High-fat and low-fat (behavioural) phenotypes: biology or environment?*

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It is now widely accepted that obesity develops by way of genetic mechanisms conferring specific dispositions which interact with strong environmental pressures. It is also accepted that certain dispositions constitute metabolic risk factors for weight gain. It is less well accepted that certain patterns of behaviour (arising from biological demands or environmental influences) put individuals at risk of developing a positive energy balance and weight gain (behavioural risk factors). Relevant patterns of behaviour include long-lasting habits for selecting and eating particular types of foods. Such habits define two distinct groups characterized as high-fat (HF) and low-fat (LF) phenotypes. These habits are important because of the attention given to dietary macronutrients in body-weight gain and the worldwide epidemic of obesity. Considerable evidence indicates that the total amount of dietary fat consumed remains the most potent food-related risk factor for weight gain. However, although habitual intake of a high-fat diet is a behavioural risk factor for obesity, it does not constitute a biological inevitability. A habitual low-fat diet does seem to protect against the development of obesity, but a high-fat diet does not guarantee that an individual will be obese. Although obesity is much more prevalent among HF than LF, some HF are lean with BMI well within the normal range. The concept of 'different routes to obesity' through a variety of nutritional scenarios can be envisaged, with predisposed individuals varying in their susceptibility to different dietary inputs. In a particular subgroup of individuals (young adult males) HF and LF displayed quite different profiles of appetite control, response to nutrient challenges and physiological measures, including BMR, RQ, heart rate, plasma leptin levels and thermogenic responses to fat and carbohydrate meals. These striking differences suggest that HF and LF can be used as a conceptual tool to investigate the relationship between biology and the environment (diet) in the control of body weight.

Dietary fat intake: Obesity: Energy balance

Problem: diet and obesity

Any consideration of dietary intake is given a perspective by the current global epidemic of obesity (World Health Organization, 1998). In simple terms the development of obesity can be attributed to a positive energy balance, i.e. energy intake exceeding energy expenditure. Most reviewers agree that energy expenditure, reflected in the amount of physical activity carried out, is too low and that sedentariness has reached unacceptable levels (Prentice & Jebb, 1995; Eggar & Swinburne, 1998). However, since some food surveys indicate that the average food consumption (energy intake) of some populations has decreased over the years, not all commentators agree that genuine overconsumption (abnormally high levels of energy intake) contributes to the positive energy balance that leads to obesity. Is it the case that obesity is not necessarily associated with a high food intake?

First, the average intake of a population may fail to indicate the behaviour of individuals in various states of energy balance or at different levels of body weight. Even with a declining mean value, some individuals could be markedly increasing their energy intake. Second, it is known that food intake records cannot be regarded as a reliable estimate of food actually consumed (Macdiarmid & Blundell, 1998). For example, using energy intake : BMR as an indicator of the acceptability of daily food diary records, it has been calculated that in one dietary survey in the UK (Gregory *et al.* 1990) reported energy intakes were unacceptably low in 39 % of women and 29 % of men. Moreover, among the obese, under-reporting reached levels of 60 % in men and 70 % in women (Macdiarmid *et al.*

Abbreviations: HF, high-fat phenotype; LF, low-fat phenotype.

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1998). Since the degree of under-reporting has increased over the years in some countries (Fogelholm *et al*. 1996), probably due to people being sensitized by a dieting culture, it is often hard to accept that food intakes have genuinely fallen. Third, it has now been demonstrated that a defect in one particular single gene can lead to obesity through a dramatic increase in food intake characterized as a form of hyperphagia (Montague *et al*. 1997; Farooqui *et al*. 1999). Taken together these findings suggest that serious consideration should be given to the idea that the frequency of obesity continues to increase in most countries due to an appetite promoting effect of the (obesigenic) environment in the face of a permissive physiological system (Blundell & King, 1996).

One characteristic of the food supply which has been identified as a likely promoter of a high energy intake and a positive energy balance is the prevalence of high-fat foods (Macdiarmid *et al*. 1996; Blundell *et al*. 1996), either of the savoury variety (Cox *et al*. 1999) or of the sugar–fat type (Drewnowski *et al*. 1992). A good deal of evidence has been assembled on this issue from both epidemiological and intervention studies. A meta-analysis has demonstrated that high-fat diets are associated with gains in body weight, and that change from a high-fat to a low-fat (high-carbohydrate) diet is associated with modest weight losses (Astrup *et al*. 1998).

However, although the presence of high-fat foods has been identified as a major environmental 'risk factor' for weight gain, it is clear that the relationship between a high-fat diet and a high BMI is not a 'biological inevitability' (Blundell & Macdiarmid, 1998). Some individuals who habitually consume a high-fat diet (at least at a certain age) do not appear to be gaining weight and are not obese. The present review will throw further light on this issue.

This issue poses a question about the habitual diet and the control of body weight. In turn it may be asked whether a habitually consumed diet that involves the expression of 'food choices' reflects a physiological drive for specific foods (mediated via sensory preferences or nutrient needs), or the impact of environmental forces. Is dietary choice a biological or environmental phenomenon, and what are the implications? These questions are important, since the choice of a particular diet (and the consumption of nutrients) constitutes a risk factor for being in positive energy balance and subsequent weight gain.

Risk factors for weight gain: metabolic

Most researchers do not have any trouble accepting the idea that the state of a person's metabolism constitutes a major risk for developing weight gain and becoming obese. However, as obesity develops, metabolic characteristics change so that the state of obesity itself is associated with a different metabolic profile from that accompanying the process of weight gain. This factor makes it important to do longitudinal studies (whilst weight is increasing) as well as cross-sectional studies (comparing lean and obese subjects). Recently, Ravussin & Gautier (1999) have drawn attention to this issue and have outlined those metabolic and physiological factors associated with weight gain and with the achievement of obesity (Table 1).

Table 1. Metabolic factors related to obesity itself, or to the development of obesity (After Ravussin & Gautier, 1999)

	Factors associated with obesity	Factors predicting weight gain
Relative metabolic rate	Normal or high	Low
Energy cost of physical activity	Normal	Low
Fat oxidation	Normal or high	Low
Insulin sensitivity	Low	High
Sympathetic nervous system activity	High	Low
Relative plasma leptin concentration	High	Low

The tendency to gain weight is associated with a low BMR, low energy cost of physical activity, a low capacity for fat oxidation (relatively high RQ), high insulin sensitivity, low sympathetic nervous system activity and a low plasma leptin concentration. In the state of obesity itself many of these risk factors (or predictors of weight gain) are reversed.

Risk factor for weight gain: behavioural

Whilst many people readily accept the concept of metabolic risk factors, it would be deduced that in the presence of a 'hyperphagia-inducing' diet, low energy expenditure (basal metabolism and activity-induced), low fat oxidation and high insulin sensitivity may be sufficient to induce fat deposition and weight gain. However, the phenomenon of hyperphagia may be brought about through differing processes which themselves constitute the risk factors which lead to hyperphagia or 'overconsumption' (high energy intake leading to a positive energy balance). These processes may be forms of eating behaviour, the sensory or hedonic events which guide behaviour, or those physiological mechanisms that lead to adjustments in behaviour. For convenience this cluster of events can be referred to as behavioural risk factors. These events may include a preference for fatty foods, weakened satiation (end-of-meal signals), relatively weak satiety (post-ingestive inhibition over further eating), strong oro-sensory preferences (e.g. for sweetness combined with fattiness in foods), a binge potential and a high food-induced pleasure response. In turn, these events may be subdivided to describe more specific components leading to a risk of overconsumption.

These behavioural risk factors can be regarded as biological dispositions which create a vulnerability for weight gain, and which manifest themselves through behavioural acts themselves, or through physiological processes which promote or permit changes in behaviour.

However, such risk factors alone would be unlikely to lead to a positive energy balance in a benign environment, i.e. one in which the food supply and the cultural habits worked against excessive consumption. In most societies, however, the food environment exploits biologically-based dispositions, and this factor promotes the achievement of a high energy intake (Table 2).

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Table 2. Proposed interactions between biologically-based behavioural risk factors and environmental features leading to increases in energy intake

Biological vulnerability (behavioural risk factor)	Environmental influence	Effect on food intake
Fat preference	Abundance of high-fat (high-energy-dense) foods	↑ Fat intake
Weak satiation (end of meal signals)	Large portion sizes	↑ Meal size
Oro-sensory responsiveness	Availability of high-palatability foods with specific sensory–nutrient combinations	↑ Amount eaten ↑ Frequency
High level of hunger	Ready availability of foods	↑ Persistent drive to seek and eat food

↑, Increase.

High- and low-fat phenotypes: biology or environment?

The combination of biological dispositions (behavioural risk factors) and the presence of a conducive food environment will lead to particular patterns of consumption characterized by the size of eating episodes, the frequency of eating or by the intake of particular macronutrients. Recently, some attention has been given to patterns of fat intake (for example, see Baghurst *et al*. 1994; Macdiarmid *et al*. 1996) and criteria for identifying individuals as high- or low-fat consumers have been established. The level of fat consumption can be determined through a food-frequency questionnaire (for example, see Margetts *et al*. 1989). Although not a perfect instrument, the use of more than one scale can improve the accuracy of identification. If these consumer types are robust, and demonstrated to be differentiated on other criteria or tests, then they may be termed 'phenotypes'.

In the case of high-(HF) and low-fat (LF) phenotypes, individuals are classified according to the type of diet habitually consumed. Table 3 indicates the way in which young adult male phenotypes differ according to the type of foods eaten. In turn, these measurable differences in the types of foods habitually selected pose the question of whether the 'choices' are biologically driven (by particular tissue needs, physiological requirements or neuro-sensory characteristics) or incidentally 'picked-up' from the food environment. In either case, it will be necessary for the physiological system to adapt to the ingestion of very large amounts of specific macronutrients.

High- and low-fat phenotypes in young adult males

Behavioural aspects

In principle, phenotypes can be identified independently of age or sex. However, in a first series of studies the characteristics of young adult males have been examined. When subjected to energy and macronutrient challenges in order to evaluate the responses of the appetite control system, clear differences between the groups were demonstrated. Initially, HF displayed higher initial hunger levels, with a much sharper decline in hunger in response to meals or nutrient loads (Cooling & Blundell, 1998*a*). After eating, hunger recovered more rapidly in HF compared with LF (Fig. 1). In addition, the size of a test meal consumed was closely related to the suppression of hunger in HF; in contrast, the appetite response system in LF appeared to be somewhat insensitive and damped. This relationship between habitual fat intake and hunger is reminiscent of a previous finding. French *et al*. (1996) found that during 2 weeks of high-fat overfeeding to normal-weight subjects, which caused a significant gain in weight, subjects displayed a progressive increase in hunger and a decrease in fullness before a test meal. Taken together these findings may indicate that eating a high-fat diet may facilitate feelings of hunger.

A further feature of these behaviour studies was that HF and LF differed in the control over meal size when offered an unlimited range of either high-fat or high-carbohydrate foods. HF consumed a similar weight of food on both diets, and therefore took in a much higher amount of energy with the high-fat (high-energy-dense) foods. In contrast, LF consumed a much smaller amount of the high-fat foods, and consequently took in a similar amount of energy on both diets. These findings suggest that signalling systems for meal termination (satiation) and post-meal inhibition of appetite (satiety) operate with differing strengths in HF and

Table 3. Anthropometric, dietary and metabolic characteristics of male high- and low-fat phenotypes (From Cooling & Blundell, 1998*b*)

Phenotype …	High-fat	Low-fat
Age (years)	20·5	20·6
BMI (kg/m^2)	22·6	22·1
Body fat (%)	9·9	9·8
Dietary fat intake:		
g/d	158·8	80·8*
% energy	44·3	32·0*
BMR (MJ/d)	6·80	6·10
Resting RQ	0·84	0·89*
Plasma leptin (ng/ml)	2·92	1·79*

Values were significantly different from those for the high-fat phenotype (two-tail): *P < 0·05.

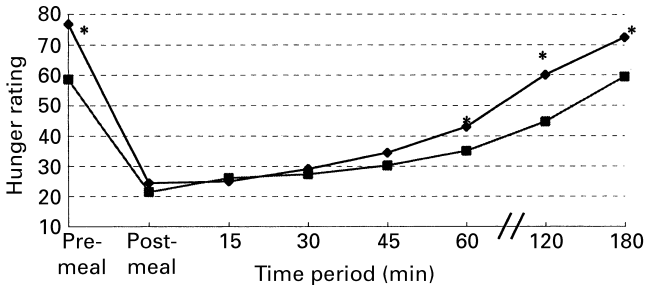

Fig. 1. Profiles of hunger rating scores for high-fat consumers (◆) and low-fat consumers (■) following high- and low-energy challenges (averaged for each consumer group). Horizontal axis shows time (min) after the end of the meal. High-fat consumers display a higher initial hunger, a sharper decline with eating and a more rapid recovery of hunger after the meal. Mean values were significantly different from those for low-fat consumers: *P < 0·05. (Adapted from Cooling & Blundell, 1998*a*.)

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LF. This finding may not be surprising in view of the fact that the gastrointestinal tract has become adapted to dealing with quite different dietary components, and this factor will have exerted a priming effect on specific satiety signals.

Physiological aspects

The existence of distinctive profiles of appetite control in HF and LF indicates different patterns of physiological responses to food ingestion. The possibility of other physiological differences was investigated using indirect calorimetry to measure BMR, RQ and dietary-induced thermogenic responses to specific fat and carbohydrate loads (Cooling & Blundell, 1998*b*).

The results indicated that HF had lower RQ than LF; this finding confirmed that fat oxidation was higher in HF, as would be expected due to the habitual high intake of fat-containing foods. However, an unexpected finding was the significantly higher BMR in HF than LF, together with different profiles of 'thermogenic' responses to the high-fat and high-carbohydrate loads (Table 3). A further important finding was that HF had higher plasma leptin levels than LF (Cooling *et al*. 1998), despite having similar levels of body fat.

Implications for energy balance?

A particular behavioural and physiological profile has been demonstrated from the study of HF and LF. The picture poses interesting questions, since these particular cohorts of young adult male subjects display markedly different intakes of dietary fat (159 g/d *v*. 81 g/d) and energy. However, despite these large differences subjects had almost identical body weights, BMI and fat masses. An obvious implication is that some aspect of energy expenditure or metabolism is balancing the high energy intake so as to maintain body weight. The observation that HF and LF differ in BMR is consistent with this idea, although the absolute size of the energy difference does not appear sufficient to preserve energy balance.

However, the notion of individuals with different BMR is consistent with the concept of 'energy-sparing' and 'energy-profligate' which has been used to describe two distinct groups of women (Goldberg, 1997). Interestingly, these two types of individuals are associated with different habitual intakes, the marginally-nourished and the very-well-nourished. For years some researchers in the field of obesity research have maintained the idea that individuals exist who are capable of consuming prodigious amounts of food yet remain lean. It is possible, therefore, that the HF and LF may constitute a useful investigative approach for examining the relationship between energy intake and energy utilization.

High- and low-fat phenotypes: biology or environment?

The observation that individuals with contrasting habitual diets differ in some fundamental aspects of physiology and metabolism does not indicate a cause for these phenomena, but it does make the search for that cause more interesting and urgent. One interpretation of the findings so far is that the habitual consumption of a high-fat diet (generating a high energy intake) leads to physiological adaptations in the form of a raised BMR. However, the converse could also be possible. This interpretation would imply that individuals with a naturally (genetically conferred)-high BMR select a high-energy diet. The two arguments can be formulated as an environmentally-driven diet selection leading to protective physiological adaptations, or a biologically-driven energy expenditure leading to an appropriate diet selection.

Phenotypes and metabolic risk factors: is there a paradox?

It is widely regarded that a high intake of dietary fat constitutes a risk factor for a positive energy balance and weight gain. There is plenty of evidence for this theory, both from epidemiological and intervention studies. However, the correlations between dietary fat and obesity indices are often quite low, indicating considerable variability in the relationship. Alongside this finding it has previously been noted that the metabolic predictors of weight gain include a low relative BMR, a high RQ and relatively low plasma leptin levels. Interestingly, all these three variables characterize LF when compared with HF. Consequently, the habitual consumption of a low-fat diet, usually regarded as being an optimal dietary strategy to prevent obesity (for example, see Macdiarmid *et al*. 1996), is associated with a metabolic profile indicating a susceptibility to weight gain. Is this feasible? On the other hand, in this group of subjects (young adult males) a habitual high-fat diet was associated with metabolic variables apparently protective against weight gain.

Of course, it must be remembered that the present study was cross-sectional and provides only a glimpse of an evolving physiological situation. HF individuals may therefore be in a state of positive energy balance and may be in the process of gaining weight. This process would be further strengthened by the reported decrease in fat oxidation with increasing age (Melanson *et al*. 1997). It could obviously take many years for a high-fat diet to adjust a BMI from 23 to 30 kg/m^2. On the other hand, LF individuals may be very vulnerable to weight gain if there is an age-related change in lifestyle characterized by reduced physical activity or an increase in the fat content of the diet. LF may be quite ill equipped to prevent weight gain in the face of such changes.

Dietary choice and routes to obesity

The establishment of those constituents of the food supply which have the greatest potential to engender a positive energy balance with consequent weight gain is beset with methodological difficulties. Epidemiological studies are inevitably compromised by invalid reporting, which gives little cause for confidence in the energy or nutrient values for specific groups. On the other hand, intervention studies which coercively manipulate the diet can be criticized for lack of compliance, for the short duration of the intervention, and for the unnatural behaviour which may become apparent when people operate under a protocol. Thus, any

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statement about the impact of a dietary factor on weight gain will constitute a value judgement from a number of sources of evidence.

In our view the total amount of dietary fat consumed remains the most potent food-related risk factor. However, other reviewers have nominated saturated fat rather than total fat, high energy density rather than fat *per se*, food generating a high glycaemic index or a high-sugar diet. It is clear that in this domain we are not dealing with a 'biological inevitability'; individuals can achieve a positive energy balance on a wide range of diets which stimulate energy intake to overtake energy expenditure. The type of diet that causes body-weight gain may depend on an individual's particular physiological profile.

The concept of 'different routes to obesity' through a variety of nutritional scenarios can be integrated with the notion of individuals varying in susceptibility to different dietary inputs. Whether by genetic determination, physiological adaptation or nutrient–gene interactions, some individuals will be better equipped physiologically to deal with a high-fat high-energy diet. Indeed, although we maintain that a diet replete with fatty foods remains the single most prominent food-related risk factor, it is clear that some individuals can remain lean on such a diet, at least for a certain period of time.

Thus, the research strategy focusing on specific behavioural phenotypes can help our understanding of the factors leading to weight gain by drawing attention to the interaction between dietary variables and individual differences in physiological features related to energy balance.

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