The Influence of Different Fats and Fatty Acids on Obesity, Insulin Resistance and Inflammation

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ABSTRACT Dietary fat and its relation to obesity has been a controversial issue for several years. In this review, several kinds of data relating to this issue are presented. There are epidemiological cross-country data and data within countries showing an effect. However, in the United States, the intake of fat appears to be declining, whereas the prevalence of obesity rises—the American Paradox. Clinical studies show that trans fatty acids can increase insulin resistance and that exercise can enhance the rate of adaptation to a high fat diet by increasing the rate of fat oxidation. The differences in response of inflammatory signals and of insulin resistance to different fatty acids indicate that not all fatty acids are the same. There are also experimental data showing that most, but not all, animals consuming a high fat diet will become obese. A number of mechanisms have been postulated for this difference, including differential sensitivities to neurotransmitters, to the intestinal peptide, enterostatin, and to individual fatty acids. One important conclusion from this review is that both total fat and individual fatty acids have to be considered when reaching conclusions about dietary fat and obesity. J. Nutr. 132: 2488–2491, 2002.

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This brief review will focus on some of the newer findings related to dietary fat, fatty acids, and obesity. The consumption of dietary fat appears to be stable or declining in relative terms although there is an epidemic of obesity (1), leading some to conclude that dietary fat is not related to obesity (2,3). However, an analysis of the cross-cultural data and trends within populations suggests that dietary fat may play a role in obesity (4–6). In the sections below, we will argue that it may be the types of dietary fats, or the interaction of fat or fatty acids with other dietary components that may be a major culprit in the current epidemic of obesity and insulin resistance.

Epidemiological Data. Several pieces of epidemiological data support a relation of fat intake or metabolism to obesity. Cross-cultural studies show a rising body mass index in countries with higher intakes of dietary fat (4). The rising prevalence of obesity in Danish inductees into the military between 1935 and 1985 parallels the rising proportion of fat in the Danish diet (7,8). In a large prospective study of men with 12 y of follow-up, the dietary intake of saturated and total fat was related to the risk of developing diabetes primarily through its association with greater body mass index (BMI) (9). Reduced oxidation of fat as measured by the respiratory quotient (RQ) is predictive of greater weight gain (10). Similarly, a lower oxidation of fat is predictive of relapse in individuals who have lost weight (11,12). The higher RQ and subsequent weight gain is consistent with the hypothesis of Flatt (13). He suggested that oxidation of carbohydrate as expressed in a higher RQ will deplete body carbohydrate stores and drive the intake of food to replenish these stores until fat oxidation rises to equal intake.

Reduced Fat Diets. If high levels of dietary fat are a factor in the development of obesity, reducing the fat in the diet would be expected to produce weight loss. When the studies that have examined the relation of fat in the diet to change in body weight are reviewed, a few conclusions are evident (4–6,14). First, the weight losses in subjects eating low fat diets tend to be modest, and may not persist over prolonged periods of time (15). Second, the higher the BMI, the greater the weight loss for a given reduction in the percentage of dietary fat (6). Third, there is a significant positive relationship between the percentage reduction in dietary fat and the decrease in energy intake. This suggests that one of the major mechanisms for the decrease in weight with a reduced fat diet is the lower energy intake. As Yudkin and Carey (16) observed many years ago, most people do not like to eat fat alone, i.e., it is more easily consumed with something else. Blundell refers to this as the passive overconsumption of foods (17). Finally, the nature of the carbohydrate or the quantity of protein consumed with the lower fat diet does not have a significant effect on the weight lost over a 6-mo period (18,19).

A clinical trial in which energy reduction or low fat diets were used in individuals who had lost weight with energy restriction showed that, over the next 2 y, those eating the low fat diet maintained significantly more of the weight loss than those eating the energy-restricted diet (20).

One problem with clinical studies of lower fat diets is that the composition of the diet must change to reduce the percentage of fat, thereby changing the energy density and hedonic properties of the diet (21). Thus, a “blinded” study of a low fat diet has been nearly impossible to achieve. The availability of olestra, a fat substitute that cooks like and has the mouth feel of normal fats but can not be digested in the intestine or distinguished in taste tests of snack foods (22), allows the replacement of fat in the diet with foods that are indistin-
guishable from normal. We conducted a 9-mo feeding trial in 45 obese men to test the hypothesis that substitution of olestra for dietary fat would significantly decrease body fat relative to a 33% fat diet or a 25% reduced-fat diet (23). During the first 3 mo, all men lost a small amount of weight, but thereafter they diverged. The control group eating the 33% fat diet stabilized and maintained their weight for the next 6 mo. The men eating the olestra-substituted diet with 25% available fat continued to lose body fat and by the end of the experiment had lost nearly 6 kg or close to 20% of their body fat, which was significantly more than the control group. In contrast, the men eating the 25% reduced fat diet began to regain weight following the initial 3 mo weight loss and by the end of the 9-mo trial were nearly back to baseline. In addition to the decline in body fat, there was a parallel decrease in visceral fat (Fig. 1). After the initial 3 mo, when visceral fat decreased in all three groups, the divergence described above for the total body fat occurred (23). We also observed significant reductions in total and LDL cholesterol and triglycerides in the group consuming the olestra-substituted diet, but not in the other two groups (unpublished results, 2002). These improvements to health risk factors seemed to be largely explained by the weight loss in the group eating the olestra-substituted diet.

Clinical Studies. In addition to the role of total dietary fat in the current obesity epidemic, there is the distinct possibility that different dietary fats may have different effects on cardiovascular risk factors, body fatness, and insulin resistance (24–27). In animal studies, the beneficial effects of (n-3) fatty acid-containing fish oils were related to the ratio of (n-3) to (n-6) fatty acids in the diet. To test this hypothesis in humans, a feeding study comparing diets differing in the total amount of fish oil, high in (n-3) fatty acids at a constant total intake of fat and a study that varied the relative amounts of (n-3) and (n-6) fatty acids in a diet with a constant fat level was needed. When this study was done (28), it was the total amount of fish oil that was important and not the relationship between (n-3) and (n-6) fatty acids. Thus, animal data could not be extrapolated to human beings in this case.

Arachidonic acid is a precursor of the prostaglandin and thromboxane series of tissue fatty acids. The transformation is accomplished by cyclooxygenase (COX) enzymes of which a constitutive (COX-1) and a nitogen-inducible (COX-2) form are known. The Toll-like receptor-4 is involved in regulating the response of the COX-2 gene to lipopolysaccharide (LPS). In recent studies, Hwang (29) showed that fatty acids modulate this receptor. Saturated fatty acids increase the responsiveness of this receptor to LPS, whereas polyunsaturated fatty acids (PUFA) reduce the responsiveness to LPS, suggesting a cellular mechanism for the effects of fish oil in modulating prostaglandin synthesis.

As a second approach to the question of the response to individual fatty acids, Lovejoy et al. (30) explored the relation of dietary fat to the fasting insulin level, as a marker of insulin resistance, in a group of 38 men and women with a wide range of glucose tolerance. Food intake was estimated from a 3-d food record. Fatty acid profiles in muscle and fat biopsies and in the plasma cholesterol esters and phospholipids were examined. There were significant correlations between plasma insulin and glucose, and total dietary fat in grams, dietary fat as a percentage of energy, the percentage of monounsaturated fatty acids, the percentage of saturated fatty acids, and the dietary cholesterol. Saturated fat and the percentage of body fat had the strongest correlations with fasting insulin. Among the fatty acids from cholesterol esters there were strong correlations of insulin and glucose with myristic acid (14:0) and di-homo-γ-linolenic acid [20:3(n-6)] (30).

These differences in the effects of saturated and unsaturated fats raised the possibility that insulin sensitivity might be altered acutely in humans by feeding different fats. To test this idea, we recruited 22 subjects who consumed a 25% fat diet for 17 d (31). On d 10 and 16, they each received a high fat meal, with 50% of the energy from fat, that provided 40% of their daily energy needs. The challenge diets contained either 20% oleic (18:1cis) or 10% oleic and 10% elaidic (18:1trans) acids and were administered in random order. Blood samples were collected hourly for 8 h after each of the test meals. The rise in glucose was similar after both challenge diets. However, to maintain the same level of glucose, the subjects had significantly higher insulin levels when they received elaidic acid, resulting in a higher insulin-to-glucose ratio. This suggests that trans fatty acids may induce insulin resistance acutely. In continuing studies, diets with higher quantities of linoleic acid left subjects with more hunger than when the linoleic acid was replaced by linolenic acid (32).

To explore the role of individual fatty acids further, DeLany et al. (33) carried out studies on the rate at which individual 13C-carboxy-labeled fatty acids were oxidized. For these studies, eight healthy men ate a 40% fat diet as out-patients. The oxidation of individual fatty acids was measured by collecting 13CO2 over 9 h while the subjects were recumbent in a bed in the metabolic unit. The rates of oxidation for the same amount of fatty acids differed more than twofold (33). More than 37% of the dose of lauric acid (12:0) was oxidized, compared with <15% of the dose of stearic acid (18:0). Linolenic acid [18:3(n-3)] was the next most highly oxidized fatty acid at 25%. Palmitic (16:0) was just above stearic. When subjects consumed a 20% fat diet for 2 wk before the test period, the oxidations of the linoleic, stearic, and palmitic acids were reduced >30%, whereas there was little effect on other fatty acids (33). The order of oxidation was lauric > linolenic > palmitic = stearic.

Exercise has a profound effect on the adaptation to a high fat diet. When the dietary fat intake of six young men was switched from 35 to 50% energy while they were living in a whole-room respiration calorimeter, there were marked individual differences in the rate of change in fat oxidation under...
these conditions of low physical activity. Some men oxidized very little of the extra fat over the 5-d study, whereas others adapted almost completely to the higher intake. Smith et al. (34) found that these individual differences in the increase in fat oxidation were strongly and positively related to baseline insulin levels, RQ, and maximal oxygen consumption. When the same men spent a second 5 d in the respiration calorimeter with ~3 h of treadmill walking, they all adapted to the higher fat diet by increasing their oxidation of fat to the point of equilibrium (35). These data support the suggestion that obesity may result from a combination of high fat intake and sedentary lifestyle, characteristics of most developed nations.

**Animal studies.** When animals are fed a high fat diet, almost all species develop obesity. This has been demonstrated in nonhuman primates, pigs, dogs, cats, ground squirrels, rats, and mice (36). Indeed, this differential susceptibility to a high fat diet in mice has been used as a basis for screening for genetic differences that underlie the enhancement of obesity by high fat diets. When rats are fed different levels of fat, there is a differential rate of weight gain (37). From these data, a dose-response curve can be constructed, which suggests that there may be a threshold of dietary fat below which obesity does not develop. In animals in this study, the cut-off point was ~28% energy as fat in the diet.

The duration of the dietary feeding period has a strong influence on the reversibility of the obesity in animals consuming a high fat diet. When animals gain weight during consumption of a high fat diet for up to 18 wk, their body weight will return to the control level when they are switched to a low fat diet (38). When the feeding interval for the high fat diet is extended to >30 wk, body weights no longer return to control levels when the dietary fat is reduced. Thus, long-term feeding of a high fat diet appears to produce “irreversible” effects.

Several features distinguish animals that become fat eating a high fat diet [Osborne-Mendel (OM) rats] from those that do not (S5B/PI rats) (39). First, they have different responses to unsaturated fatty acids (40,41). When oleic acid is infused into the duodenum of animals, it inhibits feeding. When this response is compared in the S5B and OM rats, there is a nearly complete inhibition of feeding after oleic acid infusion in the S5B rats, but only a transient one in the OM rats (40). This difference is paralleled by changes in the sensitivity of the potassium-rectifying channel in the tongue of these rats. When PUFA such as 18:2 or 18:3 are bathing the tongue, the conductance across the K channel is nearly obliterated in S5B rats, but significantly less suppressed in the OM rats (41). This suggests that there is a fatty acid-sensing system on the tongue and in the gastrointestinal mucosa that differs in the intensity of the messages that are generated in the presence of fatty acids. The rats that are resistant to obesity are more responsive to the fatty acid signal. When another intestinal signal, cholecystokinin, is used, the inhibition of food intake is essentially identical in these rat strains.

Another difference between the OM and S5B rats is the lower concentration of serotonin in the brain of the former (42). This suggests that serotonin may be involved in the modulation of fat intake. To test this directly, serotonin was infused into the paraventricular nucleus, the so-called feeding nucleus of the rat, and intakes of individual macronutrients, fat, carbohydrate, and protein were measured (43). Serotonin was a major inhibitor of fat and protein intake, but had little effect on carbohydrate intake. A similar effect on carbohydrate intake. A serotonergic receptor system is a second one that is involved in the modulation of fat intake. Using a selective 5-receptor agonist, fat intake was selectively stimulated in both strains (44). It was of interest that the ρ-agonist stimulated fat intake more in the fat-sensitive (OM) rats when they consumed the high fat diet than it did when they ate the low fat diet. In the S5B rats, the stimulation was independent of the diet.

**Enterostatin** is a pentapeptide that is cleaved from pancreatic procolipase in the intestine. This small molecule suppresses fat intake when injected peripherally or into the central nervous system (45). Because of the difference in fat intake between S5B and OM rats, we examined the response to enterostatin and found, as expected, that fat intake was suppressed in the OM rats, but that enterostatin was almost without effect in the S5B rats (46). From these animal experiments, we next moved to a test of enterostatin in humans (47). The experiment was designed to measure food intake at lunchtime 60 min after placebo or 1 of 2 doses of enterostatin given in a crossover design to 17 subjects. During the first 30 min, there was a dose-related suppression of hunger ratings using a variable analog scale technique. This hunger had nearly disappeared by the 60 min time point when lunch was consumed. There was no measurable suppression in food intake by enterostatin, but the dose-related suppression of hunger suggests that if the food had been given earlier, we might have seen a decrease in intake.

Short-chain fatty acids may also be signals for satiety. When lactate is injected, food intake is suppressed in OM rats, but not in S5B rats. Plasma pyruvate concentrations were significantly lower in OM rats than in S5B rats (48). The levels of ketone bodies (β-hydroxybutyrate) were higher in the S5B rats than in the OM rats and were transported to a greater extent across the blood brain barrier (49). This suggests that short-chain fatty acids may provide one form of satiety signal to the brain.

In this brief review, we have summarized a number of studies performed during the past decade in our laboratories suggesting that dietary fat and individual fatty acids may play a role in the development of obesity. Clearly, the last chapter of this important investigation has yet to be written.

**LITERATURE CITED**


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