Obesity: the protein leverage hypothesis

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Received 15 July 2004; revised 6 November 2004; accepted 9 November 2004

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Summary

The obesity epidemic is among the greatest public health challenges facing the modern world. Regarding dietary causes, most emphasis has been on changing patterns of fat and carbohydrate consumption. In contrast, the role of protein has largely been ignored, because (i) it typically comprises only ~15% of dietary energy, and (ii) protein intake has remained near constant within and across populations throughout the development of the obesity epidemic. We show that, paradoxically, these are precisely the two conditions that potentially provide protein with the leverage both to drive the obesity epidemic through its effects on food intake, and perhaps to assuage it. We formalize this hypothesis in a mathematical model. Some supporting epidemiological, experimental and animal data are presented, and predictions are made for future testing.

Keywords: Obesity, protein, the geometric framework.

obesity reviews (2005) **6**, 133–142

Introduction

It is conservatively estimated that more than 1 billion people worldwide are overweight (classified as having a Body Mass Index of 25–29.9) or obese (BMI ≥ 30). Rates of incidence are increasing, notably among the young, and the associated disease burden is immense (1–5). The obesity epidemic is the consequence of a complex interplay between lifestyle and dietary changes accompanying westernization (1). While reduced levels of exercise are clearly an important contributor, excess weight gain is due to an imbalance between energy intake and energy expenditure (6).

There remains considerable uncertainty about the dietary causes of obesity. The greatest emphasis has been placed on the relative roles of fat and carbohydrate in the diet, but which of these plays the bigger role has been the subject of a long-running debate with views see-sawing at regular intervals over the past 30 years (7–9). Meanwhile, substantial research effort has been directed at understanding the molecular bases of the control of fat and carbohydrate metabolism, and at the search for potential interventions (10–12). By contrast, the role of protein in the obesity problem has been largely ignored. This is for two reasons. First, protein provides the minor part of the human energy budget. Second, protein intake has remained far more constant over time and across populations than either fat or carbohydrate, both as a percentage of energy in the diet and in terms of absolute amounts eaten (13,14). Hence, while the obesity epidemic has spread, protein intake has remained relatively unchanged – giving the impression that protein cannot be responsible.

We use geometrical analysis developed from extensive studies of non-human animals (15,16) to postulate a key role for protein appetite in the obesity epidemic. We develop a model that shows how, paradoxically, it may be precisely because protein comprises a small component of the diet and is tightly regulated that it could have sufficient leverage over human ingestive behaviour to explain obesity. Focusing on this leverage over intake both clarifies the role of dietary protein in the development of obesity, and also provides a possible means of ameliorating the problem. We provide some supporting evidence for the protein leverage hypothesis from experimental, epidemiological and animal studies, and highlight key predictions for future testing.

Conceptualizing nutrient balance in nutrient space

To illustrate geometrical analysis, consider a 45-year old, moderately active adult male of height 1.8 m and stable weight 76 kg (BMI 23.5 kg m^{-2}), whose total daily energy requirements (17) are *c.* 10 700 kJ. Achieving a diet comprising 14% protein (typical of a modern Western adult) requires him to eat 1500 kJ per day of protein and 9200 kJ of carbohydrate and fat combined. This represents a daily intake of 88 g protein, and a total mass of carbohydrate and fat eaten that will depend on the relative proportions of the two in the diet, given that fat has more than twice the energy density of carbohydrate. For present purposes we will combine fat and carbohydrate into a single value for energy as their relative contributions are not germane to the logic of our argument. (As an aside, our hypothetical subject would be eating *c.* double the minimum protein intake needed to maintain nitrogen balance. Why humans eat more protein than seems to be required is an interesting ancillary question, but not our focus here, where we are concerned with observed behaviour).

This situation can be represented as a two-dimensional nutrient space (Fig. 1a). Arriving at a combined intake of 1500 kJ of protein (P) and 9200 kJ of carbohydrate + fat (C + F) represents the 'intake target' for our subject, integrated across a day. If he reaches that point he will meet simultaneously his daily needs for both P and non-P energy. Whether or not he can reach that point depends on his diet, which will be made up of multiple food items. The evidence suggests that the mechanisms regulating macronutrient intake in humans operate over a period of a day or so (18,19). This means that the model should represent the composite intake of foods over this period (i.e. the composition of the daily diet), rather than single foods, which probably cannot be resolved. A daily diet (or an individual food item) can be represented in the same nutrient space, as a line ('rail') drawn from the origin with a

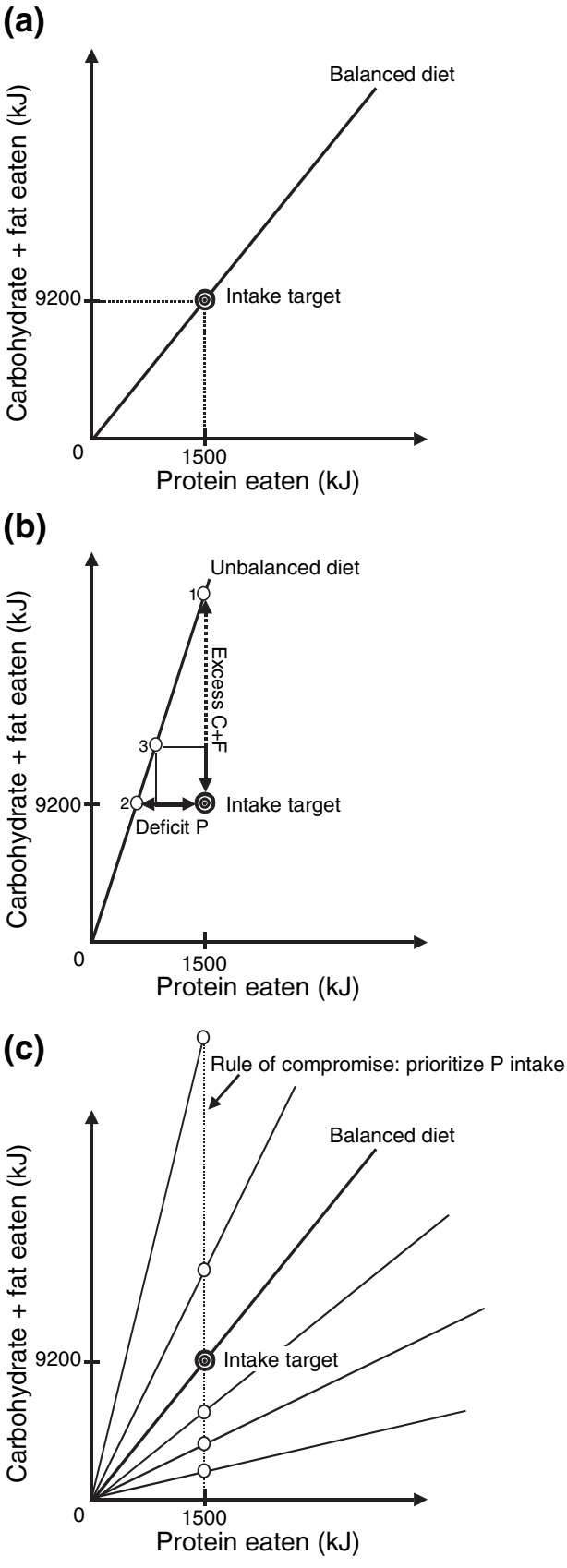


Figure 1 (a) Two-dimensional nutrient space indicating the daily intake of P and C + F (the 'intake target') necessary to maintain energy balance on a diet containing 14% of energy as P and 86% as C + F, for a moderately active, 45-year-old male (BMI 23.5). A balanced daily diet is the line which runs from the origin to intersect the intake target.
(b) The situation when restricted to an unbalanced diet (one which does not intersect the intake target). If the subject were to eat until point 1, he would have achieved the intake target level of P but ingested an excess of C + F. At point 2, he would have gained the intake target amount of C + F but under-eaten P. At point 3 a balance is struck between over-eating the nutrient group in excess and under-eating that in deficit. Here the balance represents the outcome were total energy intake being maintained.
(c) The intake array across five unbalanced diets that describes the rule of compromise in which intake of P is prioritized over that of C + F.

slope that is determined by the ratio of P to C + F it contains (Fig. 1a). A balanced daily diet is the one that intersects the intake target.

However, if the diet is not coincident with the intake target, the subject must compromise between eating more of one nutrient group and less of the other. Such a situation is shown in Fig. 1b for a diet containing a lower ratio of P to C + F than at the intake target. The subject could continue to eat until the intake target amount of P is ingested (point 1), but will have over-eaten C + F. At the other extreme, he might ingest sufficient to reach the intake target level of C + F, thereby under-eating P (point 2). Or, he could strike some intermediate compromise. One example would be to maintain total energy intake, which would require stopping at the point where the energy deficit from protein is counter-balanced by the energy surplus from C + F (point 3).

Each unbalanced diet will have its own such point of compromise, and jointly the points across the nutrient plane will form an intake array. The shape of this array describes the way in which the multiplicity of influences and mechanisms that control intake of the two nutrient dimensions interact and weight over-eating one against under-eating the other, relative to the intake target. Such 'rules of compromise' are fundamental to understanding the health and other consequences of nutritionally unbalanced diets (15,16). A central precept in the geometric models is that rules of compromise must be interpreted relative to the intake target. The intake target is not fixed, but will depend on a subject's age, sex, genotype, maternal nutrition during pregnancy, level of activity, ambient temperature, reproductive status, etc. (15,16).

What is the rule of compromise for humans?

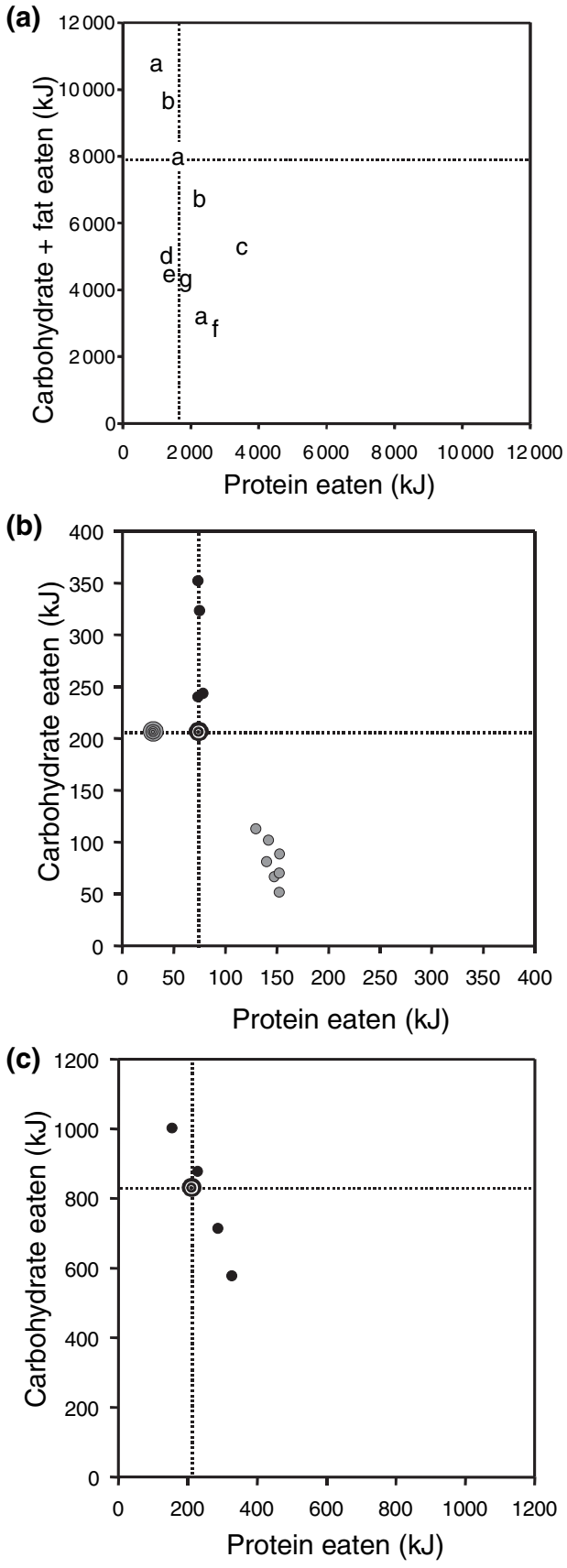
Protein is the most satiating macronutrient group for humans and is the most tightly regulated post-absorptively, although all three macronutrients exert some degree of influence over energy intake (20,21). Results from comparative studies of other vertebrates (15,16), human experiments (22–25) and population-level data (13,14) suggest that the response of humans when faced with unbalanced diets (relative to their individual intake target) is to prioritize P intake (see Fig. 2), providing a pattern that is similar to Fig. 1c.

Recently, we have used our geometric framework to explore the human rule of compromise (24) for intake of P and C + F. We performed a short-term experiment involving 10 subjects domiciled together for 6 d. For the first 2 d the subjects were provided with the opportunity to select their breakfast, lunch, afternoon snack and dinner from a buffet of items comprising a wide range of macronutrient compositions. Everything they ate was weighed and their macronutrient intake was estimated from food composition tables. For the next 2 d, one group of subjects (treatment 1) was restricted to foods that were high in P and low in C + F, while the remaining subjects in treatment group 2 were provided with only low-P, high-C + F items. For the last 2 d of the experiment (days 5 and 6), all subjects were given the same free choice of foods as on days 1 and 2. The overriding message from the experiment is that when subjects were restricted to a diet that contained either a higher (treatment 1) or lower (treatment 2) ratio of P to C + F than they had self-selected during days 1 and 2, they maintained their intake of P at the expense of regulation of C + F intake. This occurred despite there being wide variation between individuals in the position of their free-choice intake point. Thus, treatment group 1 under-ingested C + F relative to their free-choice intake point rather than over-eat P, while treatment group 2 over-ate C + F to gain limiting P.

In Fig. 2a we have plotted the results from this experiment along with data recast from several earlier publications. As we predicted, in all these cases where subjects were restricted to a diet consisting of a fixed ratio of P to C + F, either in the short- or long-term, they maintained daily protein intake at a more constant level than that of the other two macronutrients. Also consistent with the hypothesis are comparative data from the rat (Fig. 2b). Rats strongly regulated their intake of both protein and carbohydrate if offered a choice of complementary foods, but if forced to eat a diet containing a lower P to C ratio than at this intake target they maintained P intake constant, and in so doing over-ate C. In contrast, rats provided with a high-P diet did not substantially over-eat P to gain their intake target level of C. A similar pattern was reported for chickens (Fig. 2c).

The implications: four scenarios

What are the implications of having protein intake prioritized over fat and carbohydrate? We will consider four scenarios by reference to Fig. 1.



1. There is a shift to the diet containing a higher percentage of carbohydrate and fat

This could occur where fat- and/or carbohydrate-rich foods are more accessible, more affordable, in greater variety, or more palatable than alternatives (1,26), leading to people effectively being trapped on a suboptimal diet (this is discussed further below). Under such circumstances, maintaining the amount of P eaten requires over-consumption of C + F.

As protein is a minor component of the total diet, only a small decrease in percentage of P results in a substantial excess of C + F eaten – the protein leverage effect. If we take the example of the USA, using data from the FAOSTAT database (bearing in mind that these estimate nutrient availability rather than consumption), it appears that since 1961 the average diet composition has changed from 14% P : 86% C + F to 12.5% P : 87.5% C + F (Fig. 3). Maintaining P intake under these circumstances requires a 14% increase in C + F eaten (Fig. 4a). A further reduction to 11% P in the diet would lead to a 32% increase in intake of C + F (Fig. 5).

Figure 2 (a) Evidence for the rule of compromise in humans. Points labelled 'a' are data from ref. (24), in which subjects were given a free choice of foods for 2 d before being restricted to either a low-P, high-C + F, or a high-P, low-C + F diet. The dotted lines intersect at the free-choice treatment. 'b', data from ref. (22), in which subjects were restricted to a high-P or a low-P diet for 6 months; 'c', data from ref. (23), in which subjects were confined to a high-P diet for 14 d. The remaining points come from long-term studies cited in ref. (25), Table 4 ('d', Evans *et al.*, 1974 for a 20% P diet; 'e', Yudkin & Carey, 1960, 23% P; 'f', Rickman *et al.*, 1974, 48% P; 'g', Larosa *et al.*, 1980, 29% P). Taken together the data strongly suggest that protein intake is prioritized when humans are restricted to nutritionally unbalanced diets, as in all these cases where subjects were restricted to a diet consisting of a fixed ratio of protein to carbohydrate + fat, either in the short- or long-term, they maintained daily protein intake at a more constant level than that of the other two macronutrients combined.
(b) Data from rats (Theall *et al.*, 1984; Tews *et al.*, 1992 – black and grey symbols respectively) as reanalysed in refs (15,16). The black target symbol was the point to which rats in eight separate treatments converged when offered different choices of two nutritionally complementary foods. This indicates strong regulation of both P and C to an intake target. The remaining points (●) were from four treatments in which diets contained a lower P : C ratio than at the intake target. Note how P intake was maintained at the expense of over-eating C. The grey target symbol shows the regulated point of intake converged upon in six treatments from another study in which previously P-loaded rats were allowed to mix their intake from two complementary foods. When rats in seven further treatments (●) were confined to diets of higher P : C than at the self-selected point, they did not over-eat P to anything like the extent necessary to maintain C intake, i.e. P intake was prioritized.
(c) Similar data showing prioritization of P intake in chickens, from Shariatmadari & Forbes (1993) reanalysed in ref. (15). The target symbol indicates the point converged upon by birds in four free-choice treatments, while the other points show intake when chickens were confined to diets of fixed nutrient composition.

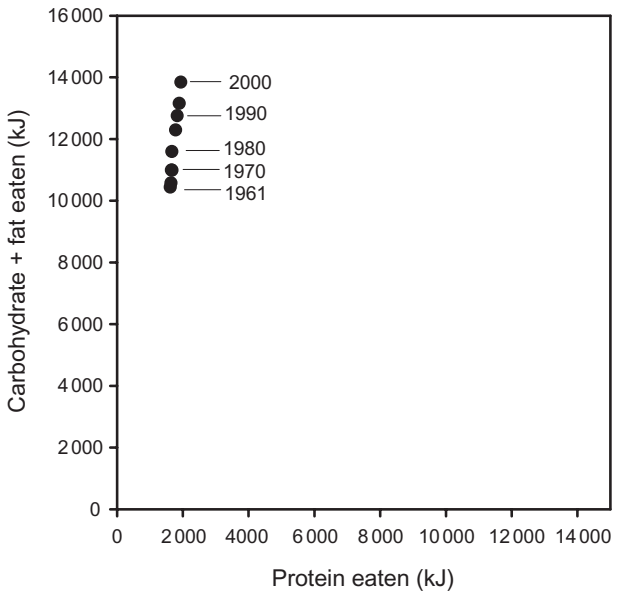


Figure 3 Consumption of P vs. C + F in the USA for 1961, 1965, 1970, 1975, 1980, 1985, 1990, 1995 and 2000, estimated from the FAOSTAT database (13) (representing nutrient supply rather than direct measures of consumption). Estimated intake of C + F has increased proportionally by 50% more than P intake, resulting in a reduction from 14% to 12.5% P in the diet.

The implications for body weight regulation are clear: unless the excess C + F ingested to maintain P intake is removed, for example, through increased physical activity or thermogenesis (27), body weight will rise, predisposing towards obesity.

One important caveat that must be considered here is that the opportunity to over-eat C + F to a sufficient extent to reach the protein intake target will depend on the energy density of the foods available. Where the ratio of P to C + F is lower than the intake target ratio, but nutrient density is low (e.g. in the diets of macrobiotic vegetarians), physical bulk may inhibit reaching the protein intake target (28), thus leading to cessation of intake before the protein target is reached. In contrast, the fact that modern processed foods are often energy-dense, with low levels of non-digestible bulk, makes it easy to achieve the protein target on a diet with a lower than optimal ratio of P to C + F (29,30).

2. There is a shift to the diet containing a higher percentage of protein

If the diet contains a higher percentage of P, yet the absolute amount of protein eaten is regulated to the intake target, the result will be that C + F intake will fall, bringing the

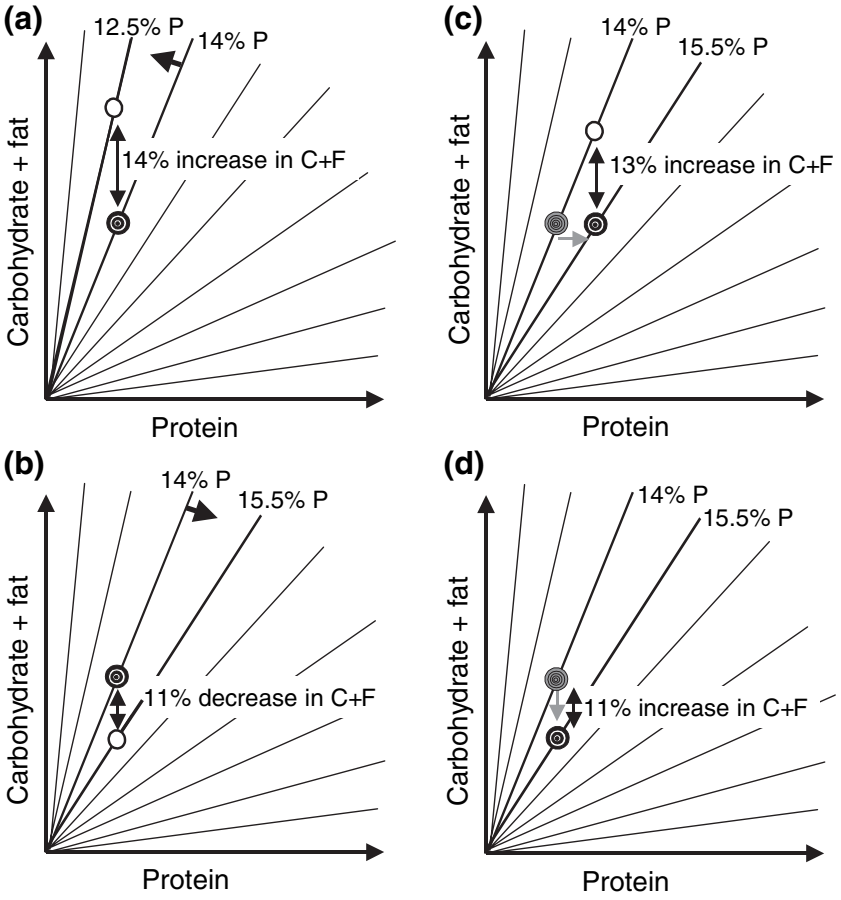


Figure 4 Schematic illustrations of four scenarios in which tight regulation of protein intake would influence energy balance through its leverage over C + F intake. The figures are not drawn to scale.
(a) The diet changes to containing 1.5% more C + F (i.e. 1.5% less P). Maintaining P intake requires over-ingesting C + F by 14%.
(b) The diet changes to containing 1.5% more P (i.e. 1.5% less C + F). Maintaining P intake is accompanied by an 11% reduction in C + F eaten.
(c) The demand for protein increases, for example, as a result of enhanced rates of hepatic gluconeogenesis as seen in the overweight and obese. If diet composition is maintained at 14% P : 86% C + F, a 13% increase in requirement for P would result in a 13% increase in C + F intake.
(d) The requirement for C + F is reduced, for example, because of reduced levels of exercise, but diet composition does not change. Maintaining P intake once again requires over-consumption of C + F.

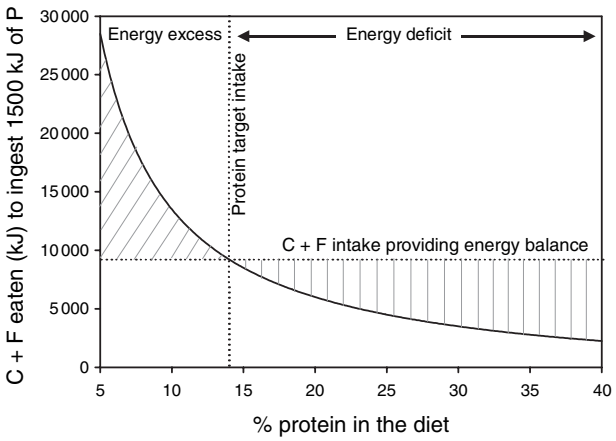


Figure 5 The protein leverage effect. The graph is based on the case where a subject requires a total daily energy intake of 10 700 kJ to remain in energy balance, of which 14% (1500 kJ) is protein. If intake of P is strongly regulated, only slight changes in diet composition will have substantial leverage over intake of C + F and thus energy balance. Because protein comprises only the minor part of the diet relative to C + F, the effect is especially marked when the shift is to a lower dietary percentage of P, where large excesses of C + F intake result (diagonal hatched region). A small increase in percentage of P in the diet, in contrast, results in under-consumption of C + F (vertical hatched region).

body into energy deficit and leading to weight loss. An increase of 1.5% in dietary P from 14% to 15.5% results in an 11% decrease in C + F eaten (Fig. 4b). As seen in Fig. 2a, available data suggest that some over-consumption for protein is tolerated, but not sufficient to maintain C + F intake. This would provide a mechanism for why high-protein diet regimes promote weight loss, at least in the short-term (25,31–33).

3. There is an increase in the requirement for protein

If diet composition remains unchanged, yet protein requirements increase, then over-consumption of C + F will result (Fig. 4c). Shifting the intake target ratio from 14% to 15.5% P in the diet leads to a 13% increase in C + F eaten – with attendant risks of weight gain. But under what circumstances might this occur?

One source of protein loss is hepatic gluconeogenesis, whereby amino acids are used to produce glucose. This is inhibited by insulin, as is the breakdown of muscle proteins to release amino acids, and therefore occurs mainly during periods of fasting. However, inhibition of gluconeogenesis and protein catabolism is impaired when insulin release is abnormal, insulin resistance occurs, or when circulating levels of free fatty acids in the blood are high. These are interdependent conditions that are associated with overweight and obesity, and are especially pronounced in type 2 diabetes (12,34). It might be predicted that the result of higher rates of hepatic gluconeogenesis will be an increased requirement for protein in the diet. Unless either more high-P, low-C + F items are included in the diet (i.e. scenario 2), or rates of removing excess co-ingested C + F are increased, weight gain will occur. And the system becomes unstable – further increases in fat deposits [especially abdominal fat (12)] will increase protein needs further, which will drive even greater weight gain.

Another circumstance in which the protein target would be expected to rise would be after a period of energy restriction in which subjects lose lean mass (35). Providing that the net movement of the target is to the right on a C + F vs. P nutrient plane (as in Fig. 2c), placing a subject onto a low-P, high C + F diet after a period of energy restriction would predispose to excessive consumption of C + F and rapid weight gain. On the other hand, restricting the subject to a diet with a higher P : C + F ratio would prevent this rebound effect. Recent data support this prediction (32).

4. Diet remains unchanged but exercise levels decline

The intake target level of non-protein energy is that required to maintain energy stasis. As such, it includes a component for energy expenditure through exercise and thermogenesis – both of which can change with lifestyle and temperature. It seems that while humans respond by increasing intake following very high levels of energetic expenditure, we are less responsive to lowered needs (6). One interpretation is that our intake target and the associated regulatory mechanisms controlling food intake have evolved to assume a certain level of non-protein energy expenditure. But if this energy is not actually expended, the excess is stored as fat. For example, in the UK energy intake has declined slightly over the past 40 years, yet obesity has risen rapidly, in direct correlation with causes of declining activity levels such as car ownership and television viewing (36). As well as lowering the demand for fuel, decreasing levels of exercise has a direct influence on metabolic physiology, being associated with increased resistance to insulin, and thus enhanced gluconeogenesis (6,37).

Therefore, the result of lowered levels of exercise is, in effect, to lower the position of the intake target on the C + F axis (Fig. 4d), while causing P requirements to increase (scenario 3). Unless the diet changes towards a higher percentage of P, the result will be weight gain. To illustrate, let us say that our hypothetical subject from Fig. 1 became more sedentary to the extent of 1000 kJ less energy expended per day. His non-protein energy needs would fall from 9500 to 8500 kJ per day, while his protein requirements would remain unchanged at 1500 kJ [at least in the short-term – over time it may rise if hepatic gluconeogenesis increases (6,37)]. To satisfy both his protein and energy needs simultaneously (i.e. reach his new intake tar-

get), he would need to eat a diet that is 15.5% P. If he did not change his diet (i.e. remained on a 14% P diet), he would have to eat 11% more C + F than needed to fuel his less active lifestyle.

Interacting consequences: a vicious cycle

The scenarios introduced above are not independent. Either shifting the diet composition to a lower percentage of P (scenario 1), or effectively doing the same by having low levels of energy expenditure (scenario 4), will result in overconsumption of carbohydrate and/or fat to maintain protein intake. This in turn will predispose towards weight gain and lead to disinhibition of gluconeogenesis, which will increase protein demand (scenario 3). Unless this increased demand is met by selecting high-P foods, protein appetite will drive increased intake of C + F, resulting in further weight gain, and so on in a vicious cycle leading to obesity and its associated diseases.

This cycle is broken when P intake is increased independently of C + F (scenario 2), which requires access to high-quality protein-rich foods that are low in C + F. Very high protein diets (>35% of energy from P) are currently promulgated in the popular diet literature, but are associated with potential health risks (25,31,33). However, it can be seen from Fig. 4b that only relatively small increases in dietary percentage of P are predicted to lower intake of C + F. The result would be to promote weight loss and the likely rectification of associated metabolic disturbances (38).

Socio-economic and population-level implications

There are obvious socio-economic implications of the protein leverage effect. Obesity is most prevalent among the less affluent sectors within societies with established market economies (2,36). Levels of exercise are lower, which results in the effects described in scenario 4 above. This effect will be exacerbated where intake of inexpensive, processed foods – which tend to be high in percentage of C + F – is greater, and by the fact that high-P foods such as lean fish and meat are relatively more expensive to those on lower incomes than to the more affluent.

The protein leverage effect predicts that small changes in dietary percentage of P should have an impact on development of obesity within a population. Figure 6 plots the change in percentages of (energy) P, C and F in available diets (13) over the period 1970–2000 against obesity levels in the early 1990s (2) for 13 countries with developed market economies. The data have their limitations, being based upon nutrient supply rather than actual consumption values. Nevertheless, it is interesting that the countries where percentage of P has risen most are those with the

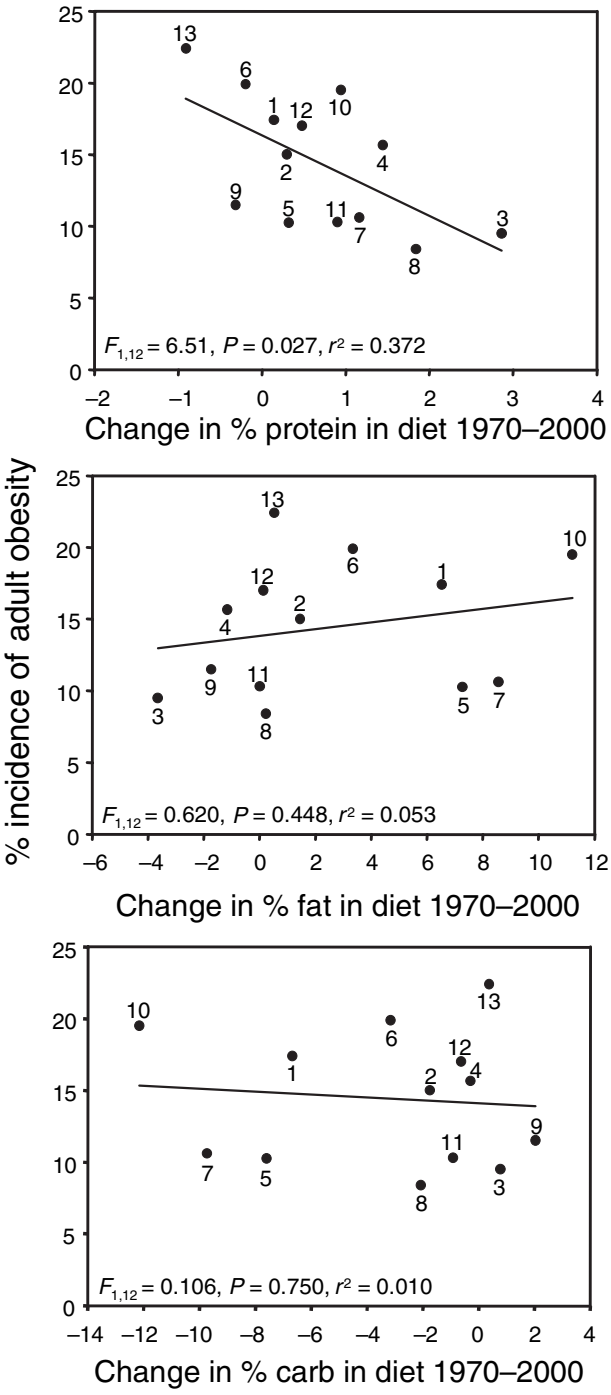


Figure 6 Plots of changes in percentage of energy as macronutrients in the diets of 13 countries with developed market economies over the period 1970–2000, against the incidence of adult obesity during the early mid-1990s. Dietary data are from the FAOSTAT database (13), and represent nutrient supply rather than consumption. Figures for obesity are from ref. (2) (pp. 8, 27). 1, Australia; 2, Canada; 3, Denmark; 4, Finland; 5, France; 6, Germany; 7, Italy; 8, Netherlands; 9, New Zealand; 10, Spain; 11, Sweden; 12, UK; 13, USA.

lowest incidence of obesity, while those where percentage of P has fallen most had the highest incidence. Neither change in percentage of C or percentage of F correlate significantly with obesity, despite the fact that both show a much larger range of percentage changes than does protein – although, of course, the two summed must mirror the trend in percentage of P. We would not wish to put too much emphasis on these data, and further analyses are required with higher resolution intake and obesity data. The results are, nevertheless, suggestive.

Population-level differences in protein target

A clear prediction from our hypothesis is that people with a higher intake target for protein will be more prone to developing obesity on a low-P, high-C + F diet than those with a lower protein target (see scenario 3 above). It is known from animal studies that organisms evolve such that their intake target reflects the composition of their natural diet (39). Humans likewise adapt to their current diet, genetically, developmentally or culturally (40–42). We might thus expect that populations which have traditionally eaten a high-protein diet would have increased susceptibility to obesity and associated diseases when making the transition to a modern Western diet. In this regard it is interesting to note the high incidence of obesity among oceanic populations that have until recently remained on a marine-based diet, rather than having shifted to terrestrial agriculture in the Neolithic (2,43,44).

Protein regulation or a protein ceiling?

The protein leverage hypothesis is consistent with humans having a specific appetite for protein – as is suggested by some studies (18,19,24) and certainly occurs in other animals that have been explored using our state–space models of nutrient balancing (15,16; see Fig. 2b,c). An alternative explanation would be that there is an upper limit to human protein intake, and that we simply continue to eat until this constraint is reached. This seems unlikely, however, for several reasons. First, the maximum rate of excretion and conversion of protein to urea for a healthy human adult is around 3.5 g kg^{-1} d^{-1} (45), which is greatly in excess of reported values for protein consumption in normal subjects. Second, humans in some populations routinely eat a diet of substantially higher protein content than is typical for populations afflicted by the obesity epidemic. It has been estimated, for example, that the average protein intake of Palaeolithic human beings was 37% of energy (46), while some extant northern-latitude foraging societies regularly ingest a diet of more that 25% protein (47,48). Finally, the data in Fig. 2 suggest that in an experimental setting humans will increase their intake of protein on diets of high percentage of P to some degree, demonstrating that the amounts of protein eaten on diets of low percentage of P are not due to a ceiling on protein intake.

However, if humans do regulate protein intake, why do we not simply select protein-rich foods to rebalance our diet? This would suggest that the feedbacks regulating excessive fat and carbohydrate intake are less acute than those for protein, as is consistent with evolutionary accounts of human nutrition, and is also seen in other animals (15,16). For most of our existence the human diet consisted of a high proportion of animal foods, partly reflecting the scarcity of readily available simple carbohydrates (48–50). Further, wild animals typically have considerably lower fat content (*c.* 4.2 g fat per 100 g meat) than does modern commercial meat (*c.* 20 g fat per 100 g) (46,47). As a result, we have limited evolutionary experience of excess carbohydrates or fats, and it seems reasonable to infer that natural selection against their over-consumption would not have been strong. A history of short supply of these sources of readily available energy has been suggested as an explanation for their high palatability, which may predispose towards over-consumption of fat- and carbohydrate-rich foods (51). Similar arguments have been put to explain aspects of human metabolic physiology, most notably the ease with which we store rather than eliminate excess ingested energy (52). For example, whereas many non-human animals metabolize and dissipate a substantial portion of over-ingested energy (27,53) (in the case of rodents, *c.* 90%), overfed humans store up to 75% of the surplus (53).

These evolutionary predispositions in turn interact with the modern environment (1,29,30). Highly energy-dense, fat- and carbohydrate-rich foods are readily available and affordable, while levels of energy expenditure are lower than that is anticipated by our regulatory physiology. It is also perhaps relevant that taste stimuli naturally associated with protein-rich foods, such as sodium and umami stimulants, are extensively used in low-protein processed foods, and may as a result subvert protein regulatory systems and lead to over-consumption of fat and carbohydrates.

In combination, it is unsurprising that we should be prone in our modern environment to being misdirected onto diets containing a higher ratio of F + C : P than is optimal. The central argument in this paper is that if you add to this the protein leverage effect, it is also unsurprising that the regulatory systems controlling intake by modern humans are prone to becoming unstable, driving a catastrophic cycle of over-consumption and obesity.

Conclusion

The key assumption upon which our hypothesis resides is that when humans are forced to trade-off protein intake against that of carbohydrate and fat on nutritionally unbalanced diets, physiological regulatory mechanisms prioritize

protein. If this is true, then all else that we say must follow – it is a mathematical inevitability. We have provided evidence in Fig. 2 and elsewhere that suggests that this is the case, but the next step must be to test the consequences on intake of manipulating dietary P : C + F under controlled experimental conditions (in our parlance, to measure the 'rule of compromise' for P vs. C + F), and to examine the relative importance of protein leverage alongside other environmental, cognitive and physiological determinants of obesity. Given the implications that follow from our hypothesis, we would suggest that this is a vital subject for future research in human nutrition. In reference (24) we suggest the design of such experiments.

Finally, our 'vicious cycle' provides a candidate-positive feedback mechanism for the spiral into morbid obesity. It predicts a key role of hepatic gluconeogenesis in the development of obesity.

Acknowledgements

We thank the Wissenschaftskolleg zu Berlin (Institute for Advanced Study) and the British Biotechnology and Biological Sciences Research Council for making this study possible. Thanks to Professor Sir John Krebs, Professor Sir Richard Southwood, Professor Sir Patrick Bateson, Dr Mark Friedman, Dr Susan Jebb and Dr James Stubbs for their comments, enthusiasm and discussion.

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