How are gastrointestinal peptides related to satiety?

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Since the early 1970s, a number of gastrointestinal peptides have been proposed to play a role in appetite control - the first satiety hypothesis concerned CCK (Gibbs et al, 1973)

Why is this area important?

- **Theoretically** - because it appears to be widely accepted that satiety is controlled by CCK and other peptides

- **Practically** – firstly, because satiety peptides may be involved in the aetiology of obesity and secondly, because peptides or peptide analogues are currently in development as anti-obesity drugs
Background (2 of 2)

- A main role of GI peptides is to manage the intestinal response to different macronutrients ingested.
- It is widely believed that the gut peptides signalling to the brain controls satiety.
- There are two ways in which this area can be studied – the effect of exogenous administration of peptides on appetite/energy intake, or by examining the postprandial peptide response to ingested food.

- Exogenous administration of these peptides has measurable effects on appetite and food intake.
- However, these effects may depend upon supra-physiological peptide concentrations.
- Or, on the action of a biologically active substance versus a non-active material (saline).
- The relationship between postprandial peptides (after food) and short-term appetite control under normal physiological levels is not well understood.
- Additionally, few studies measure a range of peptides simultaneously.
Introduction – Concept for the research approach

There are many possible designs for this type of study; it isn’t possible to do all designs and certain choices have to be made. This design was chosen in the hope of maximum impact - to emphasise a physiologically relevant peptide response to both fat and carbohydrate.
Methodology (1 of 2)

- Psychobiological approach to the study of human appetite control
- Cross-cuts several scientific domains

| Environment          | • Obesogenic  
|                      |   • Food type  
| Behaviour            | • Energy Intake  
|                      |   • Physical activity  
| Psychology           | • Hedonics  
|                      |   • Traits and cognitions  
|                      |   • Satiety sensations  
| Physiology           | • Energy expenditure  
|                      |   • Gut peptides  
|                      |   • Body composition  
| Metabolism           | • Resting metabolic rate  
|                      |   • Substrate oxidation  
| Genetics             | • Allelic variation  
|                      |   • Polymorphisms  
| Time                 | • Exercise and diet interventions over 12 weeks  

The strength of this systems approach is that different levels of the system can be examined simultaneously.
Methodology (2 of 2)

- Overweight/obese participants (Age: 46 years; BMI: 29.8 kg/m²)
- Randomised crossover design - breakfast was HF (>50% E from fat) or HCHO (<3% E from fat) – palatability, weight and energy matched (590 kcal, 685 g)
- Serial blood samples taken over 3 hours
- Simultaneous appetite ratings were tracked and analysed using electronic data capture
- *Ad libitum* energy intake at lunch to measure satiation

Experimental work was conducted at University of Leeds and the peptide analysis was conducted at Uppsala University, Sweden
Glucose and Insulin showed clearly significantly stronger responses to the CHO than to Fat.

**Glucose**

- Baseline Glucose levels increased significantly following the CHO compared to Fat.
- The difference was statistically significant with $F_{(1,15)} = 6.200, p<0.05$.

**Insulin**

- Baseline Insulin levels also showed a significant increase following the CHO.
- The difference was statistically significant with $F_{(1,15)} = 32.688, p<0.001$.
Results - Response to Nutrients (2 of 3)

CCK, GLP-1 and PYY all responded more strongly to Fat than CHO, ghrelin showed the same suppression after both meals.
In summary, despite the strong and distinctive changes in peptide profiles in response to the meals, there was no overall difference in hunger and fullness ratings following the meals.

Different macronutrient contents or different peptide profiles over 3 hours had no differential effect on energy intake.

What are the implications of this for appetite control?
Interim Conclusions

- This outcome demonstrated that the **same degree of satiety** can be reached through **distinctly different peptide profiles** implying that **no single peptide** can be regarded as the **sole biomarker of satiety**

- Can **individual peptides** be shown to be related to **satiety**?

- This has been examined by analysing the **correlations** between the profile of hunger/fullness and the profile of specific peptides
Peptides and subjective appetite change throughout the study period and do not show their peak/nadir values at the same time. The suppression of ghrelin and hunger occur at different rates, but the slopes during recovery are similar.

For this reason the two phase analysis of the postprandial period is very interesting.

Satiety Phase Analysis

- AdjTG High Fat
- AdjTG Low Fat
- AdjHunger High Fat
- AdjHunger Low Fat

Minutes

Change from baseline total ghrelin (pg/ml)

Change from baseline hunger (mmVAS)

Early Phase

Late Phase
Total ghrelin showed relationships with hunger on both HF and HCHO conditions during both ‘early’ and ‘late’ phases of satiety. GLP-1 showed a relationship with hunger on both HF and HCHO conditions, but only during the late phase of satiety.

Neither PYY nor CCK showed any relationship with subjective appetite.

Ghrelin and GLP-1 were also related to *ad libitum* energy intake, but no relationships were found for PYY or CCK.
Conclusions

- This outcome demonstrated that the same degree of satiety can be associated with distinctly different peptide profiles implying that no single peptide can be regarded as the sole biomarker of satiety.

- Peptides have multiple functions in the gastrointestinal tract - their main function is to manage the intestinal system to deal with consumption of foods.

- Proportions of macronutrients in foods create distinctive peptide signatures.

- We should not assume that satiety is completely encoded by the peptide response to food.

- Peptides act in conjunction with stomach signals that also follow food consumption.

- Certain peptides are biomarkers of satiety – does this mean they mediate satiety?
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