International Journal of Obesity (1999) 23, 1118–1121
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http://www.stockton-press.co.uk/ijo

Commentary

Low-protein overfeeding: a tool to unmask susceptibility to obesity in humans

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In search for an approach to identify physiological targets for therapeutic intervention in obesity management, we have revisited the classic human overfeeding studies of the 1960s, with new emphasis on a 'subgroup' of volunteers who were shifted between overfeeding on a typical affluent (normal-protein) diet and overfeeding on a low-protein diet. Following a re-analysis of these data, the arguments are put forward that since low-protein overfeeding is not only a potent stimulus of thermogenesis, but also an amplifier (or magnifier) of the small inter-individual variations in thermogenesis on the affluent (normal-protein) diet, it can be used as a tool to unmask some of the genetic and metabolic basis underlying human susceptibility to leanness and fatness.

Keywords: thermogenesis; energy expenditure; UCP; obesity; protein metabolism

Introduction

For more than 100 years, physiologists have been trying to unravel the mechanisms by which certain individuals can offer considerable resistance to weight gain in response to overeating. Voit,[1] in his theory of *plethora*, first suggested that excess calories may be converted directly to heat, but there was some confusion as to whether this was the same as the *Specific Dynamic Action* first described by Rubner.[2] However, Neumann[3] referred to the phenomenon as *Luxuskonsumption*, but much later (in the mid-1960's) this was replaced by the term in use today—*thermogenesis*—when Miller and Mumford[4] discussed the potential importance of variations in heat production in the aetiology of obesity. They subsequently conducted a series of overeating experiments designed explicitly to determine the capacity of humans to resist obesity by disposing excess calories as heat.[5,6] Using diets providing 3% protein (low-protein, LP) and 15% protein (termed high-protein, but actually normal-protein, NP) to overfeed university students a daily excess of 4.2 MJ (1000 kcal) or more over periods of 3–6 weeks, they reported that the efficiency of weight gain was less than predicted if the excess calories were laid down as body fat; this deviation from predictions being particularly marked during LP-overfeeding. In the absence of significant changes in digestibility, in body composition and in physical activity level, they attributed the bulk of the 'missing calories' (reflected in the low efficiency of weight gain) to an increase in heat production, and the term *dietary-induced thermogenesis* came into existence. This was subsequently shortened slightly to *diet-induced thermogenesis* and abbreviated as *DIT* by Stirling and Stock.[7]

By early 1970's, the concept of DIT as an adaptive phenomenon in the resistance to obesity gained some support with the publication of the 200 d overfeeding studies of Sims *et al*,[8] who showed that among prisoners in Vermont, certain individuals increased body weight by an expected 20–25%, whereas others resisted weight gain, even though they were consuming more calories than those who became obese readily.

DIT in humans: the controversy

Although the notion of inter-individual variability in metabolic susceptibility to obesity has since gained momentum,[9] and the importance of genes in determining such susceptibility to leanness and fatness is now recognized,[10] the importance of variations in thermogenesis in human susceptibility to obesity has been the subject of considerable controversy. In fact, as pointed out by Stock in the review that precedes this commentary,[11] the majority of overfeeding studies conducted during the past 3 decades have failed to demonstrate a high cost (that is low efficiency) of weight gain in response to overconsumption of diets typical of affluent societies, in which

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protein contributes 12–16% of energy intake. Furthermore, in a closer inspection of the gluttony experiments of Miller *et al*,[5,6] Stock shows that the cost of weight gain on the NP diet (15% protein) was more or less what would be predicted if there was no change in energetic efficiency.[11] By contrast, the cost of weight gain in those volunteers overfed the LP diet (3% protein) was well above the predicted values if the gain in weight was entirely fat, and could only be due to a large decrease in energetic efficiency—that is to the activation of DIT during overfeeding on the LP diet.

Revisiting gluttony 1 and 2

One aspect of the original overfeeding studies of Miller *et al*[5,6] that was mainly overlooked was that 4 subjects who were overfed on the LP diet for 4 weeks, were then shifted to the NP diet while maintaining the same level of overfeeding for another 3–4 weeks; a fifth subject did the reverse (4 weeks NP, 4 weeks LP). We have now re-evaluated the data for these subjects, and present in Figure 1, their energy cost of weight gain (excess MJ consumed per kg weight gained) on these two diets. It is shown that for all the five individuals, the cost of weight gain is much higher on the LP diet (range of 80 to >300 MJ/kg) than on the NP diet (range of 25–45 MJ/kg), but interestingly there is also a very good correlation ($r > 0.9$) in the energy cost of weight gain between the NP and LP diets. In other words, the low-gainers (that is those with the highest cost of weight gain) during LP overfeeding were also the low-gainers during NP overfeeding, and vice versa the high-gainers (that is those with the lowest cost of weight

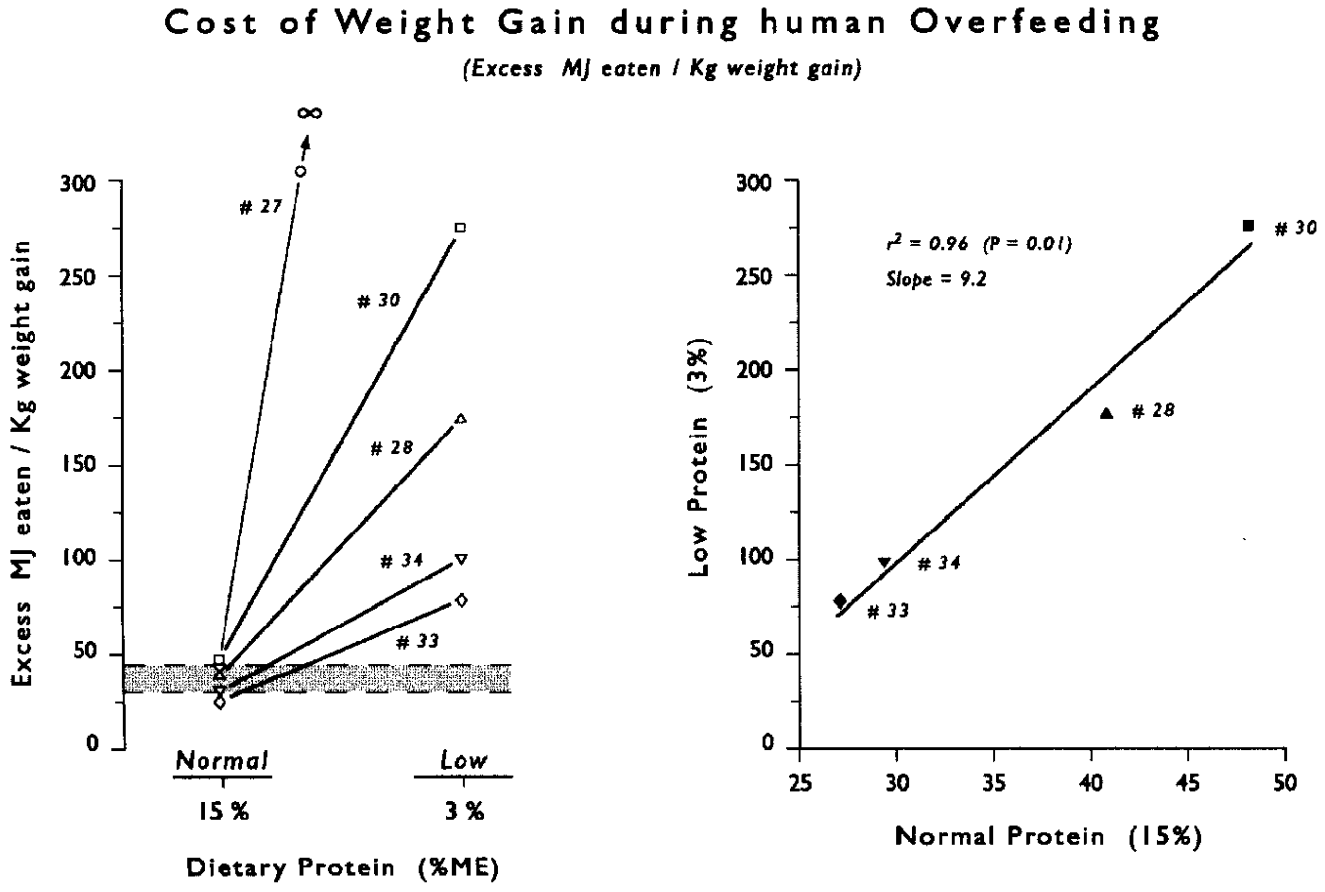

Figure 1 Unmasking of inter-individual variability in thermogenesis by low-protein overfeeding. The data represents the energy cost of weight gain (excess MJ consumed per kg weight gained) during 3–4 weeks of overfeeding in the five human volunteers who participated in *both* the normal-protein (NP) and low-protein (LP) overfeeding in the Gluttony Experiments of Miller *et al*.[5,6] The data are calculated from raw data on metabolizable energy (ME) intake and weight changes provided in Table I–III (5); all the five subjects, #27, 28, 30, 33, and 34 were young adults of normal body weight and BMI. The macronutrient composition of the diets consumed by the subjects are also provided in the Table I–III of these studies, with protein, fat and carbohydrates contributing about 3, 45 and 52% on the low-protein (LP) diet, and about 15, 45 and 40% on the normal-protein (NP) diet (which the authors refer to as 'high- protein', probably in the context of contrasting a diet higher in protein with the low-protein diet). The two horizontal broken lines (enclosing the shaded area) correspond to predicted energy cost of weight gain on the assumption that weight gain is either 100% fat (45 MJ/kg) or 60% fat (30 MJ/kg), the latter value including cost of fat-free-mass gain.[11] The greater the deviation from the predicted values, the greater the likelihood that the excess calories were dissipated via enhanced diet-induced thermogenesis (DIT). It is to be noted that subject #27 is not included in the regression analysis since the absence of weight gain in this subject during LP-overfeeding yield a value for energy cost of weight gain approaching infinity (∞), that is a zero efficiency of weight gain. Indeed, if instead of energy cost (excess MJ/weight gain) the data are expressed in terms of efficiency (weight gain/excess MJ consumed), this value can then be included in the regression analysis—in which case the correlation coefficient is also high ($r = 0.9$).

gain) during LP overfeeding were also high-gainers during NP overfeeding.

It can be inferred from the above analysis that the individual's characteristic constitutional resistance (or susceptibility) to weight gain was maintained during overfeeding on both diets. In other words, the *inter-individual variability* in the efficiency of weight gain during overfeeding on the NP-diet was conserved during overfeeding on the LP-diet, and vice versa. The existence of this relationship shown in Figure 1 therefore raise two important issues pertaining to our understanding of the functional role of DIT and to our search for physiological avenues to activate thermogenesis in the management of obesity.

Biological significance of low-protein thermogenesis

The first issue to be considered is why the *same individual* can apparently dispose of a considerable excess of energy when the diet is low in protein, but to a much lesser extent when the dietary protein level is adequate? Bearing in mind the demonstrations of the potent stimulatory effect of protein deficiency on thermogenesis (thereby underlying the low efficiency of growth) in many species including laboratory rodents, pigs, monkeys and human infants,[12–15] and that other nutrient deficiences — for example in vitamin A, copper, iron and potassium — also result in low efficiency of growth and increased thermogenesis,[16] the teleological argument can be put forward that a high capacity to activate DIT has emerged during the course of evolution as an adaptation to nutrient-deficient diets. As argued by Stock,[11] the necessity to increase DIT in the face of nutrient-deficient diets probably had survival advantage during the course of mammalian evolution since it enables the overeating (on an energy basis) of such nutrient-deficient diets in an attempt to achieve an adequate intake of the specific nutrient, but without the disadvantage of excessive fat accumulation — a hindrance to optimal locomotion, hunting capabilities, and the ability to fight or flight. Viewed in terms of survival value, it is therefore not surprising that protein deficiency is a most potent dietary stimulus of thermogenesis, and Miller, who was very much aware of this following earlier studies on protein : energy requirements for maintenance,[17] therefore selected a low-protein diet in order to test the ability of humans to resist weight gain during overfeeding.[5,6]

Low-protein overfeeding as a tool to study human variability in thermogenesis

The second aspect arising from the analysis shown in Figure 1 concerns the possibility that humans do possess a much larger capacity for DIT than is generally recognized, but that capacity is poorly recruited during overfeeding on well-balanced diets. This is even more apparent in Stock's analysis[11] of many different overfeeding studies employing a variety of balanced and unbalanced diets. Stock also shows that there is very little inter-individual variation when well-balanced diets are used, whereas overfeeding unbalanced diets unmasks a hitherto unexpected diverse range of individual responses. The extent to which the mechanisms underlying DIT are recruited would seem to be a function of both the individual (as judged by the inter-individual variability within each diet group) and the dietary protein level, with the recruitement for DIT being weak on normal-protein diets, but particularly pronounced with low-protein diets, but also evident on higher than normal (for example 20%) protein diets.[11]

Since even small inter-individual variations in the efficiency of weight gain (and hence variations in thermogenesis) on well balanced diets can — over months and years — contribute to weight maintenance in some and obesity in others, the possibility arises that overfeeding low-protein diets could serve as a tool for maximising DIT to exaggerate individual differences in energetic efficiency. In other words, low-protein overfeeding may serve as a 'magnifying glass' for unravelling the genetic and metabolic basis by which variations in thermogenesis contribute to susceptibility to leanness and fatness during overconsumption of the typical (well balanced) diets of our affluent societies.

As we enter a new millenium, with obesity in epidemic proportions and no truly effective therapy in the foreseeable future, it is fitting to reflect back on two famous quotes — the first dating more than 225 years ago by Lavoisier that '*Life is a combustion*', and Miller's[18] more recent observation that '*the fire of life seems to burn brighter in some than in others*'. So that we may find new physiological targets for therapeutic intervention in obesity management, we may need to understand as to why the fire of life seems to burn brighter in some than others. Thus, it may prove necessary to simulate the appropriate (unbalanced) dietary conditions under which DIT is recruited in order to unmask the genetic and metabolic machinery responsible for human variability in thermogenesis.

References

1 Voit C. Physiologie des Stoffwechsels. In: *Hermamm's Handbuch der Physiologie*: 1881; Vol. 6, p. 209.
2 Rubner M. *Die Gesetze des Energieverbrauchs bei der Ernährung*. Leipzig: Deutiche, 1902.
3 Neumann RO. Experimentelle Beitrage zur Lehre von dem taglichen Nahrungsbedarf des Menschen unter besonderer Berucksichtigung der notwendigen Eiweissmenge. *Arch Hyg* 1902; **45**: 1–87.
4 Miller DS, Mumford P. Obesity: physical activity and nutrition. *Proc Nutr Soc* 1996; **25**: 100–107.

5 Miller DS, Mumford P. Gluttony 1. An experimental study of overeating low- or high-protein diets. *Am J Clin Nutr* 1967; **20**: 1212–1222.
6 Miller DS, Mumford P, Stock MJ. Gluttony 2. Thermogenesis in overeating man. *Am J Clin Nutr* 1967; **20**: 1223–1229.
7 Stirling JL, Stock MJ. Metabolic origins of thermogenesis induced by diet. *Nature* 1968; **220**: 801–802.
8 Sims EAH, Danforth, Horton ES, Bray GA, Glennon JA, Salans LB. Endcorine and metabolic effects of experimental obesity in man. *Recent Prog Horm Res* 1973; **290**: 457–496.
9 Ravussin E, Swinburn BA. Pathophysiology of obesity. *Lancet* 1992; **340**: 404–408.
10 Bouchard C, Tremblay A, Després JP, Nadeau A, Lupien PJ, Thiérault G, Dussault J, Moorjani S, Pinault S, Fournier G. The response to long-term overfeeding in identical twins. *N Engl J Med* 1990; **322**: 1477–1482.
11 Stock MJ. Gluttony and thermogenesis revisited. *Int J Obesity* 1999; **23**: (in this issue).
12 Rothwell NJ, Stock MJ. Influence of carbohydrate and fat intake on diet-induced thermogenesis and brown fat activity in rats fed low protein diets. *J Nutr* 1987; **117**: 1721–1726.
13 Gurr MI, Mawson R, Rothwell NJ, Stock MJ. Effects of manipulating dietary protein and energy intake on energy balance and thermogenesis in pigs. *J Nutr* 1980; **110**: 532–542.
14 Samonds KW, Hegsted DM. Protein deficiency and energy restriction in young cebus minkeys. *Proc Natl Acad Sci* 1978; **75**: 1600–1604.
15 Kashyap S, Schulze K, Forsyth M, Zucker C, Dell RB, Ramakrishnan R, Heird WC. Growth, nutrient retention, and metabolic response in low birthweight infants fed varying intakes of protein and energy. *J Pedriatr* 1988; **113**: 713–721.
16 Jackson AA, Wooton SA. The energy requirements of growth and catch-up growth. In: *Activity*, *Energy expenditure and Energy requirements of infants and children*, B Schurch and NS Scrimshaw (eds), Proceedings of an IDECG Workshop, Cambridge, MA, USA, 1989; pp. 185–214. Nestlé Foundation: Lausanne, Switzerland.
17 Miller DS, Payne PR. Weight maintenance and food intake. *J Nutr* 1962; **78**: 255–262.
18 Miller DS. Factors affecting energy expenditure. *Proc Nutr Soc* 1982; **41**: 193–202.