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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. In 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*. 1997).

The paper of Lammert *et al*. (2000) explored the effect of overfeeding (approximately 5 MJ in excess for 21 d) of either a carbohydrate-rich (78 % of energy) or a fat-rich diet (58 % of energy) in twenty young healthy men. During this period a number of variables were measured such as body weight and body composition, digestible energy, sleeping energy expenditure, N balance as well as hepatic *de novo* lipogenesis. A new feature of the study is that physical activity was controlled within pairs of individuals, selected to have similar anthropometric characteristics and habitual activities. This means that the subjects were allowed to maintain normal daily activities except that the subjects followed each other throughout the daytime period, during which they could engage in any joint activities (described as 'Siamese' activity twins by the authors). Both diets induced a similar increase in body weight (approximately 1·5 kg, of which two-thirds was explained by a gain in fat mass (which resulted in an increase in plasma leptin) and one-third fat-free mass. When the carbohydrate-rich diet was overfed, an increase in hepatic and whole-body lipogenesis was observed. However, no difference in fat-mass storage was observed, so the authors concluded that both diets were equally effective in storing excess energy as fat.

There are three rather innovative features in this human overfeeding study compared to previous ones. First, a new approach ('Siamese' twins) has been used to control for possible confounding factors in the interpretation of the results among dietary treatments such as a change in physical activity. The dilemma is to be able to assess the effect of overfeeding without influencing spontaneous physical activity, which may change in response to the type of challenge. Confining the subject in a metabolic chamber is important for maintaining strict experimental conditions but not suited to exploring the behavioural changes in physical activity since the variety, types and intensity of activities are largely limited by the size of the room available. Fidgeting is a behavioural component which may vary among individuals and may explain the difference in energy storage as fat as demonstrated by Levine *et al*. (1999). The activation of this component may play an important role in the regulation of body weight in response to chronic excess of energy intake. Direct assessment of small spontaneous movements of the upper and lower limbs during static posture may constitute an area of interest for future research.

Second, hepatic *de novo* lipogenesis was estimated based on an elegant isotopic approach (mass isotopomer distribution analysis technique; for review see Hellerstein (1999)) and total *de novo* lipogenesis was estimated from the arithmetic difference between the amount of body fat deposition (assessed by body composition) and the metabolizable fat available for storage. In previous carbohydrate overfeeding studies (Acheson *et al*. 1984, 1987, 1988; Schutz *et al*. 1985), net *de novo* lipogenesis values were calculated exclusively on the extent to which the RQ ($V_{CO_2}:V_{O_2}$) exceeded 1·0 during the course of the day.

Third, digestibility of macronutrients was measured. With a few exceptions (Norgan *et al*. 1980; Acheson *et al*. 1987) the metabolizable energy intake (gross energy intake − (energy in faeces + urine)) was not uniformly measured during overfeeding in human subjects. Considering the surfeit 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 surfeit 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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