disproportionately high. Clinical indications for dexfenfluramine are discussed and data on short and long-term efficacy of weight loss are reviewed. *Intern Med* 1993; 9: 26-30

KEY WORDS Eating pattern, body weight, dexfenfluramine

Introduction

It is always intimidating to speak about obesity in another culture because what is considered an ideal body weight depends on social perception which has been enormously changed over the course of this century. For example, in the late 1950's, few women were considered more beautiful than Marilyn Monroe whose body, when one looks nowadays, appears plump and needs some weight reduction. The ideal today in Western countries is someone who looks like Jamie Lee Curtis, demonstrating a much leaner body shape.

The presentation below concerns studies that were done in Western cultures. It will be interesting to determine whether the same problem exists in Thailand.

Disturbed eating pattern

Many patients have difficulty in maintaining body weight in spite of their claims that they eat normally. It seems quite true that these people strictly eat nutritious meals with nothing they call delicious. However, they eat what they like in between meals. They appear to have great trouble regulating their appetite at snack time and

seem never to have met the carbohydrate they dislike. Some feel that carbohydrate improve their mood. These people show some shared characteristics: macronutrient bias—they selectively overeat carbohydrate rather than protein; they overeat at snacks rather than meals; they say that eating carbohydrate improves their mood; and changes in brain tryptophan and serotonin offer a plausible mechanism to explain the carbohydrate preference.

Carbohydrate snacking constitutes a disturbed eating pattern that may comprise about 50-75% of overeating. It is characteristic of the following syndromes: carbohydrate craving obesity, seasonal affective disorder, premenstrual disorder syndrome, and smoking cessation.

Although prevalent, carbohydrate snacking is rather difficult to study. When asked to report or write down what they eat using diet interview records, overeaters tend to omit to tell what they have eaten for snacks.

Carbohydrate craving obesity

To obtain accurate data about snacking, Wurtman et al¹ developed an innovative procedure to study snacking

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in obese patients who were hospitalized in a clinical research center. Snacking is a private behavior and people often do not want to be seen snacking. Therefore a computerized vending machine offering all food of high protein or high carbohydrate with fixed calories was put in a private place. The patient could have access to the vending machine any time and select any food they like by putting in their code numbers. Hence all of the food and calorie intake by individual patients was recorded and analyzed by computer. The results were quite interesting in that obese people tended to have carbohydrate snacks 2 times a day, between 2 and 4 pm in the afternoon and, then in the evening while they were watching television (Figure 1).

Most obese patients snacked almost exclusively on carbohydrates, but about 25% of patients could be called *mixed snacker*. They ate anything, either protein or carbohydrate. Carbohydrate snackers and mixed snackers showed very similar distributions of snacking frequency, ie, maximal in the afternoon and evening.

There is some controversy about whether snacking is really a good way to eat. If one could take the total allocation of healthy calorie intake for the day and distribute it across the day, a pattern called *nibbling*, it might be a very good way to maintain weight. However, what really happens is that people tend to eat their full allocation of 2,000 kcal at meals and then they also eat their snacks, picking up another 800-900 kcal to reach a total daily intake of about 3,000 kcal.

That is what gives them a weight management problem which is totally different from a dieting strategy that involves *nibbling* at 2,000 kcal distributed across the day.

When one compares the intake of obese carbohydrate cravers and mixed snackers, their overall calorie intake is comparable. Carbohydrate cravers take in a little more carbohydrate in their main meal as compared with mixed snackers, but they take in a much greater proportion of carbohydrate at snack time. One explanation that has been proposed emphasizes a psychological preference for sweet tasting and pleasurable snacks. But carbohydrate cravers snack on many foods that are not sweet, including potato chips, pretzels and bread. This suggests another mechanism, which is that intake of a carbohydrate (either sugar or starch) raises the blood ratio of tryptophan/other large neutral amino acids, whereas protein intake reduces this ratio. That ratio predicts the amount of tryptophan that enters the brain across the blood-brain-barrier and is then converted to brain serotonin.

Protein contains about 1.6% of amino acid as tryptophan and about 25% of other large neutral amino acids,

ie, tyrosine, phenylalanine, leucine, isoleucine, and valine, all of which require the same carrier mechanism to cross the blood-brain-barrier. As a result, when one eats protein there is a rise in blood levels of tryptophan but a much greater relative rise in the other neutral amino acids that compete for the same carrier. Therefore the ratio of blood tryptophan/other neutral amino acids declines, brain tryptophan influx declines and brain serotonin synthesis declines as well (Figure 2).

If one eats carbohydrate, which contains no amino acids including tryptophan, insulin secretion is triggered, which causes most of the large neutral amino acids to leave the blood and be taken up by muscle. Tryptophan is an exception because it binds to albumin. As a result, tryptophan remains in the blood and crosses the blood-brain-barrier, hence increasing the brain serotonin synthesis.

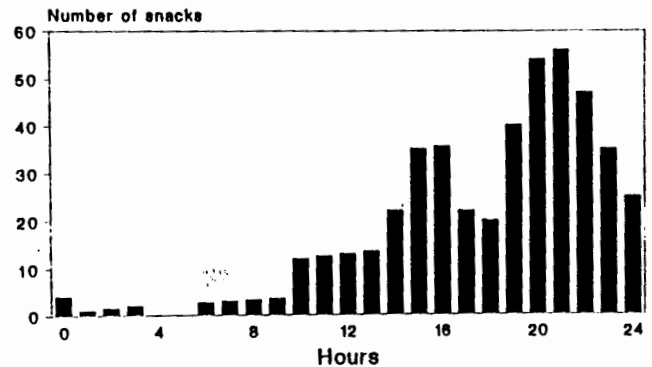


Fig 1. Distribution of carbohydrate-rich snacks during the day¹. The total number of carbohydrate-rich snacks consumed hourly day and night by the 20 subjects over 3 days.

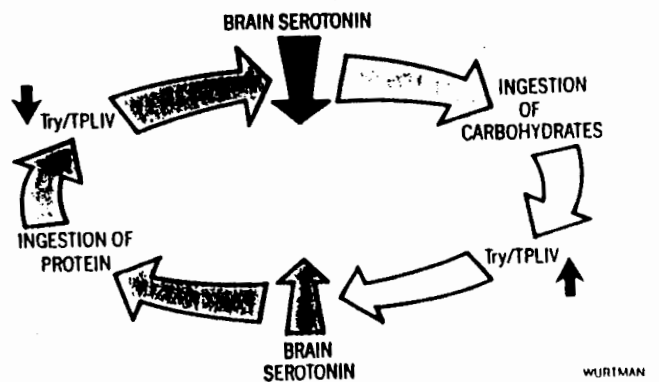
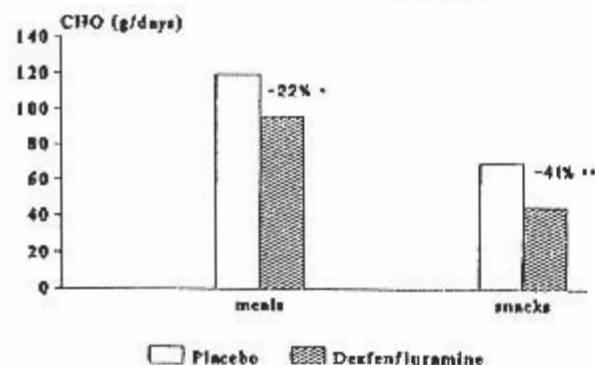
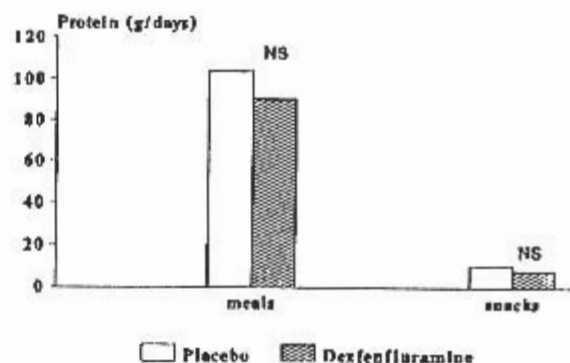


Fig 2. The role of serotonin in the control of eating behavior. Try = Tryptophan, T = Tyrosine, P = Phenylalanine, L = Leucine, I = Isoleucine, V = Valine. Try/TPLIV = Ratio on of Tryptophan to five other amino acids.

CARBOHYDRATE INTAKE DURING AND BETWEEN MEALS



PROTEIN INTAKE DURING AND BETWEEN MEALS



* $p < 0.01$ ** $p < 0.001$, compared to placebo

Fig 3. Carbohydrate and protein intake during and between meals in dexfenfluramine and placebo treated obese patients (mean consumption of the 20 subjects over 3 days).

Much of the brain's serotonin is located in midbrain raphe neurons that play an important role in regulating sleep onset, mood and appetite. The consequence of increasing brain serotonin in a normally functioning brain is probably to trigger the sleep onset mechanism, making the individual drowsy. Consider a brain, however, in which a functional deficiency of serotonin is causing depressed mood, anxiety, irritability or overeating. Here we may expect to see positive mood changes as carbohydrate increases the brain serotonin and corrects the deficiency. Thus, we should expect to see positive mood changes after eating carbohydrate in people who have the carbohydrate craving syndrome, or sleepiness after eating carbohydrate in those who lack this syndrome.

That prediction was confirmed by Lieberman et al² who studied the mood changes in equally obese people who were either carbohydrate cravers or mixed snackers. The investigators found that when mixed snackers ate carbohydrate, they become more fatigued, more sleepy and less alert. On the other hand, the carbohydrate cravers showed minimal change in sleepiness after eating carbohydrate, but they became less depressed.

Seasonal affective disorders

Rosenthal et al³ found similar results. Patients with seasonal affective disorders (SAD) have a syndrome in which they become depressed and overeat carbohydrates in the fall and winter. Their symptoms go away with the return of longer days and warmer weather in the springtime. When studying SAD patients in the winter, SAD patients became more activated, less fatigued and less

apathetic after they ate carbohydrate, but not after they ate protein.

Premenstrual distress syndrome

Wurtman et al⁴ studied the mood changes and eating behavior of women with or without premenstrual distress syndrome (PMS) during the late luteal phase before the onset of menstruation. There was minimal effect on the mood of the non-PMS group, whereas those with PMS showed positive mood change, less depression, less fatigue and less anger after eating carbohydrate.

Dexfenfluramine and disturbed eating behavior

Dexfenfluramine, a drug that is a releaser and reuptake inhibitor of serotonin, shows a relatively specific action to increase brain serotonin without affecting postsynaptic receptor binding of serotonin.

Wurtman et al¹ have demonstrated that dexfenfluramine significantly reduced carbohydrate intake at snacktime by 41%, while having minimal effect on protein intake. A similar but smaller effect was observed at meals: 22% decrease in carbohydrate intake and nonsignificant effect on protein intake (Figure 3).

The net effect was that dexfenfluramine produced a 41% and 16% decrease in calorie intake at snacks and meals, respectively. The results also demonstrated that dexfenfluramine is a diet selector because its effect on carbohydrate was much more pronounced than its effect on protein.

Dexfenfluramine also has more pronounced effect when carbohydrate intake is disproportionately high, as

demonstrated by Wurtman's study⁵ in which mixed snackers or carbohydrate cravers were treated with dexfenfluramine or placebo. Dexfenfluramine had no effect on the snack intake of mixed snackers. In contrast, dexfenfluramine significantly reduced carbohydrate intake in carbohydrate cravers.

Just as dexfenfluramine works best in individuals whose carbohydrate intake is disproportionately high, it works best at times when carbohydrate intake is the highest. For example, dexfenfluramine, compared to placebo, reduces snack intake in the evening and midafternoon, both of which are peak snacking times. At other times when snack intake was not very high, there was no significant difference between the drug and placebo.

In conclusion if there is no problem of overeating carbohydrates, dexfenfluramine is not very useful. However if there is a problem, the drug seems to suppress overeating of carbohydrate.

Smoking cessation impulse eating

This syndrome is receiving a lot of attention in the U.S.A. Many people want to stop smoking but are afraid to do so because they worry about gaining weight. A recent epidemiological study⁶ has demonstrated that the average weight gain after quitting smoking is 6 lbs in men and 8 lbs in women, although some people gain less or considerably more. For the most part, then smokers seem to be worried about a weight gain that is a cosmetic concern rather than the much more serious health risks presented by smoking.

Although nicotine withdrawal may cause some slowing of metabolism, overeating is the greatest contributor to weight gain after smoking cessation. Spring et al⁷ observed an increase of 300 kcal/day in food intake that became evident in the first 48 hrs after quitting smoking and persisted for 4 wks. Ex-smokers overate carbohydrate in particular. They showed a 70% increase in carbohydrate intake immediately after quitting smoking : a 40% and 30% increase in carbohydrate at snacks and meals, respectively. In contrast, protein intake showed no increase. Dexfenfluramine inhibited the increase of calorie intake after quitting smoking, whereas placebo did not prevent it. Dexfenfluramine also suppressed the increase of carbohydrate consumption. Not surprisingly, given their overeating, the placebo group gained weight during the first month after stopping smoking. Their average weight gain was 3.5 lbs. In contrast, the average patient in the dexfenfluramine group lost about 1.8 lbs.

Control of tension and anxiety

One can observe an increase in anxiety and irritability

during the first week after smoking cessation. Dexfenfluramine suppressed both the anxiety (Figure 4) and the irritability induced by nicotine withdrawal (Figure 4).

We have found that it is possible to prevent withdrawal symptoms nutritionally by giving a combination of 60 mg/kg tryptophan in high carbohydrate diet to people who are quitting smoking⁸. Unfortunately this does not prevent the weight gain eventhough it suppresses the withdrawal symptoms.

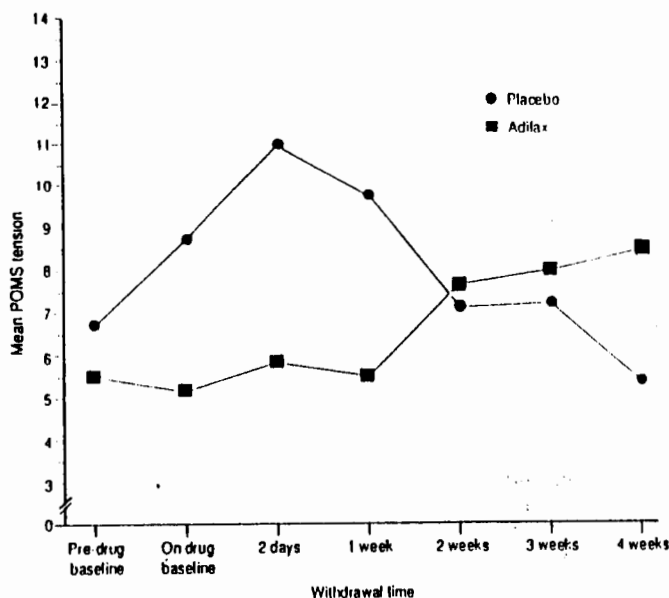


Fig 4. Effect of dexfenfluramine on tension and anxiety in smoking cessation assessed by POMS (Profile of mood states, McNair, Lorr and Droppelman 1971).

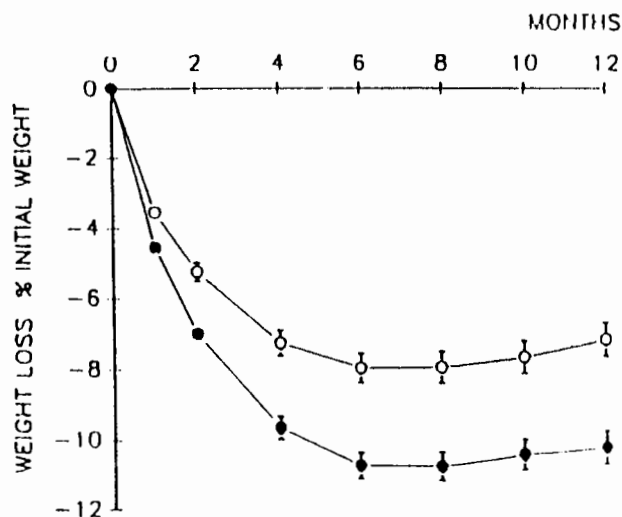


Fig 5. Changes in weight in patients treated with dexfenfluramine (n = 256) or placebo (n = 227). Mean (SEM) are expressed. P < 0.001, dF vs placebo, T2-T12. P < 0.05, weight gain in placebo group, T6-T12.

Dexfenfluramine and weight loss

Guy-Grand et al⁹ have conducted a multicenter trial in 24 centers in 9 European countries involving 822 obese patients. This double-blind, placebo-controlled study compared the efficacy and acceptability of long-term (1 yr) dexfenfluramine vs placebo. In total, 418 patients received placebo and 404 received dexfenfluramine. The initial characteristics of the 2 groups were quite similar. The mean weight loss at 12 months after treatment was significantly greater with dexfenfluramine than with placebo ie, 10.3% vs 7.2% of the initial weight (Figure 5).

Drop-out rates were lower in the dexfenfluramine group than in the placebo group (37% vs 45%), mainly because of dissatisfaction with weight loss in the latter group. More dexfenfluramine-treated patients reported transient side effects, ie, tiredness, diarrhea, dry mouth, polyuria and drowsiness, which were not harmful.

Conclusion

Carbohydrate preference causes a problem in weight management in several clinical syndromes, including carbohydrate craving obesity, seasonal affective disorder, premenstrual distress syndrome and smoking cessation.

Individuals with these syndromes overeat selectively on carbohydrate rather than protein-rich snacks. They report that eating carbohydrates improves their mood.

Dexfenfluramine and other serotonergic drugs improve mood and normalise carbohydrate intake especially in individuals and at times when the intake is disproportionately high.

Dexfenfluramine helps obese patients to adhere to a diet and to maintain the weight loss achieved without harmful side-effects.

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