Dietary Fats and Thermogenesis

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INTRODUCTION

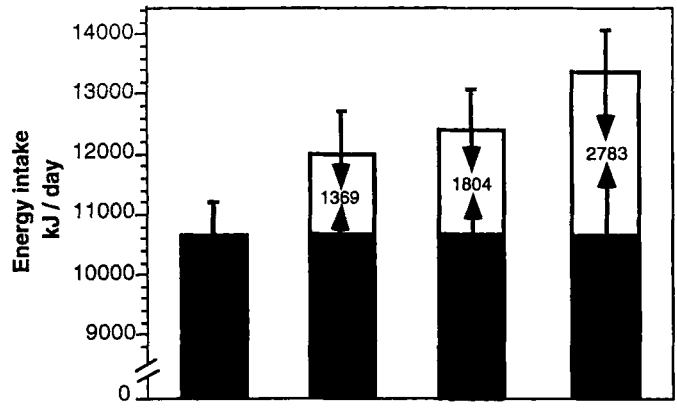
The demonstration of a significant relationship between energy and macronutrient balance, both in animals[1] and in humans,[2] has been one of the most-significant scientific contributions in the study of energy balance over the last decade. It implies that energy balance is likely to occur under free-living conditions when macronutrient balance is also reached. In addition, this concept has drawn attention to the fact that the precision with which substrate balance is maintained is not the same for alcohol, protein, carbohydrate, and lipid.

Numerous factors contribute to the stability of a given macronutrient balance over a period of time. These include the ability of a substrate to inhibit subsequent food intake and to promote its utilization. The stability of a given substrate balance also depends on the metabolic pathways that contribute to the disposal of an excess substrate intake. As described in this paper, fat balance seems to be the most-vulnerable component of an excess intake. Moreover, this vulnerability appears to be particularly pronounced in individuals predisposed to obesity. However, why obesity-prone individuals accumulate more fat before restoring body weight stability has never been clearly established. This paper focuses on this issue and considers environmental and genetic factors that can influence energy and fat balance and the predisposition to obesity.

DIET COMPOSITION AND ENERGY BALANCE

Numerous human studies have shown over the last decade that an increase in the fat content of the diet is associated with an increase in daily energy intake and body fatness.[3-6] This hyperphagic effect of fat is related to its reduced ability to inhibit subsequent food intake and to promote satiety in comparison to protein and carbohydrate.[7-10]

The impact of alcohol on energy intake has also been investigated in epidemiological and experimental studies. In general, it has been demonstrated that alcohol does not inhibit the intake of macronutrients to the extent that it would fully compensate for its energy content.[11-14] Recent data obtained in our laboratory revealed that the hyperphagic effect of alcohol is additive to that resulting from a high-fat diet[15] (FIG. 1). Furthermore, we also recently reported that the overfeeding associated with the



Dietary conditions:	Low-fat No alcohol	Low-fat Alcohol	High-fat No alcohol	High-fat Alcohol
Alcohol (% kJ)	0.8	10.3	0.7	9.0
Fat (% kJ)	29.3	26.7	45.4	42.1

FIGURE 1. Mean daily increase in energy intake (open bars) above the value (black bars) observed in the low-fat, no-alcohol condition. Values are presented in relation to the mean percentage of energy as alcohol and fat in each condition. Reprinted from reference 15 with permission.

combination of alcohol and high-fat foods is not fully explained by their high-energy density.[16] These observations suggest that, under nutritional conditions characterized by high-alcohol and high-fat intake, satiety cannot be reached without overfeeding. They also suggest that some afferent signals eliciting satiety are less influenced by fat and alcohol than by carbohydrate or protein.

SUBSTRATE OXIDATION AND ENERGY BALANCE

An increase in the fat content of a meal does not promote a significant increase in postprandial fat oxidation,[17] which contrasts with the stronger potential of carbohydrate to favor its own utilization. In addition, both carbohydrate[2] and alcohol[18] are known to inhibit fat oxidation. Experimental evidence also suggests that the composition of ingested fat affects postprandial fat utilization. For instance, it has been reported[19-21] that polyunsaturated fat has a greater potential to increase lipid oxidation and energy expenditure compared to saturated fat. Other data suggest that this effect of polyunsaturated fat is associated with a stimulation of sympathetic nervous system activity.[22] These observations indicate that, in the short term, fat oxidation is not increased in proportion to fat intake, particularly saturated fat, and is even decreased by the intake of other energy substrates.

The inability of fat intake to promote its utilization is, however, not unlimited.

After several days of high-fat intake, fat oxidation seems to increase in proportion to the amount of ingested fat, but this effect is not seen in all individuals. This was demonstrated by Thomas *et al.*,[23] who found a significant positive association between fat oxidation and intake after several days of high-fat feeding in lean subjects. On the other hand, essentially no increase in fat oxidation was observed in response to the high-fat diet in obese individuals.

Other experimental data also tend to confirm that the risk for excess body fat storage is related to a reduced capacity to oxidize fat. The comparison of postobese and lean individuals is an approach that has been frequently used to determine whether individuals prone to obesity are characterized by a reduced potential to oxidize fat. In general, fat oxidation was found to contribute a lower fraction of daily energy needs in postobese subjects than in lean subjects.[24-27] Recent evidence also suggests that this difference is more likely to be observed in the postprandial state.[28] Since fat gain is associated with an increase in fat oxidation,[29,30] an increase in body fat storage in people predisposed to obesity likely represents a necessary adaptation to restore energy and fat balance when exposed to an environment promoting positive energy balance. The association between fat oxidation and body weight stability has also been investigated in prospective designs. For instance, Zurlo *et al.*[31] demonstrated that an increased RQ, reflecting a reduced relative fat oxidation, is a risk factor for body weight gain over a follow-up period of a few years. This finding was subsequently confirmed by other investigators.[32]

The possibility that the reduced potential for *in vivo* fat utilization in obesity-prone individuals is related to a low skeletal muscle metabolism has been recently examined. These investigations have shown that a low skeletal muscle oxidative potential is associated with an increase in total body fat[33,34] and visceral fat deposition.[35] This is concordant with the observation that a high level of skeletal muscle lipoprotein lipase activity predicts a high potential to oxidize fat.[36]

It has not been possible up to now to clearly establish whether the relative ability to use fat calories is attributable to environmental or genetic factors. Among environmental factors, physical activity is probably the one that exerts the strongest impact on fat utilization. Indeed, prolonged vigorous physical activity is known to increase the postexercise metabolic rate and fat oxidation.[37-39] In trained individuals, the regular practice of aerobic exercise is associated with an increase in sympathetic nervous system activity,[38,39] which is likely mediated by a specific increase in skeletal muscle beta-adrenergic receptor stimulation.[40] Since overweight individuals are known to be less active under free-living conditions[41,42] or in a confined environment such as a respiratory chamber,[43] it is likely that a decrease in physical activity participation predisposes to an increase in body fat stores.

Genetic factors also influence energy expenditure and substrate oxidation. Several studies have shown that a significant fraction of variation in the resting metabolic rate,[44,45] energy cost of standardized activities,[45] and resting and exercise RQ[45] was explained by genetic heritability. Finally, recent results obtained in our laboratory suggest that cycles of profound body weight loss and regain can substantially reduce daily energy expenditure.[46]

In summary, the evidence described in this section supports the concept that fat gain is a necessary adaptation in some individuals to restore energy and fat balance

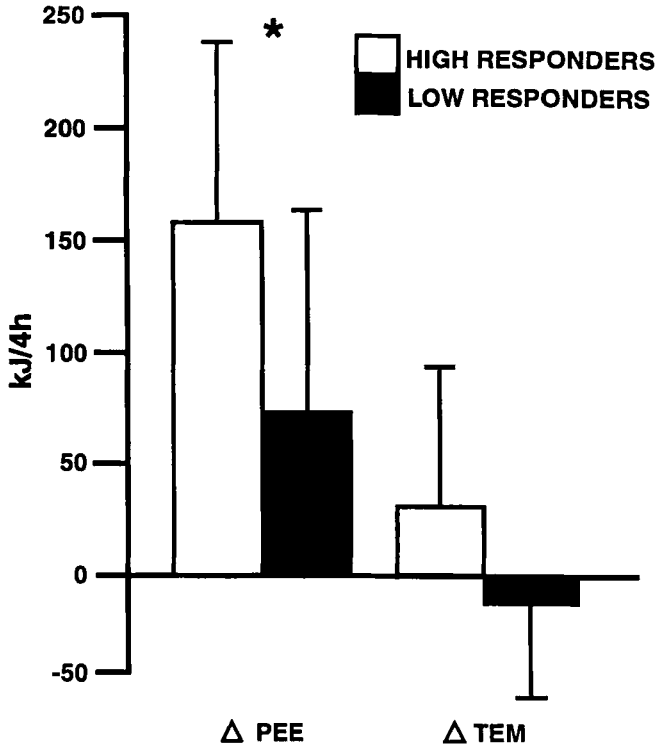


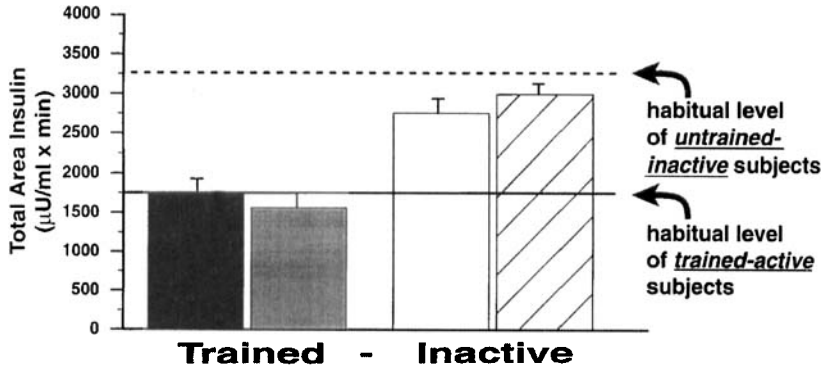
FIGURE 2. Changes in postprandial energy expenditure (PEE) and thermic effect of a meal (TEM; PEE above resting metabolic rate) in subjects displaying a high or a low response in postprandial plasma insulin to overfeeding. $\bar{X} \pm$ SD; *, $P < 0.05$. Reprinted from reference 53 with permission.

in a context promoting excess energy intake. This is likely explained by both environmental and genetic factors modifying the regulation of energy balance.

GENOTYPE-ENVIRONMENT INTERACTION AND ENERGY BALANCE

A paradigm incorporating interactions between environmental and genetic factors probably offers the most-realistic explanation for the increase in the prevalence of obesity that has been observed in industrialized countries in this century. This concept suggests that some individuals are at greater risk to develop obesity in an environment promoting positive fat and energy balance.

Our laboratory has been engaged in the study of genotype-environment interaction effects on energy balance for more than a decade. In a series of studies, we have subjected monozygotic twins to standardized overfeeding or exercise-training protocols to determine whether individuals sharing the same genetic background were more alike in their response compared to subjects having no genes in common by descent. These studies have generally demonstrated a more-homogenous response within than



Energy intake (kcal/day)	0	2076	3291	4262
Estimated energy balance (kcal/day)	-2600	-550	+700	+1250

FIGURE 3. Effect of short-term detraining on the insulin response to intravenous glucose in trained individuals subjected to different levels of energy intake. The insulin response is compared to the habitual level measured in untrained-inactive and trained-active subjects. Adapted from reference 55.

between twin pairs for resting and exercise energy expenditure and body composition as a result of both overfeeding[47,48] and exercise-training.[49,50] This supports the notion that one's genotype is partly responsible for the physiological response to environmental factors altering energy balance. This observation is important, but it also emphasizes the need for this research to be pursued at the molecular level. Thus, it would be relevant to consider genes coding for molecules involved in regulatory mechanisms linking peripheral metabolism and neurosystems that influence energy balance. Insulin plays a role in this context and the discussion of its potential effects on energy balance is particularly relevant in this symposium.

INSULIN AND REGULATION OF ENERGY BALANCE

The peripheral effects of insulin on substrate disposal and anabolic processes are well established, but the search for mechanisms still remains the object of many investigations. Insulin also participates in the regulation of energy balance via central effects that influence both energy intake and expenditure. Hyperinsulinemia with euglycemia increases sympathetic nervous system activity, as reflected by an increase in plasma norepinephrine[51] and muscle sympathetic nerve activity.[52,53] As illustrated in FIGURE 2, we have shown that, under conditions of experimental overfeeding, a high increase in postprandial insulin is associated with a greater increase in postprandial energy expenditure.[54] This agrees with a prospective study in Pima Indians that revealed that hyperinsulinemia is associated with a reduced long-term body weight

gain.[55] These observations are also concordant with results presented in FIGURE 3, which demonstrate that a considerable increase in plasma insulin occurs in trained individuals after several days of detraining, provided that this interruption of exercise is accompanied by positive energy balance.[56]

Recent studies have also identified potential neuropeptides that could mediate the effects of insulin on energy balance. This is the case for neuropeptide Y (NPY), whose gene expression, level in the arcuate nucleus, and probably orexigenic effects are inhibited by insulin.[57] Another potential mediator of the effects of insulin is corticotropin-releasing hormone (CRH), whose supplementation decreases insulinemia and interrupts weight gain in obese rats.[58] Since NPY[59] and CRH[60] also influence sympathetic activity, they and their receptors represent prime candidate genes for the study of molecular mechanisms affecting individual differences in energy balance.

CONCLUSIONS

A lifestyle characterized by high-fat and alcohol intake as well as sedentariness favors positive fat and energy balance. These factors also impose an increased demand on regulatory mechanisms responsible for the maintenance of body weight stability. Insulin seems to be involved in these mechanisms since hyperinsulinemia occurs when energy intake exceeds expenditure. Hyperinsulinemia can induce a substantial increase in sympathetic nervous system activity and is related to an increase in thermogenesis under conditions of positive energy balance. Hyperinsulinemia is also associated with a reduced risk for long-term body weight gain. An increased risk to develop the metabolic syndrome potentially represents a detrimental side effect of a mechanism that promotes energy balance and body weight stability.

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