Role of Energy Excretion in Human Body Weight Regulation

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Food intake and energy expenditure are the typical determinants of body weight. Yet, recent observations underscore that a third and often-neglected factor, fecal energy loss, can influence energy balance. Here, we explore how macronutrient excretion modulates human energy homeostasis and highlight its potential impact on the propensity to gain weight.

Energy Balance: Excreted Calories Weigh In

Obesity develops as the result of a sustained positive energy balance. This etiological explanation surmises that calorie consumption must exceed calorie combustion for weight gain to occur. However, not all ingested nutrients are absorbed by the gastrointestinal tract. A fraction of food consumed ends up being excreted in feces. Moreover, even the nutrients that reach the circulation can still escape the body, such as by being filtered through the kidneys (Figure 1A) [1,2]. This collective excretion or loss of nutrients represents a frequently neglected component of energy balance regulation. Thus, more accurately: weight gain only occurs when the amount of absorbed (and retained) energy, exceeds the number of calories that are oxidized. The fact that calories from food can ‘disappear’ in feces (and urine) is an understudied component of overall energy balance [3]. Moreover, it is potentially also a variable that protects some individuals from obesity while making others prone to weight gain [4,5].

Human Overfeeding: Fecal Energy Loss Confronts Luxuskonsumption

Overfeeding studies in humans show that weight gain varies substantially among individuals. As such, one classical study reported a weight gain range of 4.3–13.3 kg in 12 pairs of monozygotic twins who were overfed by a total of 84,000 kcal for a period of 100 days [6]. Two human phenotypes have more recently been proposed to explain this variability. While ‘thrifty’ individuals easily gain weight during times of caloric surplus, ‘spendthrift’ individuals are less prone to adiposity, despite being exposed to the same obesogenic environment (Box 1)[7,8]. Alterations in energy dissipation, such as heat-producing processes, have traditionally been used to explain why humans respond differently to perturbations in energy balance. Yet, after several decades of research, scientists still debate to what extent weight gain is counteracted by so-called ‘Luxuskonsumption’, that is, an adaptive increase in energy expenditure that exceeds that expected by the obligatory needs of a greater body mass [4,8]. In a recent study, it was reported that 8 weeks of overfeeding (40% above baseline energy needs), only triggered a small induction of 24-h energy expenditure of 23 kcal/day, on average. Hence, the authors concluded that metabolic adaptation was ‘unlikely to confer strong resistance to weight gain’ [8]. Additionally, a counterintuitive observation was made by analyzing the individual responses: the subjects with the greatest induction in energy expenditure were those who gained the largest amount of weight during overfeeding [8]. These findings both support that Luxuskonsumption is not an essential protective mechanism against experimentally induced adiposity and suggest the existence of other weight gain-defense systems.

In 2011, an inpatient feeding study used bomb calorimetry to show that, on average, ~5% and ~0.5% of ingested energy are lost in feces and urine [3]. An interindividual variation in fecal energy loss of 2–9% was reported [3]. The same group recently confirmed these findings in adults with obesity who underwent two 3-day interventions with a total energy intake of 150% and 50% of their weight maintenance energy needs [5]. Here, Baloso, Hohenadel, and Ang et al. showed that relative fecal energy loss was on average 6% during overfeeding and 9% during underfeeding (the absolute fecal energy loss was accordingly highest in the overfeeding intervention). Similar observations were made for urinary energy loss, which averaged around 1% and 2% for overfeeding and underfeeding, respectively [5]. These numbers are in line with previous reports. A study that aimed to define energy absorption reference values for healthy free-living volunteers showed that the 95% confidence interval for energy absorption was 87.7–91.0%. Yet, the total individual variability in fecal energy absorption ranged from 80% to 94.8% [9]. The physiological importance of this variation is obvious and can be exemplified by a female participant who lost the energetic equivalent of half a liter of sugar-sweetened soft drink in her feces (i.e., a loss of 53 g/day carbohydrate) [9]. However, this study was not designed to include strict dietary control and dietary records were used for estimating total energy intake. This limitation could have inflated the ranges, especially given that women, who have a wider absorption range compared with men, tend to underestimate their true energy intake [9]. During the early 1980s, Heymsfield et al. demonstrated that humans without malabsorption diseases extracted 89–99% of ingested energy [10]. This finding fits with the 2–10% fecal energy loss reported in the controlled study by Baloso and coworkers [5]. Scrutinizing the individual values reported by Baloso et al. reveals two subjects with fecal energy losses of ~80 kcal/day and ~500 kcal/day, respectively. They can be regarded as examples of the
of ~80 kcal/day (corresponding to 2%) was, in reality, overfed by ~147%. By contrast, for the subject with the pronounced fecal energy waste (~500 kcal/day, corresponding to 10%) the degree of overfeeding was in reality (only) ~135% [5] (Figure 1B). The potential long-term implications of such differences must be emphasized. If these data are representative and, importantly, if it turns out that the calories excreted in stools during periods of positive energy balance correlate closely with longitudinal weight gain, fecal energy loss could in fact explain a large proportion of the population-wide weight gain variation. In other words, an important component of human obesity resistance might reside in the gut – unrelated to the release of classical satiety hormones, but reflective of a lower energy harvest in lean humans.

**Calorie Excretion: A Cause of (Constitutional) Thinness?**

It is intriguing to speculate further and consider that energy excretion might be elevated in individuals with constitutional thinness (CTs). This condition is characterized by a normal body fat percentage but a very low body weight (body mass index (BMI) <18 kg/m²). These subjects report a desire to gain weight and data indicate that they ingest the same absolute amount of energy as those of normal body weight [11,12]. Moreover, both resting and total energy expenditure appear to be similar to those of control subjects when correcting for differences in fat-free mass [11]. CTs and controls do not differ with regard to fecal fat excretion [11] but, to our knowledge, it is unknown whether an altered excretion of other macronutrients partly explains this phenotype. Given that interindividual variation in carbohydrate and protein absorption appears to vary more than fat absorption [1,9], it would be worthwhile investigating whether total fecal energy loss differs between CTs and control subjects. Interestingly, a recent metabolomics analysis of urine from subjects with CT indicated that a higher 24-h urinary excretion of

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**Figure 1.** The Implications of Fecal and Urinary Energy Loss for Human Energy Balance and Body Weight. (A) If food intake exceeds energy expenditure, energy balance becomes positive (1). However, this is only true if the amount of ingested energy also exceeds both the number of calories that escape absorption within the small (2) and large intestine (3) and the energy-containing macronutrients that are lost in the kidneys (4). Apart from energy excretion, calories can be ‘wasted’ via nonexercise activity thermogenesis (5) and diet-induced thermogenesis (6). Most remaining energy (i.e., the energy that has not been lost or wasted) subsequently ends up being stored as lipids in adipose tissue or as glycogen in, for example, liver (7). (B) Fecal energy loss varies between subjects and around 2–10% of total energy intake appear to be lost in healthy humans. Hence, in response to overfeeding, a large fecal energy loss can significantly lower the positive energy gap, whereas a small fecal energy loss leads to a greater positive energy gap. Based on [5].
Humans inherit different susceptibilities to weight gain [6]. Although body weight regulation is biased towards weight gain, it is noticeable that a minor group of individuals are partly protected against overweight, even when exposed to highly obesogenic environments [7]. In humans, predisposition to weight gain spans a wide continuum, but two markedly different phenotypes have been proposed to exist at the outermost ends [7,8]. As such, humans who are susceptible to obesity have been proposed to be equipped with a ‘thrifty’ phenotype compared with more obesity-resistant subjects with a ‘spendthrift’ phenotype [7,8]. Thrifty subjects tend to conserve energy both during underfeeding and overfeeding. As a consequence, they have a natural propensity for weight gain and, in addition, find it difficult to lose weight [7,8]. By contrast, individuals with a spendthrift phenotype waste more energy both when dieting and when eating in excess. Therefore, they find it not only easier to lose weight, but also more difficult to gain weight. From an evolutionary point of view, the thrifty phenotype might have been advantageous because it favored survival by saving energy and increasing fat deposition during periods of limited food availability [8].

Identifying these two phenotypes in overfeeding studies has been challenging due to the low sample size often used in such studies [8]. Yet, another strategy to map obesity susceptibility and resistance has been to place individuals in metabolic chambers and subject them to acute, short-term fasting and (low-protein) overfeeding, respectively [7,8]. Also, studies have started to explore whether endocrine factors and/or metabolic tissues (e.g., leptin, FGF21, skeletal muscle, and brown fat) mediate individual metabolic responses [7,8]. However, the exact contribution from these factors has not been clearly defined. It also remains unknown whether, and to what extent, energy loss in feces and urine contributes to the physiological differences between thrifty and spendthrift phenotypes (Figure 1).

Box 1. Human Thrifty versus Spendthrift Phenotypes

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Future Unfolding: New Fuel for Old Thoughts?

Given the findings discussed earlier, we wonder whether many dietary, pharmacological, and genetic manipulations that alter energy balance might do so, in part, by impacting fecal and urinary energy loss, but that this has gone unnoticed so far. As an illustrative example, oral supplementation with polyphenols in male New Zealand black mice attenuated high-fat diet-induced obesity partly by increasing fecal energy loss [13]. Moreover, human antiobesity treatments specifically developed to target energy excretion, either via impairing intestinal lipid digestion (orlistat) or renal glucose reabsorption (SGLT2 inhibitors) show modest, but significant, benefits on body weight [14,15]. Also, before the widespread use of Roux-en-Y gastric bypass and vertical sleeve gastrectomy, severe obesity was treated surgically by jejunoileal bypass, a procedure that increases fecal energy excretion to a level that matches that of malabsorption (350–850 kcal/day) [10]. Lastly, it is evident that the metabolizable energy, or ‘fuel value’ of macronutrients, varies between individuals [2]. Dietary fiber content, food matrices, and mechanical food processing, such as chewing, cooking, and industrial processing, all affect food digestibility [1,2]. Moreover, factors such as physical activity, stress, age, health, and alcohol consumption might also influence the amount of energy that is extracted from foods [2]. Given the cumulative evidence, including the highlighted new insights into fecal and urinary energy loss, nutrient retention and calorie excretion have emerged as two components that potentially affect human body weight. Thus, exploring the regulation of energy excretion and the relative impact on energy homeostasis are important areas for future research.

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Childhood cancer patients undergoing cancer therapy can be rendered infertile during adulthood. With more girls surviving cancer, fertility preservation in young cancer patients is a major clinical challenge. Advances in egg culture may offer benefits for the fertility of these patients in the future.

Surviving Cancer and the Loss of Fertility
The global incidence of childhood cancer is increasing, with estimates of 6.7 million cases between 2015 and 2030 [1]. Advances in oncology mean that >80% of these children will survive past 5 years, presenting long-term challenges for post-treatment health including difficulties in pubertal transitions and adult infertility. The reproductive system has powerful effects on female identity and sexuality, and options to protect or restore fertility have a positive impact on the quality of life for cancer survivors (Box 1). There is strong interest in developing options to prevent the loss of fertility in young female cancer patients who face lifesaving but fertility-destroying cancer treatment.

Existing Fertility Preservation Options for Young-Adult Cancer Patients
Women are born with a complete complement of oocytes, which are enclosed in a set of somatic cells that make the hormones estrogen and progesterone, in an oocyte–somatic cell unit known as a follicle. Protecting follicles is key to preventing infertility. Current methods to protect fertility in post-pubertal women include traditional ovarian stimulation, a process whereby hormones are used to support follicle development and in vivo oocyte maturation. Once matured, oocytes can be cryopreserved for later use or immediately fertilized through in vitro fertilization (IVF) to create an embryo. This is the most mature technology available to adult females.

While oocyte or embryo cryopreservation is the best fertility preservation option for many women with cancer, ovarian stimulation and oocyte collection are contraindicated in prepubertal girls for ethical and practical reasons. Furthermore, some young patients will not have time for hormonal stimulation and will also opt for ovarian tissue cryopreservation and future transplantation. Ovarian tissue cryopreservation and future transplantation involves the collection of tissue before cancer treatment and its cryopreservation until the patient desires to have it autografted. The American Society for Reproductive Medicine no longer classifies this technique as experimental. Ovarian tissue cryopreservation and transplantation captures the reproductive potential of oocytes residing in primordial and primary follicles of the ovarian cortex, but not oocytes from antral follicles (Figure 1). Ovarian tissue cryopreservation and transplantation is currently the only recognized fertility preservation option for prepubertal girls and while this technique using ovarian tissue from adult patients has led to live births, there have been no offspring using this procedure from pediatric cancer patients, although there have been births using tissue from girls without cancer (e.g., in a patient with sickle-cell anemia [2]), demonstrating