Serotonin and Dietary Fat Intake: Effects of Dexfenfluramine

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Traditionally, serotonin (5-HT) has been most commonly linked with carbohydrate (CHO) intake. However, in recent years it has been demonstrated that serotoninergic drugs such as dexfenfluramine also reduce energy intake and reverse body weight gain in rats exposed to weight-increasing high-fat diets. Dexfenfluramine is also effective in decreasing food intake and body weight gain of rats that gain weight on a high-fat cafeteria diet. The basic science studies indicate that serotoninergic activity—induced by dexfenfluramine—can act as a sufficient stimulus for the reduction of fat consumption. High-fat diets do not appear to impede the suppressive effect of dexfenfluramine on food intake. In human studies with dexfenfluramine, it has often been the case that the fat content of test foods has been held constant—with only protein and CHO allowed to vary. These studies therefore cannot display any direct effect on fat. However, when food choice is not limited by experimental constraints, a significant reduction of fat intake by dexfenfluramine has been demonstrated in obese patients. In other experimental studies, dexfenfluramine has suppressed fat intake to a greater extent than other macronutrients when free selection of foods has been permitted. Taken together, these studies demonstrate that dexfenfluramine is effective at reducing energy intake with a diet high in fat and may under certain conditions cause a selective avoidance of high-fat foods.

IN RECENT YEARS it has become recognized that consumption of dietary fat in many countries is too high, and advisory bodies have recommended a reduction of fat intake from about 40% to 30% of total energy intake.[1,2] In the United Kingdom, the *Health of the Nation*[3] document has set targets for the reduction of dietary fat intake and a decrease in the prevalence of obesity to be achieved by the year 2005.

A number of large-scale surveys in various countries have demonstrated a positive relationship between the percentage of fat in the diet and weight gain or body mass index.[4-9] Other studies have shown the complementary effect. For example, the Four Seasons Program (*Vier-Jahres-zeiten-Kur*) in Germany reported that a reduction in obesity was associated with a decrease in the amount of fat consumed.[10]

The antiobesity drug dexfenfluramine is currently being used to treat obesity in more than 62 countries and has been administered to more than 20 million people worldwide. In a 1-year clinical trial performed in 16 centers in nine European countries (the INDEX study), the drug produced an increasing weight loss for 6 months and thereafter maintained body weight at the new level for 6 months.[11] In another clinical study, dexfenfluramine has been sufficiently potent to produce further weight loss even after patients have already lost an average of 15 kg on a very–low-calorie diet.[12]

Considering the effect of dexfenfluramine on energy intake, the appetite system in obese subjects has been shown to be sensitive to a serotoninergic challenge.[13] Moreover, the pattern of eating is adjusted so that large meals are reduced in size and some snacks are eliminated from the eating repertoire.[14] Therefore, the effect of the drug is to reduce meal size (intensify satiation) and to strengthen the inhibitory effects of food ingestion on appetite (intensify satiety).[15] Given that dexfenfluramine is an effective antiobesity drug and that obesity is linked to a high intake of dietary fat, it is worth considering whether the demonstrated effect of dexfenfluramine on energy intake incorporates an action against the consumption of dietary fat.

BASIC-SCIENCE STUDIES

For some years, the relationship between serotonin (5-HT) and nutrient intake has been conceptualized within a framework that emphasizes the postabsorptive action of carbohydrate (CHO) on brain 5-HT synthesis via the uptake of tryptophan by the brain.[16,17] This biobehavioral cycle has provided the theoretical basis for many studies on the action of serotoninergic agents on the selection of macronutrients in animals offered choices from various diets. It is worth noting that the methodological problems involved in diet-selection studies are formidable.[18] Moreover, decisive outcomes after pharmacological treatments are rare[19]; one major issue concerns the number of choices of diets available to experimental animals. When the major focus of interest was the relationship between dietary protein, CHO, and 5-HT, it was believed to be necessary only to provide animals with the opportunity to choose between the two nutrients. The proportion of fat in the diets was held constant.[20,21] Consequently, this type of dietary regimen precludes the possibility of disclosing any selective effect of a drug on intake of fat.

The evidence for a preferential action of serotoninergic agents in two-choice diet paradigms remains equivocal. In some experimental circumstances, serotoninergic drugs do reduce CHO intake.[22] However, it is clear that a large intake of CHO is not a sufficient condition for suppression by serotoninergic agents[23] and that a low intake of CHO does not necessarily prevent suppression.[24]

One way to introduce fat as a variable in dietary-selection experiments is to provide animals with a choice between three diets, each one either a pure macronutrient or containing a predominance of one macronutrient only.[25] Interestingly, under these experimental circumstances, 5-HT administration produced a selective reduction of fat intake.[26] In addition, in early studies on the microinjection of serotoninergic agents directly into the paraventricular

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nucleus, it was reported that fenfluramine reduced the intake of CHO and fat.[27]

In addition to diet-selection studies, a potent effect of fat on eating behavior can be demonstrated through the use of cafeteria diets or fat-supplemented diets. The phenomenon of diet-induced obesity in rats[28] is a reliable observation in which the daily energy intake is markedly increased largely through an increase in meal size.[29] Moreover, because of the composition of foods provided in this paradigm, the difference between energy intakes on a cafeteria diet and chow diet is almost entirely due to the additional consumption of fat.[30] It is therefore significant that in rats exposed to a cafeteria diet, chronic administration of dexfenfluramine suppressed the hyperphagia and reduced body weight gain.[31] This effect was most marked when rats had reached the plateau phase of obesity,[32] and the effect of the drug persisted for at least 76 days.

A further procedure to induce body weight gain in rats is to administer a specially designed high-fat diet (50% to 60% of energy as fat) and compare the effects with those of a low-fat diet (4% to 5%). In Osbourne-Mendel rats that are sensitive to high-fat feeding, dexfenfluramine completely abolished the excess food intake and weight gain associated with the high-fat diet.[33] This effect is consistent with the results of an earlier study that demonstrated low-dose dexfenfluramine was clearly effective at reducing the energy intake and weight gain on a fat-supplemented weight gain–inducing diet in which rats consumed 65% of energy as fat.[34] Moreover, no tolerance to the suppressive effect of dexfenfluramine was seen after 40 days.

This analysis of animal studies demonstrates two features. First, exposure of rats to high levels of dietary fat (leading to hyperphagia and weight gain) does not impede the suppressive effects of serotoninergic agents on food intake or body weight. Indeed, dexfenfluramine appears to be particularly effective, and for long periods with very–high-fat diets. Second, in those circumstances where rats have been offered choices of diets including fat, serotoninergic agents have demonstrated at least some suppression of the fat choice, and in certain cases, a preferential suppression of fat intake. Although most animal studies have not provided an opportunity to observe any selective effect of serotoninergic manipulation on fat preference, it is clear that dexfenfluramine administration is a sufficient stimulus to block the hyperphagia and antagonize the weight gain associated with high levels of dietary fat.

HUMAN STUDIES: DEXFENFLURAMINE AND FAT INTAKE

Outcomes of experiments on food choice in humans are influenced by methodology to the same degree as in animal studies. The proposed relationship between 5-HT and CHO-protein intake has influenced the design of human food-choice experiments. Usually, subjects have been offered foods that are high in either CHO or protein, with the amount of fat held constant. Interestingly, for most foods offered, although the manipulated variable was the protein/CHO dimension, the foods contained high levels of fat. For example, available snacks contained an average of 51% fat, and meals, an average of 55% fat.[35] Significantly, energy intake was reduced by 16% and 41% for meals and snacks, respectively. CHO was reduced more than protein, but owing to the nutrient composition of the test foods, this action involved an obligatory reduction in fat intake. In a complementary study using foods freely available in a vending machine, foods contained an average of 51% of energy as fat.[36] Subjects preferentially consumed snacks containing CHO rather than protein, and dexfenfluramine reduced the intake of those high-CHO snacks. Once again, because of the nutrient composition of the snacks, the greatest suppression of any single nutrient occurred with fat.

Interestingly, it has become clear that the action of dexfenfluramine on the eating pattern will inevitably produce a major reduction in fat consumption. The studies mentioned earlier, together with others,[37] demonstrate that one prominent effect of dexfenfluramine is a reduction of snacking. As Drewnowski[38] has pointed out, snack foods contain large amounts of fat (40% to 60%) and some snack items used in experiments contain as much as 81% fat. Therefore, any inhibitory action on the consumption of snack foods will induce an obligatory reduction in dietary fat, which normally makes the greatest contribution to energy of any single nutrient.

This effect has been further demonstrated in a study on food intake in women with premenstrual depression.[39] Foods available in the experimental unit varied in protein and CHO content but were consistently high in fat ($\sim$45% to 60%). Items were designed to be iso-fat, and sometimes butter, cream, or mayonnaise were used to increase the fat content. During the luteal phase, subjects showed an increased preference for CHO snacks (which contained large quantities of fat) and this tendency was antagonized in dexfenfluramine-treated subjects. Therefore, dexfenfluramine reduced CHO together with fat.

It is worth considering that the outcomes of these studies are consistent with some action of serotoninergic manipulations related to the consequences of CHO ingestion. However, because of the association between CHO and fat in many foods (with fat usually contributing the most to energy content), the main effect of blocking CHO selection will be a reduction of fat intake. These studies demonstrate that the presence of large amounts of fat in food does not hinder the action of dexfenfluramine. Indeed, dexfenfluramine exerts a strong inhibition on the consumption of high-fat foods.

Even though dexfenfluramine reduces the intake of high-fat foods, it can be questioned whether serotoninergic agents produce any selective avoidance or suppression of dietary fat intake. For this to be demonstrated, it is necessary for the study design to provide food choices that permit subjects to display a selective reduction of any macronutrient. This usually means giving subjects a "free-selection" test meal in which a large variety of different foods is available. In one experimental situation that made this possible, dexfenfluramine suppressed macronutrient intake by 20%, 17%, and 14% for fat, CHO, and protein

intake, respectively,[36] but these differences were not statistically significant. However, when subjects were free to select foods from a food dispenser, dexfenfluramine produced a 13% reduction in meal size, which reflected a significant reduction only in fat consumption.[40]

In a recent clinical study on obese subjects, further evidence has been provided for an action of dexfenfluramine on fat intake. Thirty obese subjects with a degree of excess weight of 20% to 80% of ideal weight were assigned to 3-month treatment periods on either placebo or dexfenfluramine (30 mg/d). The main focus of the study was an examination of basal metabolic rate and postprandial thermogenesis, but body weight and energy intakes were also monitored.[41] At the end of the 3-month treatment period, the measured energy intake of the dexfenfluramine group was 16% less than that of the placebo group. (Food intake was measured objectively for 1 day in the metabolic ward.) This consisted of a 13% reduction from meals and a 23% reduction from snacks. The energy reduction was characterized by a selective decrease in dietary lipids from 34% to 30% of total energy. By calculation, this represents a 25% reduction in the amount of fat consumed. Therefore, this result appears to show a selective avoidance of fat foods by subjects receiving dexfenfluramine. The drug did not exert a significant effect on CHO, perhaps because CHO intake was not excessive in these subjects.

Taken together, these human studies demonstrate that high-fat foods do not impede and may even strengthen the suppression of eating by dexfenfluramine. Whenever high-fat foods have been offered to subjects, dexfenfluramine has shown an effective reduction of intake. Moreover, there is also some evidence that administration (short-term or prolonged) of dexfenfluramine can induce a selective avoidance of high-fat foods and lead to an overall reduction in dietary lipids.

FAT AND SATIETY SIGNALS

In considering the relationship between fat and satiety, a paradox becomes apparent. On one hand, fat in the intestine does appear to generate potent satiety signals.[42] On the other hand, exposure to high-fat foods leads to a form of passive overconsumption, which suggests that fat has a weak action on satiety.[43] The paradox can be expressed as the puzzle of fat-induced satiety and high-fat hyperphagia.

It has been demonstrated that infusion of Intralipid (an emulsified fat; Pharmacia) into the intestine inhibits hunger and slows the rate of gastric emptying.[44] However, Intralipid infused intravenously has no inhibitory effect on appetite. Similar effects have been demonstrated in rats.[45] Moreover, the inhibitory action of Intralipid can be blocked by lorglumide, an antagonist of cholecystokinin (CCK) A-type receptors.[46] Taken together, these studies suggest that fat in the intestine generates potent preabsorptive satiety signals that are mediated at least in part by a CCK mechanism.

However, when rats are placed on high-fat diets or given fat supplements, they take in excessive amounts of energy and rapidly gain weight. Moreover, human subjects exposed to a range of high-fat foods also increase their energy intake and gain weight as compared with subjects who consume a medium- or low-fat diet.[47] In addition, high-fat foods markedly increase meal size (measured in terms of energy),[48] and this effect is particularly marked in obese subjects.[43] What is the explanation for the apparent contradiction between fat-induced satiety signals and the easy overconsumption of high-fat foods?

Although pure emulsified fat delivered to the intestine (duodenum or jejunum) produces prompt satiety signals, consumed fat takes some time to reach the intestine in similar form and its action is likely to be diluted by other nutrients. Hence, consumed fat may engender more slowly arising satiety signals. Two features of fat favor the rapid consumption of energy. First, fat produces potent oral stimulation, which facilitates intake, and second, high-fat foods normally have a high energy density. This means that a large amount of fat energy can be consumed before fat-induced satiety signals become operative. The signals are apparently too weak or too delayed to prevent the intake of a large amount of energy.

SEROTONIN AND FAT INTAKE: POSSIBLE MECHANISMS

It is clear from published experiments that a serotoninergic drug such as dexfenfluramine potently antagonizes the consumption of high-fat foods, may cause selective avoidance of fats, and reduces daily lipid intake. What mechanism is responsible for this phenomenon? One possibility involves preabsorptive satiety signals.[49] Fat in the intestine appears to inhibit appetite via CCK A-type receptors. In turn, it has been shown that the inhibitory effect of CCK on food intake can be antagonized by 5-HT blockers[50] and that this probably involves 5-HT_{1C} (now called 5-HT_{2C}) receptors.[51] Moreover, 5-HT_{2C} receptors are critically involved in mediation of dexfenfluramine-induced suppression of eating.[24,52] In addition, the effect of dexfenfluramine is blocked by the CCK A-type receptor antagonist devazepide.[53] Since fat is a potent stimulus for CCK release, the involvement of 5-HT receptors in this circuit provides a cogent explanation for the inhibitory effect of dexfenfluramine on fat intake.

Another possibility is that dexfenfluramine operates a serotoninergic blockade of a feeding reward system activated by the hedonistic properties of a high-fat diet.[33] It has also been proposed that adaptation to different types of fat (saturated or unsaturated) exerts different effects on 5-HT synthesis in raphe nuclei.[54] Consequently, a number of candidate mechanisms are available to account for the dexfenfluramine anti-fat effect.

Considering the paradox of fat-induced satiety signals and high-fat hyperphagia, it may be proposed that any agent that could intensify or advance fat-induced satiety signals would enhance the likelihood of blocking high-fat hyperphagia. This would take the form of a reduction in the size of meals, and this is known to be one of the main effects of dexfenfluramine.[15] For the moment, a provisional hypothesis to account for the antagonistic effect of dexfenfluramine on fat consumption is via the sensitization or priming of 5-HT–mediated (and CCK-mediated) fat-induced satiety signals.

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