Gut Hormones in Health and Obesity: The Upcoming Role of Short Chain Fatty Acids

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Obesity

- Obesity is a complex condition that, in simple terms, is caused by a chronic imbalance between energy intake and energy expenditure,
- Clinically - obesity is diagnosed as a body mass index greater than 30 kg/m^2.
- Since 1975, the level of obesity worldwide has almost tripled.
- According to the WHO, 1.9 billion people worldwide are overweight, with 650 million of those considered obese.

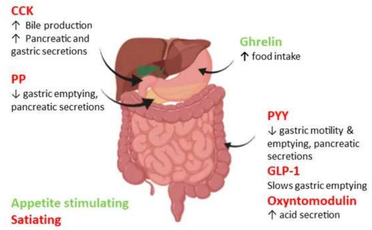
Obesity & Related Diseases

- Non-communicable diseases, which are associated with obesity, are the leading cause of death worldwide
- Obesity is linked to an increased risk of developing a variety of diseases such as type 2 diabetes mellitus (T2DM), coronary heart disease, stroke and certain types of cancer
- Obesity can significantly impact a patients' quality of life and places a huge burden on health services.
- Medical expenses for obese individuals can be 6%–45% higher than for their normal weight counterparts.
- Globally, between 0.7% and 2.8% of a country's total health expenditure is associated with obesity related costs

Current Obesity Treatments

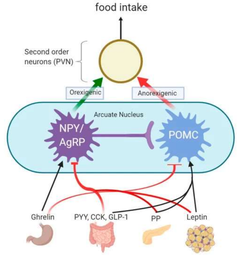
- The first line of treatment for obesity involves lifestyle interventions to change dietary and physical activity patterns to promote weight loss.
- There are very few pharmacological treatments available (e.g. Orlistat) and they typically have strong side effects with limited effects on maintaining weight loss.
- The last line of treatment is Roux-en-Y gastric bypass (RYGB) surgery. However, this is a last resort due to its costs, invasive nature, side effects and is suitable only for certain patients. Furthermore, up to 20% of patients who undergo RYGB experience significant weight regain.
- Therefore newer, more accessible treatments are required.

Gut Hormones



The gut and gut hormones play an integral part in energy homeostasis Ghrelin, the orexigenic hormone in green, is released from the stomach and stimulates food intake. The anorexigenic hormones shown in red (Cholecystokinin (CCK), Pancreatic Polypeptide (PP), Peptide YY (PYY) and Glucagon-Like Peptide 1 (GLP-1)) are released from various organs in the gastrointestinal system and work together to decrease food intake by slowing gastric motility, emptying and reducing acid and pancreatic secretions.

Appetite Regulation

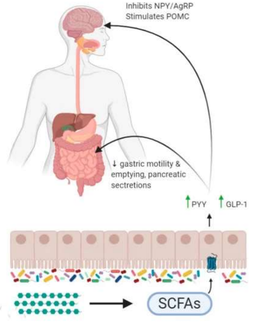


At the central nervous system level, appetite is controlled by the balance between anorexigenic (appetite suppressing) and orexigenic (appetite stimulating) signalling pathways.
Ghrelin is released from the stomach, stimulates the orexigenic Neuropeptide Y (NPY)/Agouti-related Peptide (AgRP) and inhibits anorexigenic proopiomelanocortin (POMC) neurons in the arcuate nucleus. While Leptin from adipose tissue, pancreatic polypeptide (PP) from the pancreas and peptide YY (PYY), Cholecystokinin (CKK) and glucagon-like peptide 1 (GLP-1) from the intestines stimulate POMC while inhibiting NPY/AgRP. This then feeds into the second order neurons in the Paraventricular nucleus of hypothalamus (PVN) to influence food intake.

Gut Hormones & Obesity

- Gut hormones are critical to energy homeostasis
- Gut hormones can be regulated differentially in obesity although it is not known whether this is a driver or consequence of disease
- Some studies show that obese individuals have lower levels of PYY and GLP-1 than normal individuals.
- Similarly, the gut hormones PP and ghrelin are lower in obese children.
- These imbalances in gut hormone levels can lead to increased food intake and lower feelings of satiety driving obesity
- After gastric bypass gut hormone levels of GLP-1 and PYY are increased.
- It is believed this may help prevent weight regain.
- Therefore the therapeutic potential of GLP-1 and PYY have been trialed for weight loss or reducing food intake effects.
- The majority of these studies have led to large side effects of nausea or dizziness
- However the GLP-1 agonist Liraglutide is now offered for some cases of obesity alongside diet/exercise changes but many discontinue treatments due to nausea and other side effects

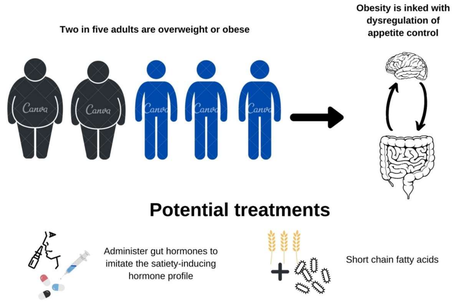
Short Chain Fatty Acids & Obesity



An alternative strategy to increase gut hormone levels may be through increasing short chain fatty acids through increasing fibre or directly increasing levels of SCFAs.

The gut microbiota help to breakdown dietary fibre to produce short chain fatty acids. This in turn stimulates increases in the release of the gut hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) from the L-cells of the colon. The increased levels of GLP-1 and PYY can decrease gastric motility and emptying, as well as reduce pancreatic secretions. The release of gut hormones also inhibits NPY and AgRP neurons, whilst stimulating POMC neurons of the CNS and reduces appetite.

Summary



- Obesity is a major epidemic with 2 in 5 adults worldwide being obese or overweight
- It is clear that obesity links to dysfunctional appetite regulation and can lead to weight gain
- Overall, gut hormones have an important role in regulating appetite and weight and these can be modulated by supplementing with SCFAs.
- Future treatments may rely on the supply of gut hormones or SCFAs to treat obesity.

Future Directions

Future studies should evaluate these main unanswered questions:

1) Do gut hormone therapies have a meaningful impact on obesity, and the maintenance of weight loss?
2) Can different administration routes and doses be assessed to minimize side effects as well as the burden on patients?
3) Can different hormone therapies be combined to mimic the hormone alterations seen after RYGB?
4) The role of SCFAs should be investigated further: how do they affect appetite regulation? how safe are they? how do they affect obese individuals?

References

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