Appetite control after weight loss: what is the role of bloodborne peptides?

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Abstract: The literature presented in this paper argues that our limited ability to maintain energy balance in a weight-reduced state is the product of our difficulty in compensating for the weight loss-induced reduction in total energy expenditure. The end result, translated into the overwhelming complexity of preserving long-term weight loss, is presented as being a consequence of compromised appetite control. Given the present-day food landscape and the resultant susceptibility to passive overconsumption, the focus of this review will be on the peripheral (“bottom-up”) signals (leptin, PYY, ghrelin, and GLP-1) and the evidence highlighting their influence on feeding behaviour. As we continue studying paradigms of body mass reduction, specifically the data emerging from patients of bariatric surgery, it is becoming clearer that counter-regulatory adaptations, possibly through down-(leptin, PYY, and GLP-1) or upregulation (ghrelin) of peptides, have an impact on energy balance. In itself, food deprivation influences some of the peptides that ultimately provide the physiological input for the overt expression of feeding behaviour; these peripheral adaptations are expected to serve as feeding cues — cues that, in the end, can serve to compromise the maintenance of energy balance. In a potentially novel intervention to increase compliance to long-term reductions in energy intake, it is proposed that manipulating the pattern of food intake to favourably alter the profile of gastrointestinal peptides would lead to better dietary control.

Key words: weight loss, appetite, gut hormones, energy balance.

Introduction

The fact that rates of obesity are increasing all over the globe is now well documented (WHO 2003). The countless nonsurgical approaches that have been developed to combat excess adiposity still only result in limited success, as evidenced by the fact that many individuals are still obese or overweight after weight loss (Tremblay and Doucet 2000). Furthermore, resistance to slimming is often observed (Miller and Parsonage 1975), and the relapse to initial levels of adiposity is, in more cases than not, the fate of most weight losers (Anderson et al. 2001). These effects could be facilitated by counter-regulatory adaptations that appear in response to prolonged energy-restricted diets (Tremblay and...
Doucet 2000; MacLean et al. 2004, 2006). As such, it would be relevant to consider these counter-regulatory adaptations when designing weight-loss and weight-maintenance interventions aimed at increasing the compliance to long-term reductions in energy intake.

**Obesity treatment: a partly successful endeavour**

The fact that obesity has now reached the status of global epidemic (WHO 2003) is no longer debated. Regardless of the observation that energy-restricted diets can produce significant weight loss (Wadden 1993; Miller et al. 1997; Anderson et al. 2004) and substantial improvements of the determinants of the metabolic risk profile (Wing and Jeffery 1995; Tremblay et al. 1999), the fact remains that most weight losers will likely regain (Anderson et al. 2001) or even overshoot their preintervention body mass when severely food deprived (Dulloo et al. 1997). The cyclical path of weight loss to weight regain is in itself a troublesome situation, as the number of previous weight-loss attempts is a risk factor for subsequent major weight gain (Korkeila et al. 1999). Some results have also shown that humans (Dulloo et al. 1997) and animals (Ouellet et al. 1997) often overshoot their initial levels of body fat after being food deprived. In fact, there is evidence from a meta-analysis that reduced-obese subjects only maintain 20% (3 kg) of their initial weight loss after a 2 to 5 year follow-up (Anderson et al. 2001), in which case the term “reduced-obese” refers to an individual who was successful at achieving weight loss but could still be classified as an obese individual based on his/her post weight-loss body mass index. The high incidence of relapse supports the perception that energy balance may be compromised in a reduced-obese state. In a study that surveyed the characteristics of a cohort of reduced-obese individuals who were successful at maintaining their weight after weight loss, the reduced-obese subjects consumed low-calorie – low-fat diets (~1400 kcal/day with less than 25% dietary fat) and also engaged in purposeful physical activity in excess of 2800 kcal/week from vigorous physical activity or roughly the equivalent of 1 hour of exercise per day (McGuire et al. 1999). It is becoming clearer that weight maintenance after weight loss is illusive and that body mass relapse is explained, at least in part, by counter-regulatory adaptations that appear in response to energy deprivation. In this paper, we will argue that feeding behaviour is compromised during and after body mass reduction.

**Appetite in the regulation of body energy reserves**

This review will focus on the homeostatic control (“bottom-up”) of food-intake control. As such, it is not intended to diminish the complexity of feeding to a mere “bottom-up” regulation, or the idea that feeding is initiated and terminated based solely on peripheral cues (humoral, hormonal, mechanoreceptive, chemoreceptive, etc.). In fact, this representation is incomplete and only characterizes one limb of an integrated two-tier system guiding feeding behaviour (Berthoud 2000). The other limb of this model consists of so-called indirect pathways, or a “top down” pattern of organization involved in the interpretation of both external and internal stimuli (Cameron and Doucet 2007). Although both sides of the “two-tiered” model of feeding must be acknowledged, from this point onward, the impact of peripheral signals, namely bloodborne peptides that have been shown to contribute to the regulation of appetite and food intake in humans and animals, will be discussed. These peripheral signals are integrated on a hierarchy of levels and have the potential to influence feeding behavior; however, it is understood that up- or down-regulation of these signals does not necessarily translate into cause–effect changes in feeding.

Furthermore, in addressing the “bottom-up” regulation of feeding, both acute and long-term controls must also be briefly discussed. Since the issue has been extensively reviewed elsewhere (Druce and Bloom 2003, 2006a; Korner and Leibel 2003; Woods 2005), only a short description will be given here. Gastrointestinal factors (peptides, nutrients, mechanoreceptors, chemoreceptors, etc.) act mainly in the satiety cascade to limit meal size (Havel 2001). This pathway has been coined the short-term signaling of feeding regulation. In contrast, the long-term modulators of feeding and energy intake are up- or down-regulated according to fluctuations in body energy reserves, mainly adipose tissue, in line with Kennedy’s adipostat theory (Kennedy 1953). Leptin (Considine et al. 1996), ghrelin (Cummins et al. 2002), and insulin (Woods et al. 1974) are amongst these long-term modulators and consequently fluctuate with changes in energy reserves. Current obesity trends and the apparent lack of success in treating excess adiposity may also indicate that these peptides are more potent in their protection against energy deprivation (Bowles and Kopelman 2001) than against chronic overfeeding.

Considering that energy expenditure is continuous and that food intake is episodic, it is remarkable that, over an individual’s lifetime, there is a rather precise regulation between energy intake and expenditure (Jéquier and Tappy 1999), as body mass gain for most individuals is the result of slight energy imbalances that are sustained over prolonged periods of time. Nevertheless, there is evidence to support that the control of food intake is compromised when body energy reserves are being depleted. A well-documented observation is that the reduction in body mass leads to a decrease in energy expenditure (Bray 1969; Doucet et al. 2000c) — a decrease that has been shown to be even greater than that predicted from changes in body mass and composition (Leibel et al. 1995; Dulloo and Jacquet 1998; Doucet et al. 2001, 2003). Data from animal models have shown that these changes actually contribute to weight relapse (MacLean et al. 2004, 2006). Oddly, despite a decrease in total energy expenditure, there seems to be a concomitant increase in the drive to eat under such circumstances (Doucet et al. 2000a), an effect that is also observed early into energy deprivation (Doucet et al. 2004a) and that has been shown to predict weight relapse (Pasman et al. 1999). In practical terms, a reduction in energy expenditure as observed after weight loss is not necessarily accompanied by a proportionate decrease in the drive to eat. Further evidence as to the effect of a reduction in body energy reserves on appetite are presented in the reanalysis (Dulloo et al. 1997) of the Minnesota semi-starvation study by Ancel Keys and colleagues (Keys et al. 1950). Briefly, this experiment involved a 24 week food deprivation period (50% of caloric needs), followed by a 12 week restricted refeeding and, finally, by an additional 8 week free-feeding period.
Both fat-free mass and, to a much greater extent, fat mass were reduced. Of interest to this review is the fact that, during the free-feeding phase of the experiment, subjects had sustained hyperphagia (up to 160% of baseline energy intake) beyond the point where they had reached their baseline fat mass and body mass. It is agreed that the conditions of this study are not typical of usual weight-loss strategies. Presented in Fig. 1 is a compilation of results from our own work that employed a ~25% reduction in energy needs (more typical of widespread weight-loss programs) to induce weight loss (Doucet et al. 2000a, 2001), or to measure the acute effects of an energy-restricted diet (Doucet et al. 2004a). As could be expected, body mass, fat mass, and resting energy expenditure all progressively decreased as the energy-restricted diet progressed. What is also apparent in Fig. 1 is that there was an increase in hunger ratings that appeared very early during the energy-restricted diet and continued to progress throughout the food deprivation period.

As mentioned earlier in the text, weight loss is accompanied by a decrease in energy expenditure (Bray 1969; Doucet et al. 2000c). In addition, there is evidence to support that, matched on body mass, the reduced-obese tend to display lower energy expenditure than never-obese subjects (Astrup et al. 1999). The problem of maintaining energy balance after weight loss is then likely to be one of reducing the energy intake to compensate for a chronic decrease in energy expenditure, considering that large amounts of energy from purposeful engagement in exercise programs are needed to maintain weight stability after weight loss (McGuire et al. 1999).

**Feeding-related peptides and their changes during food deprivation**

In recent years, many peptides originating from the gut or adipose tissue have been linked with feeding in both humans and animals (Korner and Leibel 2003; Druce et al. 2004; Broberger 2005; Cummings et al. 2005; Druce and Bloom 2006a). Of interest to this review are those peptides that have also been shown to fluctuate with acute and chronic food deprivations. These peptides include leptin, ghrelin, peptide tyrosine-tyrosine (PYY), and glucagon-like peptide (GLP) 1. Although other peptides, such as insulin, fall into this category, they will not be discussed in this paper. The following sections illustrate how changes in the circulating levels of these peptides contribute to the fragility of appetite control upon food deprivation.

**Leptin**

The fact that leptin is primarily produced and secreted by white adipose tissue (Zhang et al. 1994; Masuzaki et al. 1995) is commonly recognized, even if other sites, such as the gastric mucosa, secrete this hormone (Mix et al. 1999, 2000). Whether acute food intake impacts leptin concentrations is still a matter of controversy, as some investigators reported a postprandial increase in leptin concentration in response to a single meal test (Pratley et al. 1997; Dallongeville et al. 1998; Joannic et al. 1998; Romon et al. 1999; Imbeault et al. 2001), whereas others did not (Considine et al. 1996; Dagogo-Jack et al. 1996; Sinha et al. 1996; Clapham et al. 1997; Weigle et al. 1997). There is, however, greater agreement regarding the notion that fat loss triggers a decrease in plasma leptin (Considine et al. 1996; Doucet et al. 2000b); furthermore, the decrease in leptin is greater than that predicted by the reduction in body fat (Considine et al. 1996; Wadden et al. 1998; Doucet et al. 2004a). Several studies have shown that the decrease in leptin observed after acute energy deprivation (Doucet et al. 2004a) and after weight loss (Heini et al. 1998a, 1998b; Doucet et al. 2000a) is associated with increased appetite ratings. Given the effects of leptin on energy balance, it is not surprising that recombinant leptin therapy in human subjects with congenital leptin deficiency has proven to be an effective weight-loss intervention (Farooqi et al. 1999). However, this therapy has limited potential when applied to overweight subjects, as exemplified by their very modest weight loss (Heymsfield et al. 1999). That peripheral leptin does not produce significant weight loss under such circumstances is likely explained by the fact that obese individuals not only show grossly elevated plasma leptin concentrations (Considine et al. 1996; Wadden et al. 1998; Doucet et al. 2004a), but also demonstrate resistance to signaling at the level of the blood brain barrier (Banks 2001). It should nonetheless be pointed out that when leptin therapy is used in conjunction with dietary energy restrictions, it seemingly attenuates both the weight-loss-induced reduction of energy expenditure (Rosenbaum et al. 2002) and the increase in appetite (Westerterp-Plantenga et al. 2001). In brief, leptin is decreased upon food deprivation, leading to weight loss, and this decrease has also been shown to be associated with the increase in appetite observed under such circumstances. © 2007 NRC Canada
**Ghrelin**

Ghrelin, a ligand for the GH secretagogue receptor, and the only known orexigenic hormone, was isolated from gastric extracts (Kojima et al. 1999). Unlike leptin, ghrelin is acutely reduced in response to nutrient intake (Ariyasu et al. 2001). As reviewed elsewhere, carbohydrates seem to have the greatest effect on ghrelin suppression, with proteins and fats exerting a lower suppressing effect on this peptide (Cummings et al. 2005; Overduin et al. 2005; Gil-Campos et al. 2006; Prodam et al. 2006). It has also been suggested that the preprandial rise in ghrelin could serve as a meal initiation signal (Cummings et al. 2001), and that intravenous administration (Wren et al. 2001) and subcutaneous injection (Druce et al. 2006b) of this peptide can increase appetite and food intake in both lean and obese humans (Druce et al. 2005). These observations led to the assumption that this orexigenic hormone plays an important role in the acute regulation of energy and nutrient intake. The fact that ghrelin is reduced in obesity (Tschop et al. 2001; Lindeman et al. 2002), increased in anorexia nervosa (Otto et al. 2001), and in response to sustained energy restriction leading to weight loss (Cummings et al. 2002; Hansen et al. 2002) implies that ghrelin is, as is leptin, influenced by energy imbalances. Given the role of ghrelin in the short-term regulation of feeding, its post weight-loss increase could complicate the control of meal size and frequency.

**Peptide tyrosine-tyrosine**

Other peptides secreted by endocrine L-cells in the distal part of the small intestine and proximal colon have been shown to exert a potent effect on the short-term downregulation of appetite and energy intake (Batterham et al. 2003b; Cohen et al. 2003). One of these, peptide tyrosine-tyrosine (PYY)3–36, a truncated version of PYY1–36, exhibits anorectic effects in humans (Batterham and Bloom 2003a; Batterham et al. 2003b). PYY3–36 was first isolated from colonic extracts (Tatemoto and Mutt 1980) and is part of the same pancreatic peptide family as are polypeancreatic peptide and neuropeptide Y (NPY) (Onaga et al. 2002). The postprandial increase of PYY3–36 has been extensively documented in numerous species (Onaga et al. 2002) and has been shown to be proportional to calories ingested (Adrian et al. 1985a). Furthermore, PYY levels rise within 30 min of nutrients reaching the gut (Anini et al. 1999), reaching maximal levels within 1 to 2 h (Adrian et al. 1985b; Laviolette et al. 2005). Recent results support the idea that, when equicaloric meal challenges are given, the greatest postprandial PYY levels are observed under the high-protein condition in both lean and human subjects (Batterham et al. 2006), although earlier results had shown that fat elicited greater secretion of PYY (Onaga et al. 2002). Of note is the fact that PYY levels were comparable between the high-fat and high-protein conditions in lean subjects during the first 2 h of the measurement (Batterham et al. 2006), which may help reconcile this apparent difference between the two studies. Contrary to ghrelin, when administered intravenously, PYY3–36 reduces appetite and energy intake (Batterham and Bloom 2003a; Batterham et al. 2003b), but recent results have shown that pharmacological levels need to be achieved for these effects to occur (Degen et al. 2005). PYY3–36 infusion also attenuates the pre-meal rise in ghrelin (Batterham et al. 2003b). It could be postulated from these observations that part of the anorectic effects of PYY3–36 may be, in part, mediated by the reduced levels of ghrelin (Batterham et al. 2003b). To date, a single study has reported the effects of dietary-induced weight loss on PYY. In this study, fasting total PYY was shown to increase after successful weight loss in children (Roth et al. 2005). In contrast, there is also limited evidence to indicate that acute food deprivation leads to a decrease of PYY levels in adults (Doucet et al. 2004b; Chan et al. 2006b). In fact, Chan et al. (2006b) have recently reported that, after a 2–3 day fast, fasting circulating total PYY was reduced by as much as 50%. In agreement with this previous study, we also reported a decrease (~11%) of both fasting and postprandial total PYY after 4 days of a 25% reduction in energy intake (Doucet et al. 2004b) (Fig. 2). In summary, PYY has been shown to be a potent downregulator of appetite and energy intake in both humans and animals. Some evidence supports the idea that PYY may also be downregulated in response to food deprivation, an effect that could likely impact appetite control upon food deprivation.

**GLP-1**

Like PYY, GLP-1 (Lund et al. 1982; Bell et al. 1983) is secreted by endocrine L-cells and is increased after the ingestion of a mixed meal (Holst 1994; Naslund and Hellstrom 1998), whereas carbohydrates elicit a greater secretion of this peptide (Elliott et al. 1993). There is evidence to show that GLP-1 reduces energy intake (12%) and appetite, when administered intravenously to human subjects (Flint et al. 1998). A contributing factor to the GLP-1-induced decrease in energy intake may be its effects on gastric emptying and the ileal brake (Nauck et al. 1997). Moreover, there seems to be an additive effect when both PYY3–36 and GLP-1 are administered simultaneously (Neary et al. 2005). Whereas some investigators have reported hypere-
cretion of GLP-1 in the obese (Fukase et al. 1993), others have reported lower secretion of this peptide, particularly in the severely obese (Verdich et al. 2001). Similarly, there are also discrepant results for post-weight loss GLP-1 levels. Indeed, one study has shown GLP-1 response to a standard meal to be increased in reduced-obese subjects (Verdich et al. 2001). In contrast, two more recent studies have shown GLP-1 to be reduced after weight loss. In the first of these studies, it was reported that fasting and nutrient-stimulated GLP-1 were reduced after a 6 kg weight loss (Adam et al. 2005). Despite the fact that no differences in fasting GLP-1 levels were seen in this second study, a significantly blunted postprandial response was also observed after weight loss (Adam et al. 2006). Evidence reviewed in this section suggests that post-weight-loss secretion of GLP-1 in response to a meal test may be blunted. If GLP-1 does indeed play an important role in the short-term regulation of feeding, its reduction following weight loss could contribute to looser controls of meal and frequency.

As we continue studying paradigms of body mass reduction, it is becoming clearer that food deprivation triggers counter-regulation adaptations, possibly through down-regulation of peptides known to affect energy balance. The literature reviewed in this section supports a role for peptides secreted by the gut and by adipose tissue in the expression of appetite control. This idea is congruent with the notion that the main role of some of these peptides, namely leptin, might be to safeguard energy reserves in response to food deprivation (Bowles and Kopelman 2001), and that there may well be other hormonal players in the series of adaptations that operate to re-establish energy balance during periods of food deprivation. From a thermodynamic perspective, successful long-term treatment of obesity is dependent on the ability to compensate for the weight-loss-induced decrease in total energy expenditure, either through increased physical activity or via a sustained decrease in food intake. However, as emphasized throughout this review, peripheral adaptations that serve as feeding cues would, in the end, compromise the maintenance of energy balance and contribute to relapse obesity upon cessation of weight-loss interventions. Evidence in support of this position comes from the observation that reduced-obese individuals with the greatest levels of hunger are likely to regain more body mass over a 14 month follow-up (Pasman et al. 1999). Taken together, these observations emphasize the need for interventions that minimize the impact of weight loss on appetite.

**Manipulating peripheral feeding signals**

As emphasized in the previous section, food deprivation impacts some of the peptides that ultimately provide the physiological input for the overt expression of feeding behaviour. However, long-term treatment with agonists/antagonists of these peptides largely remains to be investigated, or has yielded disappointing outcomes, such as with leptin (Heymsfield et al. 1999). Another avenue that has yet to be explored is whether dietary manipulations that could in theory favourably impact gut hormone profiles, would in turn lead to an increased compliance to long-term reductions in energy intake. Evidence from studies that investigated bariatric surgery patients lends support to the possibility that increased endogenous levels of some of these peptides could actually contribute to successful obesity treatment. Amongst other possibilities, the success of this approach is at least partly related to the low levels of hunger reported by these individuals. Korner et al. (2005) reported an early and pronounced postprandial increase in PYY in obese subjects after Roux-en-Y surgery, a finding that has been since reproduced on several occasions (Chan et al. 2006; Korner et al. 2006; le Roux et al. 2006; Morinigo et al. 2006). It is generally concluded that this favourable PYY profile contributes to successful weight maintenance by possibly attenuating the effects of weight loss on appetite. In addition, two other studies have also reported that GLP-1 secretion in response to a standard nutrient intake is also significantly more elevated in gastric bypass subjects that in obese or lean controls (le Roux et al. 2006; Morinigo et al. 2006). Finally, data from animals also support these findings, as it has been shown that ileal transposition (moving a 10 cm segment of the distal small intestine proximal to the ileocecal valve and transposing it to a location within the jejunum) produced marked increases in postprandial PYY and GLP-1 in these animals compared with the sham-operated controls (Strader et al. 2005). In addition, these animals gained significantly less weight over a 45 day period (Strader et al. 2005). Taken together, these findings support the important role of PYY and GLP-1 in energy balance. A question that can be derived from the integration of this literature is whether it would be possible to structure food intake and meal patterning in a way to favourably alter daily gut peptide profiles in the absence of surgery. This issue will be addressed in the next section.

**Meal frequency, energy intake, and gut peptide profiles**

In addressing the question as to whether structuring food intake is possible to take advantage of repeated nutrient intake on gut peptide secretion and, ultimately, on energy intake, it is relevant to summarize some of the literature on increased meal frequency and energy intake. It has even been hypothesized that an increased periodicity of eating could favour the release of gastrointestinal hormones associated with improved appetite control (Speechly et al. 1999), but studies have yet to be conducted to confirm this postulation. Nonetheless, there is evidence, albeit controversial, to the effect that increased meal frequency is associated with a lower energy intake. Several epidemiological studies have observed a lower body mass in individuals eating smaller quantities more frequently, suggesting that increased meal frequency could lead to a decrease in food intake (Bellisle et al. 1997). There is also evidence that high-frequency eating is associated with leanness in men, but not in women (Drummond et al. 1998). Generally, energy intake in obese and lean individuals seems to be lower when following a regular meal pattern with higher frequency than during an irregular meal pattern with lower frequency (Drummond et al. 1998; Speechly et al. 1999; Westerterp-Plantenga et al. 2002; Farshchi et al. 2005). Some reports have also observed an inverse relationship between the number of meals consumed in a day and the degree of adiposity (Bellisle et al. 1997; Speechly et al. 1999). It should nonetheless be
pointed out that the finding of reduced appetite (Farshchi et al. 2005) and reduced energy intake (Taylor and Garrow 2001) after frequent meal consumption is not always consistent among studies (Farshchi et al. 2005). In summary, there is evidence to suggest that increased meal frequency can lead to beneficial effects on energy balance; whether this effect is indeed partly explained by the regular release of gastrointestinal peptides implicated in the satiety cascade remains to be determined.

Overall, the integration of the literature presented in this review suggests that it is relevant to consider postprandial secretion of gastrointestinal peptides to maximize dietary control, particularly after weight loss, and that increasing meal frequency may be a way to test this hypothesis. It is within this paradigm that the following is proposed. Although the idea of designing low-calorie snacks to improve dietary control is not new, the wealth of knowledge emerging from research aimed at better understanding how humans regulate feeding, particularly in the context of food deprivation, warrants further studies in this area. In fact, it would be interesting to propose that offering snacks, specifically designed to elicit secretion of PYY and GLP-1 for example, so that their maximal (or minimal for ghrelin) post-snack levels would coincide with main courses, could lead to better dietary control. Considering the literature on the nutrient-specific effects of the peptides reviewed in previous sections, it is proposed that a relatively high-protein and high-carbohydrate content should be included into this mixture. Accordingly, if such a nutrient challenge leads to increases in pre-meal PYY and GLP-1, then it is reasonable to assume that it could also attenuate the pre-meal rise in ghrelin (Batterham et al. 2003b) and, possibly, energy intake.

Conclusion

Weight relapse after prolonged food deprivation is an outcome of obesity interventions. The literature presented in this paper argues that the limited ability to maintain energy balance in a weight-reduced state is a consequence of the incapacity to adequately compensate for the weight-loss-induced reduction in energy expenditure through sustained changes in food intake. With the understanding that peripheral output (i.e., peptides that fluctuate with acute and chronic nutrient balance) merely acts as cues that inform feeding centers on the direction of feeding behaviour, it becomes nonetheless relevant to investigate strategies, be they nutritional or pharmacological, to try to alleviate their influence on appetite upon food deprivation.

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