

Dietary fat oxidation as a function of body fat.

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Dietary fat oxidation as a function of body fat

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Purpose of review

Is trafficking of dietary fat involved in the development of obesity?

Recent findings

Studies on energy expenditure and substrate utilization during overfeeding, studies on individual differences in substrate utilization between individuals fed at energy balance, and differences in responses in energy expenditure and substrate utilization in individuals after weight reduction, illustrate that the capacity of fat oxidation is a potential determinant for the development of obesity.

Summary

The ability to store dietary fat seems to be involved in the susceptibility to gain weight during a positive energy balance. Obese individuals show less oxidation and more storage of dietary fat as compared with the lean phenotype. Differences in fuel trafficking make individuals prone to overeating in the current obesogenic environment with a high availability of energy-dense fatty foods. It is difficult to get rid of excess body fat as energy requirement for weight maintenance after weight reduction is lower than predicted from the new body composition reached and thus, there is a high risk for weight regain.

Keywords

energy balance, energy expenditure, overfeeding, substrate utilization, weight reduction

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Introduction

Fat, as a substrate for energy metabolism, is at the bottom of the oxidative hierarchy that determines fuel selection [1]. Changes in alcohol, carbohydrate, and protein intake elicit auto regulatory adjustments in oxidation, whereas a change in fat intake fails to elicit such a response. Several studies [2–4] have shown that fat intake does not stimulate its own oxidation when fat is consumed in excess of energy requirements. Even when diet composition was isoenergetically switched from low fat to high fat, it took a week before fat oxidation was raised sufficiently to match fat intake [5]. In between, fat balance was positive at the cost of a negative carbohydrate balance.

Here, the focus is on fat oxidation in relation to body fat. Is a reduced capacity to oxidize fat involved in the development of obesity? Evidence for the capacity of fat oxidation as a determinant for the development of obesity comes from studies on energy expenditure and substrate utilization during overfeeding, studies on individual differences in substrate utilization between individuals fed at energy balance, and differences in responses in energy expenditure and substrate utilization in individuals after weight reduction.

Energy expenditure and substrate utilization during overfeeding

When healthy adults are overfed, the energy equivalent of weight gain is lower than the excess energy intake. The efficiency of weight gain, as a response to overfeeding, is mainly determined by the diet-induced thermogenesis of nutrients and the cost of energy deposition. Reported diet-induced thermogenesis values for separate nutrients are 0–3% for fat, 5–10% for carbohydrate, and 20–30% for protein [6]. On a mixed diet, fed above energy requirements, energy balance is closely related to fat balance, that is, dietary carbohydrate and protein are oxidized and fat ingested in excess of energy requirements is stored. Models for the calculation of energy requirements and energy balance use an energy efficiency of 80%, close to the figures for deposition of dietary fat as body fat [7,8]. Thus, energy and substrate overload by overeating is disposed of by downregulation of fat oxidation and resultant fat storage [9*].

Overfeeding studies show large interindividual variation in weight gain, but comparing metabolically efficient and inefficient individuals showed no differences in energy expenditure changes [10]. There is no elevation in

metabolic rate above obligatory costs, that is, energy expenditure associated with an increased diet-induced thermogenesis due to the increased amount of food eaten, tissue gain, and an increased body size. Only one study [11] showed evidence for changes in energy expenditure as a principal mediator of resistance to fat gain with overfeeding. Here, the increase in energy expenditure was not only explained by diet-induced energy expenditure and storage costs but additionally by an increase in nonexercise activity thermogenesis. Sixteen nonobese volunteers were fed 4.2 MJ/day in excess of estimated weight-maintenance requirements for 8 weeks. The unique observations were firstly that on average, more than 50% of the excess energy ingested was dissipated through increased energy expenditure and secondly that fat gain varied 10-fold among volunteers, ranging from a gain of only 0.36 kg to a gain of 4.23 kg, and was inversely related to the increase in energy expenditure, mainly through activity energy expenditure.

The observed increase in nonexercise activity thermogenesis does not comply with overfeeding studies in the controlled environment of a respiration chamber with 24 h monitoring of energy expenditure, where the effect of overfeeding on energy expenditure was more pronounced during the inactive part of the 24 h interval, that is, the night, than during the day [12,13]. The concept of nonexercise activity thermogenesis is potentially a 'neat' way to control weight but new evidence has been scarce since the first publication 10 years ago.

When overload of energy by overeating is stored as fat, in the absence of a mechanism to expend extra energy by elevating metabolic rate above obligatory costs for diet-induced energy expenditure and tissue gain, there might be individual variation in the efficiency of tissue gain. A classic long-term overfeeding study [14] in identical twins showed considerable differences in changes in body composition and topography of fat deposition. There was about three times more variance among pairs than within pairs, suggesting a genetically determined tendency to store excess energy as fat or lean tissue. An interaction between environmental factors, including food intake, and genes involved in adipose tissue metabolism may determine the susceptibility to obesity. Peroxisome proliferator-activated receptor- γ (PPAR γ) regulates the expression of genes involved in fat storage [15]. An increase in PPAR γ expression during overfeeding was positively correlated to fat mass gain [16]. Thus, the ability to increase PPAR γ activity might be involved in the susceptibility to gain weight during a positive energy balance. Results of an intervention study, in which individuals received a placebo or the PPAR γ ligand rosiglitazone, suggested that ligand availability was of minor importance in fat mass generation [17]. However, rosiglitazone induced pronounced reductions

in fat oxidation and tended to increase food intake [18]. Thus, a shift in substrate usage leading to a preference for fat storage might contribute to susceptibility to obesity.

Differences in substrate utilization between individuals fed at energy balance

A study [19] in Pima Indians showed higher carbohydrate oxidation relative to intake is a predictor of fat gain. Substrate utilization was measured over 24 h in a respiration chamber on a weight-maintenance diet, followed by 3-day observation of food intake on an ad libitum diet. Carbohydrate oxidation and balance predicted subsequent ad libitum food intake and can influence short-term weight changes, which indicates that carbohydrate balance is a contributing metabolic factor affecting food intake. The physiological mechanism for the association between carbohydrate balance and food intake would be a stimulation of food intake by low glycogen stores. However, manipulation of muscle glycogen stores did not produce support for the postulated mechanism. Subsequently, it was suggested that changes in liver glycogen, as opposed to muscle glycogen content, play a central role in food intake. Further studies, including other populations than Pima Indians as well, should focus on the mechanism for the effect of carbohydrate oxidation on body weight regulation.

Most studies on substrate utilization and energy balance focused on fat oxidation. Individuals relying less on fat oxidation as a substrate for energy production would have a greater tendency to gain weight by storing fat. In the study on Pima Indians referred above, fat oxidation was not a predictor of subsequent ad libitum food intake. Thus, results of earlier studies, showing that inhibition of fat oxidation stimulated food intake in men [20] and an increase in fat oxidation decreased appetite in women [21], were not confirmed. However, a recent animal study [22**] showed that a reduced capacity to oxidize fat is involved in the cause of diet-induced obesity. Rats with inherited susceptibility to diet-induced obesity showed a lower fat oxidation and a greater feeding efficiency than rats resistant to diet-induced obesity. It was suggested that the susceptibility to diet-induced obesity was based on a limitation in transporting fatty acids into hepatocytes and in initiating β -oxidation of fatty acids.

A recent review [23] concluded that the partitioning of dietary fat between tissues might play an important role in the resistance or susceptibility to obesity. The relative metabolism of dietary fat, favoring oxidation over storage, may be associated with more robust signaling of positive energy balance and resistance to dietary-induced obesity. Trafficking of dietary fat between oxidation and storage has been studied with ^{13}C or ^{14}C and ^2H -labeled fatty acids, in which label recovery in, respectively, breath and

body water, reflects oxidation. In the postprandial state, most of the dietary fat is channeled into adipose tissue [24[•]]. The storage of dietary fat in visceral and subcutaneous depots has been observed by providing meals containing ³H or ¹⁴C-labeled fatty acids and then performing tissue biopsies about 24 h later. Thus, it was suggested that net fat retention is a function of preferential fatty uptake by adipocytes and not due to defective release [25].

We showed that dietary fat oxidation, as measured over 12 h after a breakfast containing deuterated palmitic acid, was negatively related to body fatness, in which lean individuals showed the highest and obese individuals the lowest values [26^{••}]. All individuals were observed under similar sedentary conditions in a respiration chamber, without activity equipment or an imposed activity protocol. In an animal model, differences in the partitioning of dietary fat between oxidation and storage were associated with obesity [27]. Obesity-prone rats showed less oxidation and more storage of dietary fat as compared with obesity-resistant rats; obesity-prone rats were only slightly heavier than the lean phenotype. In the human study, individual differences in body weight and consequent differences in body fat were much larger. The lower dietary fat oxidation in overweight and obese individuals could be a cause or a result of the difference in body fatness. Indeed, increased fatty acid trapping by adipose tissue was observed in obese women [28]. Whatever the reason, the aim should be a reduction in the storage of dietary fat in obesity-prone and obese individuals. They are the individuals with the highest risk for fat gain. The most effective way to reduce the risk of fat gain is a reduction of energy intake, most effectively reached with a high-protein diet (see last paragraph of the Discussion).

Differences in responses in energy expenditure and substrate utilization in individuals after weight reduction

Opposite to the lack of evidence for adaptive thermogenesis in response to overfeeding, there is convincing evidence of adaptive thermogenesis during under eating. During overfeeding, there is no elevation in metabolic rate above obligatory costs, that is, energy expenditure associated with an increased diet-induced thermogenesis due to the increased amount of food eaten, tissue gain, and an increased body size as described above. However, a decrease in energy intake below maintenance requirements results in a decrease in energy expenditure beyond what could be predicted from the decreases in diet-induced thermogenesis and the loss of fat-free mass and fat mass [29]. As an example, long-term weight loss after vertical banded gastroplasty resulted in a sustained reduction of metabolic rate as a persistent risk

factor for weight regain [30]. The ratio measured versus predicted metabolic rate was 1.02 ± 0.05 before weight loss, 0.91 ± 0.08 in a group with 34% weight loss at 12 months ($P < 0.05$), and 0.94 ± 0.08 in a group with 29% weight loss at a mean of 98 months ($P < 0.05$). Thus, the reduction of metabolic rate adjusted for body composition was sustained as long as weight loss was maintained, up to 150 months after weight loss started.

The weight loss-induced adaptive reduction of energy expenditure favors fat storage [31[•]]. In the weight-reduced state, carbohydrate becomes the preferred fuel for energy needs and dietary fat is diverted to adipose tissue. Weight reduction induces an improvement of whole-body insulin sensitivity, facilitating energetically efficient repletion of fat stores. Obesity-prone rats showed less fat oxidation when fed the same low-fat diet under ad libitum conditions after energy restriction, than a continuously ad libitum fed control group [32^{••}]. The preferential trafficking of dietary fat to adipose tissue was supported by the formation of new adipocytes. The same amount of excess energy resulted in a difference in substrate utilization of animals with ad libitum access to food after weight loss.

The major saving on energy expenditure during semi-starvation, and thus on the saving of body fat, is caused by a reduction in physical activity. In the classical Minnesota experiment, in which energy intake was reduced by 8.0 MJ/day over 24 weeks and individuals reached a new energy balance at a daily energy turnover of 6.6 MJ/day, the energy saving on physical activity was 4.7 MJ/day [33]. One-third of the reduction was caused by a reduction in body weight and two-thirds by a reduced body movement. Activity energy expenditure decreases during energy restriction and it is difficult to overcome the reduction with exercise training [34]. Exercise training has beneficial effects on plasma lipid and lipoprotein profiles, especially in sedentary overweight individuals with dyslipidemia [35]. Under ad libitum food conditions, exercise training does not necessarily lead to a reduction in body weight but body composition changes are favorable. Body fat can be reduced by physical activity although women tend to compensate for the increased energy requirement with increased energy intake, resulting in a smaller effect on fat mass as compared with men. However, when exercise training is combined with an energy-restricted diet, it does not add to the diet-induced loss of fat mass, neither in women nor in men [36].

Weight reduction is most successfully reached by a reduction in food intake, preferably by cutting down on fat intake. Energy requirement for weight maintenance after weight reduction is lower than predicted from the new body composition reached and thus, there is a high risk for weight regain.

Discussion

The current worldwide increase in the incidence of obesity, as a result of an imbalance between intake and expenditure, is a consequence of over consumption or an increasingly sedentary lifestyle. Objective measurements of energy requirement with doubly labeled water suggest that physical activity expenditure has not declined over the same period in which obesity rates have increased dramatically, and daily energy expenditure of modern man is in line with energy expenditure in wild mammals [37^{*}]. Subtle differences in fuel trafficking might make many individuals prone to overeating in the current obesogenic environment with a high availability of foods high in fat with potent sensory qualities and palatability. Additionally, the energy value of fat is 37 kJ/g, more than twice as high as the energy value for carbohydrate and protein. The difference in fuel trafficking might have a genetical basis in which individuals with a higher percentage body fat store a larger fraction of consumed fat than lean individuals [26^{**}].

Diets in the 'battle against obesity' have evolved from low fat through low carbohydrate to high protein. The apparent success of any diet 'rule' is first of all related to a reduction in dietary intake through a restriction of the variety of the diet. Additionally, the recent success of high-fat, low-carbohydrate diets can be ascribed to the fact that these diets are high in protein [38]. An elevated protein intake plays a key role in body weight regulation through increased satiety related to increased diet-induced thermogenesis, its effect on thermogenesis, body composition, and decreased energy efficiency [39].

Conclusion

A shift in substrate usage leading to a preference for fat storage might contribute to susceptibility to obesity. Differences in the trafficking of dietary fat may play a role in human obesity by inducing excess intake. Prevention of weight gain is most successfully reached by a reduction in food intake, preferably by cutting on fat intake. It is difficult to get rid of excess weight. Energy requirement for weight maintenance after weight reduction is lower than predicted from the new body composition reached and thus, there is a high risk for weight regain.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 67).

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