



Hunger and satiety

Full4Health is an EU-FP7 funded project comprising 19 academic and industry partners from across Europe which is investigating the mechanisms of hunger and satiety with the aim of developing solutions to address obesity, related chronic disease as well as under-nutrition. **Tehmina Amin** and **Julian G Mercer** describe some of the progress to date.

Introduction

The spiralling global increase in obesity and overweight can be broadly attributed to the overconsumption of calories relative to energy expenditure. Increasingly easy access to cheap, palatable food that is relatively high in sugar and fat, coupled with a decline in activity, is placing an escalating burden on healthcare systems due to the concomitant increase in incidence of metabolic disease, including heart disease and type II diabetes. Therapy to address obesity is limited as a number of marketed drugs have been withdrawn due to unacceptable side effects. The growing use of **bariatric surgery** can be effective for some, but is not suitable for all and is not a

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straightforward solution. Another approach to addressing caloric overconsumption and weight gain involves methods to control overall appetite, which require a more detailed understanding of the mechanisms governing hunger and **satiety**.

European research

Full4Health ^[1] is a €9M research project funded by the EU bringing together 19 academic and industry partners. These researchers are combining multidisciplinary approaches to understand the mechanisms of hunger and satiety, which may lead to the development of solutions for appetite control. Full4Health combines clinical and pre-clinical research approaches to

investigate gut-brain interactions and the interface of food with the gastrointestinal tract and microbiota. It is investigating the potential for dietary manipulation through macronutrient form and structure, the neuropsychology of food choice and reward and how the developmental process affects the food-gut-brain axis across lifespan. It also includes a major study comparing human volunteers during childhood, adolescence, adulthood and in later life.

The Full4Health project is based around the concept of the food-gut-brain axis. In essence, the food and drinks we consume interact with the gut (gastrointestinal tract) at various levels from the mouth through to the lower

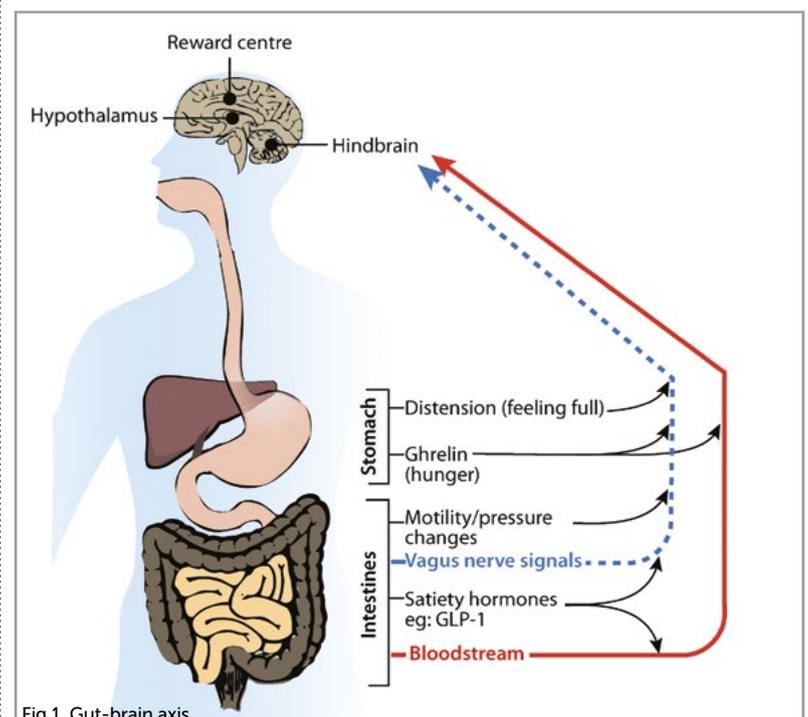


Fig 1. Gut-brain axis



bowel (Fig 1). These interactions not only provide for the digestion of food and the assimilation of nutrient into the body, but also generate feedback signals to the brain relating to physical fullness, passage of digesta and nutrients down the gut, localised and blood-stream hormone and metabolite concentrations and the digestive process itself. These signals, which may be neural (such as through the vagus nerve which innervates most of the gut) or hormonal (blood-borne peptides secreted by specialised cells within the gut) are integrated in the brain to help inform subsequent decisions about what to eat, how much, and when. Interestingly, almost all of these gut peptide hormones induce satiety, i.e. terminate meals and reduce food intake: only one peptide, ghrelin, produced by the stomach, stimulates food intake. A complex network of brain centres and transmitter molecules is involved in integrating incoming neural, hormonal and metabolic signals. The main brain centres are the hindbrain, where the vagus nerve feeds into the brain, the **hypothalamus** and the distributed forebrain structures that make up the **reward circuitry**. The hypothalamus is generally accepted to be the energy balance centre of the brain and contains a number of discrete nuclei

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and specialised transmitters. These systems function to try to maintain energy balance i.e. the balance between energy intake and energy expenditure, but with a critical built-in bias to prevent negative energy balance (and thus starvation). This in part explains the difficulty experienced by most people trying to lose weight on conventional calorie-restricted diets. The reward or hedonic systems appear to monitor many of the same hormonal signals from the gut and periphery that are being read by the hypothalamus and these systems appear to have an over-ride capability. Thus, consumption of palatable, rewarding food may be sustained beyond the requirement to achieve and maintain energy balance. This apparent hierarchy almost certainly goes some way to explaining over-consumption of calories in our current environment, which is characterised by abundant, easily obtained, energy-dense, palatable foods that are high in fat and sugar.

To address this complex signalling in an integrated physiological system, Full4Health has component research projects targeted along the food-gut-brain axis. Its overarching aim is to understand how appetite is regulated by signals from

the gut that arise in response to the passage of specific food components and by validating that understanding through intervention studies to generate evidence-based recommendations about food composition that preserve the satisfying properties of food and its nutritional value, while reducing overall calorie intake.

By working with partners from the food industry, the intention is to accelerate the translation of understanding into practical solutions. Such a food solution, exploiting natural mechanisms of hunger and satiety, would have many advantages over a pharmaceutical approach.

With the benefit of Full4Health partners' expertise in different areas, we now report on selected findings, including how the protein content of a meal affects overall energy intake, how the physical form of macronutrients may affect satiety and how gut bacteria affect the regulation of body fat and hunger.

The Protein Leverage Hypothesis predicts that appetite in humans, as in other species, prioritises dietary protein over carbohydrate and fat. Evolutionarily this makes sense as growth, development and reproduction cannot occur if protein levels are too low. So in a situation where food is low in protein but rich in carbohydrate, consumption might continue until the total required intake of protein is attained. Where this gives rise to an increase in overall energy intake, weight gain would result. Such a negative

BOX 1 - SUMMARY

Satiety – the continuation of fullness and suppression of hunger between meals. Satiety starts after the end of eating and prevents further eating before the return of hunger.

Satiation – the development of fullness and reduction of hunger during a meal. Satiation occurs during an eating episode and brings it to an end.

Hypothalamus – brain centre controlling energy balance

Reward/Hedonic Circuitry – forebrain centres that can override energy balance systems, allowing over-consumption of energy-dense palatable food and potentially leading to weight gain.

Bariatric surgery – weight loss surgery

Gastric bypass – Surgery to reduce stomach size and the length of small intestine. Food then bypasses most of the stomach and part of the small intestine.

Sleeve gastrectomy – surgery which creates a narrow tube (sleeve) from the stomach, reducing stomach volume by 75%.

BOX 2 - BUG FACTS

Human microbiome – the totality of cells constituting the microbial (mostly bacterial) complement of the body

Germ-free – animals bred to be free from gut bacteria i.e. have no microbiome

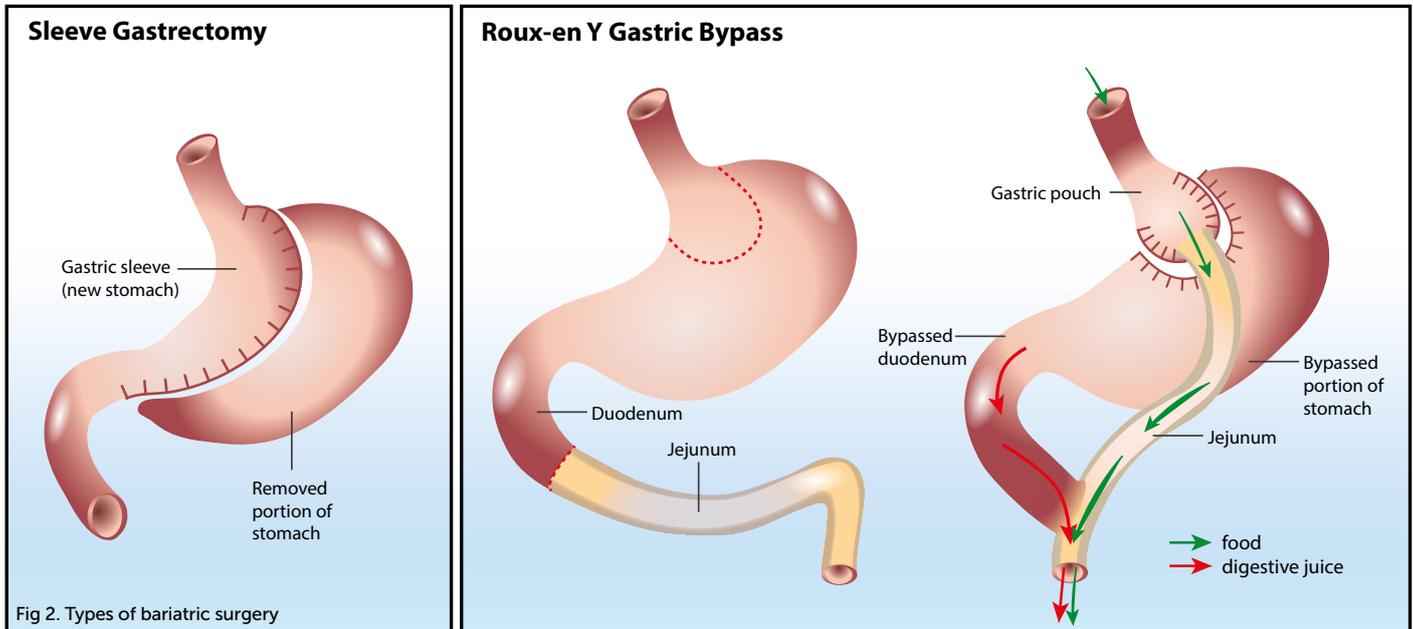


Fig 2. Types of bariatric surgery

association between dietary protein content and total energy intake (i.e. low protein, high energy intake) suggests that even small reductions in dietary protein content could lead to significant increases in overall energy intake, and thus be a driver towards weight gain [2].

However, human studies carried out by Full4Health partners at the University of Maastricht, led by Margriet Westerterp-Plantenga, have provided evidence to support one arm of the Protein Leverage Hypothesis, but not the other. In 2013, Martens *et al* [3] performed studies on lean humans, feeding them meals varying in protein content over three 12-day periods. It was found that overall energy intake decreased with elevated protein content, thus reducing the potential for weight gain. This supports findings from numerous earlier studies [4]. However, although individuals underate relative to energy balance from diets containing high protein content, there was no evidence for protein leverage effects from diets containing a lower ratio of protein, i.e. overconsumption of calories.

The higher protein arm of the

more satiating foods could help limit caloric intake whilst enabling consumers to continue enjoying their food

Maastricht study substantiates previous work showing that protein is more satiating than the other macronutrients, fat and carbohydrate [5-7]. This property has been exploited in the design of higher protein calorie-counted commercial ready meals as an aid to weight management. In Full4Health, a group at the University of Aberdeen is looking at **satiating** and satiety in the context of other properties of the food we eat – energy density and structure. For example, we eat when we are hungry, but what makes us stop eating and how is it influenced by the physical form of the food (whether it is solid or liquid) even if the total calorie content is the same? When food is ingested and first received by the gut, information is sent to the brain relating to the size and composition of the meal via both activation of vagal nerve cells and secretion of peptide hormones. The hormones may act locally in the gut or be released into the circulation to act on the hindbrain and other areas involved in nutrient sensing. Currently it is not known how the structure and composition of food affects satiety

and satiation, so diets high in protein, fat or carbohydrate will be fed in either solid or liquid forms to investigate this [8].

Another area being investigated is how bacteria in the gut may affect obesity by sending signals to parts of the brain regulating body fat and hunger. It was thought until recently that gut bacteria were simply involved in digestion of food, but it now appears that microorganisms in the **human microbiome**, which outnumber our own body cells by ten to one, are likely to affect many aspects of our physiology. This is implied by the observations that **germ-free** mice are leaner than normal mice, obese and lean individuals have different bacteria in their gut and antibiotic therapy of obese mice reduces body weight. Our Full4Health partners in Gothenburg, led by John-Olov Jansson, have compared gene expression of food-intake-regulating peptides in the hypothalamus and brainstem in germ-free and conventionally-raised mice. These studies demonstrated that conventionally-raised mice showed reduced expression of the genes encoding

two body fat-suppressing neuropeptides, implying a role for gut microbes in the regulation of body fat [9].

One of the more successful ways of addressing extreme obesity has been to prevent overeating through bariatric surgery, including **gastric bypass** and **sleeve gastrectomy** (Fig 2). However, although current surgery can be effective, there are considerable reoperation and mortality risks. Even where cost-benefit analysis does support surgery, the volume of surgical procedures required is not feasible. Thus the development of new minimally invasive procedures would be a significant advance. For many years, botulinum toxin, or Botox, has been used as a therapeutic in cosmetic procedures. In preclinical trials, Full4Health partners Duan Chen and his group in Trondheim, Norway, found that Botox injection into the stomach wall of high-fat diet-induced obese rats reduced food intake and body weight by 30% compared to controls over 4 weeks. Botox also resulted in 25% weight loss in obese rats that underwent sleeve gastrectomy but failed to lose weight [10]. Botox blocks release of the neurotransmitter, acetylcholine, from nerve terminals. The stomach wall is heavily innervated by the vagus nerve, which communicates physiological signals between gut and brain and the role of Botox is now being investigated further in relation to this component of the gut-brain axis. A Phase II clinical trial [11] in St. Olav's Hospital, Trondheim, Norway is now underway to assess whether Botox injections into the human stomach via gastroscopy (a procedure performed in conscious patients) may be a viable and less invasive alternative to bariatric surgery. The potentially significant cost savings may make this an important clinical development.

It is clear from the developments described that a number

of interconnected strands in Full4Health have made contributions to furthering our understanding of the mechanisms of hunger and satiety. Full4Health is closely associated with a thematically-related EU project, SATIN, (SATiety Innovation) [12]. Whilst Full4Health is focused on understanding the physiological mechanisms underpinning satiety, SATIN is exploring which ingredients and processing methods for several food components (proteins, carbohydrates, fats) and categories (bread, fish, dairy etc.) accelerate satiation during a meal, suppress appetite and extend satiety i.e. the inter-meal interval. The aim is to see whether satiety-enhancing foods can help with energy intake and weight control. Ultimately it is hoped SATIN studies could inform the regulatory environment.

Conclusion

Full4Health is an ambitious multidisciplinary programme of research seeking answers to the growing global problems of caloric overconsumption, non-communicable disease and under-nutrition. The project was conceived to advance understanding of fundamental physiological mechanisms governing hunger and satiety, which could underpin the move towards design of beneficial,

functional, foods. Food is, not unreasonably, identified as being one of the major causes of the current obesity epidemic – our current diets providing a surfeit of choice of hyper-palatable foods rich in fat, sugar and energy. Nevertheless, there is little incentive for a return to a monotonous, repetitive diet of low palatability, which might naturally stifle our propensity to over-consume. The EU-funded projects Full4Health and SATIN offer the opportunity to assess whether food could also become part of the solution to the problem of overweight, by harnessing its physiological interactions with the gut. There is unlikely to be a single strategy to combat the problem of overweight and obesity and for individuals who already have a significant weight problem, surgery is likely to be a more viable approach than a diet-based intervention. However, for most people weight gain is a process that takes place slowly over years or decades due to relatively trivial but cumulative positive energy balance. In these cases it is realistic to believe that more satiating foods could help limit caloric intake whilst enabling consumers to continue enjoying their food [13] and that strategies that mimic the effect of bariatric surgery but without the need for an operation could prove effective.



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www.fstjournal.org/features/29-1/hunger-&-satiety



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Full4Health is coordinated by **Professor Julian G. Mercer**. Julian is the Leader of the Obesity and Metabolic Health Theme at the Rowett Institute where his research interests are centred on dietary behaviour and molecular mechanisms.

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Online only:

Keywords: appetite/hunger/satiety/satiation/energy balance

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