Invited commentary

Human overfeeding experiments: potentials and limitations in obesity research

The maintenance of body weight and body composition depends upon an efficient matching between substrate intake and substrate utilization thus insuring an adequate regulation of substrate balance. Perturbation of the human system by overfeeding constitutes a way to enable better understanding of how well the human system is regulated when exposed to a 'stressful' nutritional situation.

Overfeeding studies are important to carry out in human subjects for several reasons. First, the ingestion of surfeit energy occurs in real life either voluntarily in certain ethnic groups (Pasquet et al. 1992) or spontaneously in many individuals (acute ‘feasting’ or chronic disturbances in food intake behaviour such as binge eating). Second, in order to delineate adaptive mechanisms of metabolic and behavioural natures in response to weight gain, overfeeding studies in human subjects are mandatory. Third, overfeeding studies allow the unravelling of subtle metabolic mechanisms which may be difficult to identify under maintenance conditions where a change in the proportion of macronutrient (carbohydrate:fat ratio) has little effect on energy needs (Shah, 1996; Hirsch et al. 1998). Fourth, overfeeding low-protein diets has been also suggested as a tool to unmask metabolic susceptibility to leanness or to fatness in human subjects (Dulloo, 1999). This is because according to a recent review by Stock (1999), protein-deficient diets seem to be, in overfeeding conditions, a potent stimulus of thermogenesis in man.

Taken together, human experimental studies in which a surfeit of energy is imposed constitute an interesting model for our understanding of the control of energy expenditure and its components.

The number of studies published since the early 20th century on acute overfeeding in humans is not very large probably due to a number of practical, technical, methodological, financial and ethical difficulties. In these studies, the typical experimental design has been to deliberately and steadily overfeed at a certain energy level (so that the energy intake is ‘clamped’) for a certain duration, which can range from days to weeks. The effect of the proportion of macronutrient in the food given in excess has been the subject of a very limited number of studies (Horton et al. 1995) so that the study of Lammert et al. (2000) is timely.

One issue which has been of concern to some investigators is the extent to which the type of diet deliberately overfed in these experimental studies resembles that which can be realistically eaten in real life under ‘spontaneous’ overfeeding conditions. The dilemma is that, on one hand, the investigator is interested in testing the effect of diets containing a high proportion of a macronutrient of interest (e.g. carbohydrates) in order to activate certain metabolic processes (e.g. de novo lipogenesis) and on the other hand, the type of diet force-fed in experimental studies should be similar to ad libitum feeding in real life. Furthermore, in normal daily living, overfeeding does occur spontaneously at some occasions but passive overconsumption of fat is much easier than of carbohydrate (Blundell et al. 1997, 1999). In contrast to experimental studies, subsequent spontaneous correction of food intake is possible since the diet is taken ad libitum. However, overfeeding studies in free-living conditions are hampered by the fact that spontaneous food intake is difficult to assess accurately over a prolonged period of time (Black et al. 1991; Goldberg et al. 1991).

The first overfeeding studies date back to the early 20th century. The term ‘luxus consumption’ was proposed when it was thought by early investigators that the body possesses efficient mechanisms to allow dissipation of excess energy into heat and hence can substantially limit weight gain during overfeeding. A subsequent reexamination of these classical studies (based on single subjects i.e. the investigators themselves!) demonstrated that the conclusions could be challenged (Forbes, 1984). Basically, an increase in energy ‘disappearance’ (or the so called ‘missing calories’) during overfeeding can occur through several mechanisms: decreased energy absorption, decreased energy storage following enhanced obligatory (and regulatory) diet-induced thermogenesis, increased macronutrient turnover and activation of energetically costly processes such as de novo lipogenesis as well as spontaneous increases in the rate of physical activity. In acute experimental overfeeding studies the subjects are investigated in a transition phase (so called dynamic phase) during the initial onset of the metabolic adaptation period. Indeed, according to mathematical empirical models, it takes several years to obtain a steady body weight, during which the energy balance reaches a new equilibrium thanks to a new level of body weight (Weinsier et al. 1993).

In an ideal overfeeding study design (somewhat unrealistic in free-living conditions), all the components of macronutrient balance should be assessed together with an independent evaluation of body composition. If one is primarily interested in the effect of overfeeding on body fat storage, two major variables should be measured which should give consistent results: (1) overall fat balance during the entire overfeeding period. This requires measurement of total fat input (i.e. metabolizable fat intake) and total fat output (i.e. total fat utilization); (2) body fat storage by measuring initial body fat minus final body fat using an accurate and precise body composition methodology.
experimental overfeeding studies, fat (energy) input is fixed by design. Fat output (fat ‘oxidation’) is generally estimated by continuous indirect calorimetry combined with the assessment of total urinary N excretion (Schutz, 1995). Body-fat storage has two major origins: exogenous fat storage and de novo lipogenesis from carbohydrate, the latter being negligible in fat overfeeding studies but may be substantial in carbohydrate-overfeeding conditions. The increased body fat observed with prolonged carbohydrate overfeeding results from both a decrease in fat oxidation and a stimulation of de novo lipogenesis of hepatic and extra hepatic (adipose tissue) origin (Schutz, 1999). The latter process seems to be of particular importance (Aarsland et al. 1980; Acheson et al. 1987) the metabolicize energy intake (gross energy intake – (energy in faeces + urine)) was not uniformly measured during overfeeding in human subjects. Considering the surplus energy intake, the average weight gain observed (1.5 kg in 3 weeks) was not substantial, suggesting that the individuals had a mechanism to counteract the effect of excess energy intake. Surprisingly, some subjects lost (insignificant) weight during overfeeding indicating that either the adherence to the diets was difficult to maintain over time and/or the excess energy fed was burnt off by inducible metabolic and/or behavioural mechanisms. An increase in the rate of spontaneous physical activity is nevertheless difficult to imagine as the only mechanism since the excess energy fed (5 MJ/d), translated into walking activities for a person of 75 kg (taking an average net energy cost walking of 2.1 kJ per kg body weight and per km distance), approximates a walking distance of 32 km/d! One issue which has plagued nutritionists and physiologists performing human studies for several decades is the degree of compliance to the diet, and above all, the maintenance of adherence to the prescribed diet over time. During overfeeding studies, the dietary compliance can be biased only unidirectionally since one cannot imagine that the subjects will be able to cheat and eat more (for example extra snacks) than what is prescribed to him (or her) whereas a bias in the opposite direction is still possible since, by design, overfeeding is imposed and continuous. This does not give a chance for the organism to initiate homeostatic mechanisms allowing subsequent compensation for the surplus energy in an attempt to re-establish long-term energy balance.

Finally, it is important to calculate accurately the excess energy intake fed over energy requirement (estimated from maintenance energy intake or total energy expenditure) in order to assess the proportion of excess energy burned off by thermogenesis and/or by possible changes in physical activity or conversely to calculate the percentage of the excess energy which is stored in adipose tissue. Recalculation of the data of Lammert et al. (2000) has shown that about one-third of the excess energy intake was stored during overfeeding, with a slightly larger value for the high-fat diet as compared to the high-carbohydrate diet but this difference may not reach statistical significance. This value is surprisingly low as compared to previous overfeeding studies obtained under controlled conditions in which two-thirds to three-quarters of the excess energy intake was stored (Ravussin et al. 1985; Schutz et al. 1985). However, due to the small amount of weight gain observed, the exact size of the energy storage is difficult to assess with great accuracy given the actual imprecision of body composition measurements used (Jebb et al. 2000).

Future experimental studies should concentrate on the
evaluation of longer-term overfeeding in lean and pre-obese subjects genetically predisposed to obesity including the assessment of the metabolic handling and turnover of exogenous protein (Schutz et al. 1999), exogenous fat (Maffeis et al. 1999) and exogenous carbohydrates (Rueda-Maza et al. 1996) as well as the quantification of metabolic processes susceptible to activation during overfeeding and which may also contribute to body-weight regulation (e.g. net de novo lipogenesis). The evaluation of de novo lipogenesis during overfeeding with other types of diets such as balanced high-protein diets and imbalanced low-protein diets seem to be of particular interest. Interest in the former arises from a practical point of view (there is a tendency for certain individuals to ingest huge amounts of protein acutely and chronically) and the latter from a mechanistic point of view considering the new challenging conceptual idea on dietary-induced thermogenesis recently developed by Stock (Stock, 1999).

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References

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