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BRIEFING
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Hunger and satiety: More than a (gut) feeling

SUMMARY
The sensation of hunger is a physiological signal that ensures animals attend to their caloric needs. Recently, researchers have made progress into understanding brain circuits that generate the sensation of hunger and those that communicate signals of food intake from the gut. The understanding of these systems may aid in treatment of medical conditions that affect food intake.

BSN British Society for Neuroendocrinology

Hunger originates in the hypothalamus

Fundamental behaviours essential for survival are ultimately controlled by our brains. These include sleeping, regulation of body temperature and reproductive, sexual and eating behaviours. The majority of these processes are initiated by small groups of neurones in the hypothalamus, located in the middle of the brain on its bottom surface. Distinct groups of neurones are identified by the neuropeptide (chemical signals) that they contain. In the hypothalamus there are a diverse range of these neuronal groups involved in a similarly diverse range of fundamental processes. But a given region of hypothalamus can contain multiple types of neurones. This poses a challenge to researchers studying the behaviours associated with activity in these cells since it is difficult to manipulate only the neurones of interest.

Scientists are now able to overcome this challenge and use refined techniques to test the function of different types of neurone. At the core of this methodology, named optogenetics, are light-sensitive proteins which can be expressed experimentally by neurones and modify a neurone's electrical activity in response to specific wavelengths of light. Neurones use electrical signals, and by inserting these proteins into the neuronal cell membrane they can be 'switched on' by light. Specificity is obtained by expressing these cellular 'light switches' in only one type of neuron in a particular part of the hypothalamus.

Using optogenetics, it has been shown that a small group of cells containing a neuropeptide named Agouti-related protein (AgRP) are responsible for feelings of hunger. When these AgRP cells were stimulated in mice by light these animals were motivated to consume food, even if they had already eaten. Stimulation of AgRP cells causes mice to behave very similarly to when they are have been fasted which demonstrates the activity of these cells is capable of driving food seeking, perhaps indicating the sensation of hunger.

A question that remains is how do the AgRP cells 'know' when to signal hunger? One way in which they do this is by monitoring the levels of hormones in the blood. In hungry animals (including humans) there is an increased level of the hormone ghrelin. This hormone is released from the stomach into the blood where it is then able to reach the AgRP cells in the hypothalamus. Due to its presence in fasted animals and its effect on food intake through AgRP cells, ghrelin may be one of the major signals to indicate hunger, including under periods of prolonged fasting.

Hunger dominates over other needs

Hunger-driven food intake is of paramount importance to the survival of an animal and the evolutionary success of a species. This importance is reflected in the behaviour of fasted animals. In the laboratory, hungry mice are less interested in fighting or mating with other mice, instead prioritising food seeking and eating. In the wild, mice are prey animals and have evolved to habitually avoid open, brightly-lit spaces. In the lab, hungry mice show reduced fear of entering open spaces when food is available in its centre. This shows that hungry mice are willing to take greater risks in order to get food, relieve the sensation of hunger and avoid starvation.

When AgRP cells are stimulated, mice not only seek and eat food but also show fewer behaviours associated with aggression, mating and anxiety. Hunger or AgRP

stimulation suppress other, competing, behaviours indicating the prioritisation of food intake in the hierarchy of needs. This is remarkable since AgRP cells make up only a tiny fraction of brain cells but their activation can orchestrate complex animal behaviours and reorient the animal's priorities and decision-making processes.

Satiety – restoring the balance

We are familiar with the satisfying feeling of a full stomach after being hungry. The gut is lined with specialised cells that are sensitive to stretch and the nutrient content of food. These endocrine cells release hormones including cholecystokinin and glucagon-like peptide 1. The vagus nerve monitors the state of many internal organ systems including the gut and reports changes to the brain, in particular neuronal groups in the brainstem. Gut-derived hormones, when released, activate the vagus nerve to send signals to the brainstem before it is relayed to other brain regions, including the hypothalamus. Some of these gut hormones also reach the brain to have direct actions on neurones, including AgRP neurones.

This gut-brain axis exists to allow for the sensory detection of ingested food and to calculate its nutritional content in order to provide within-meal feedback to the brain. This helps to ensure appropriate suppression of hunger and meal termination. In addition, signals from the vagus nerve activate brain regions associated with pleasure and reward to generate the satisfying feeling of fullness.

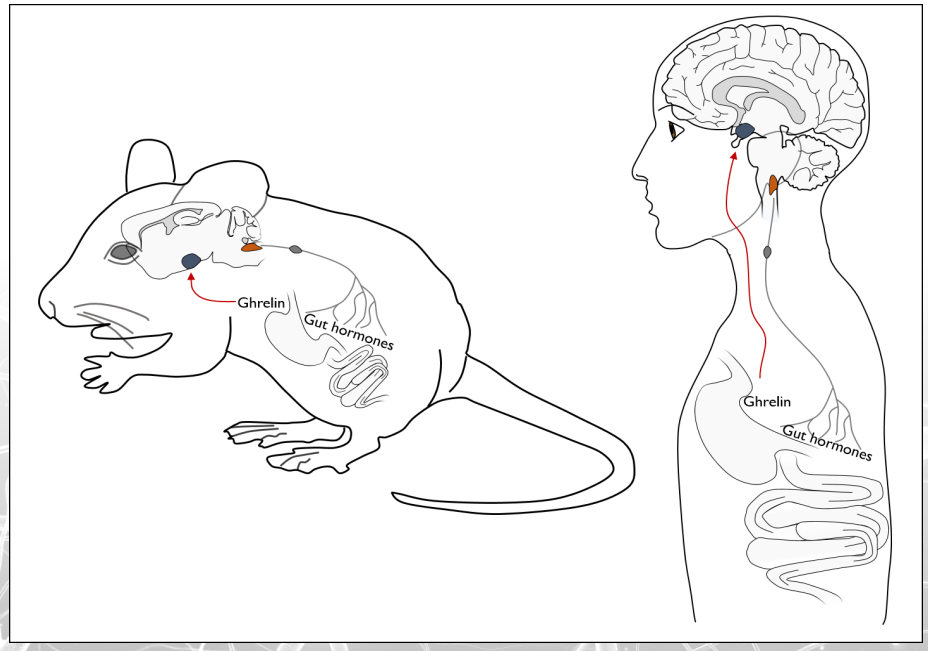
Sometimes we eat too much which can result in us feeling nauseous. The same vagal pathway from the gut tells the brain when this occurs, and while nausea also suppresses appetite, it is distinctly unpleasant compared to satiety. It is not exactly clear how these two sensations are encoded in the brain; whether nausea represents and extreme feeling of satiety (i.e. a greater activity in neural satiety circuits) or, alternatively, a 'switch' after a given amount of food is ingested from satiety to nausea (potentially indicating activation of a distinct brain circuit). At present scientists are trying to understand this overlap between satiety and sickness controlling mechanisms to further our knowledge about the opposing rewarding and aversive feelings associated with food intake.

Hacking feeding control systems to restore appetite

In addition to eating too much, some illnesses can reduce our appetite. Conditions like cancer and HIV/AIDS as well as chemotherapy treatment can induce a state called cachexia. Reduced appetite in severely ill patients is accompanied by muscle wasting and persistent feelings of sickness, which can exacerbate the original condition. By understanding the brain processes that underlie hunger, satiety and nausea it is possible we may one day be able to manipulate this system in order to restore appetite or alleviate nausea in seriously ill people.

As we have learned from experiments in mice, it is difficult to design treatments to selectively target only a tiny fraction of cells in the brain, but as our understanding of these systems grows, this challenge may become surmountable.

Figure: The brain controls the balance between hunger and satiety in mammals. Left shows a diagram of a mouse (not to scale) while right shows a human (again, not to scale). Hunger originates in the hypothalamus (blue). AgRP cells in this brain area react to ghrelin released from the empty stomach into the circulation. When these AgRP cells are active there is a strong drive to seek and ingest food. Once food is ingested, endocrine cells lining the gut release hormones to stimulate the vagus nerve and signal satiety to the brainstem (orange). Resulting activation of cells in the brainstem reduces food intake by relaying information from the stomach to higher brain centres, including the hypothalamus.
Mouse cartoon edited from scidraw.io.



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