Orbiter (2008), carry diverse payloads that will ensure that the fundamental geophysical, geological, and geochemical data needed to make informed decisions about where to land on the Moon will be available within the current decade. In the nearly 40 years since the Apollo 11 landing enthralled and inspired humankind, scientific information gained in the interim can guide and inform future missions, contributing to a rich and sustained program of lunar discovery.

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13. Radar observations of the lunar polar regions yield conflicting interpretations regarding the presence of high-backscatter regions that could be indicative of water ice (*17*, *18*). Neutron spectroscopy from Lunar Prospector (*19*) shows the presence of hydrogen in both near-polar craters and various other parts of the Moon, and could correspond to either water or hydrogen nuclei implanted by the solar wind (*20*).
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BIOMEDICINE

Separation of Conjoined Hormones Yields Appetite Rivals

Ruben Nogueiras and Matthias Tschöp

When we refer to our "gut feelings," not many of us actually visualize how the gastrointestinal tract spills myriads of small peptide hormones into our bloodstream to activate defined circuits of the central nervous system. Nevertheless, that picture does reflect a current scientific concept called the "gut-brain axis." This model consists of a complex network of hormonal and neuronal signaling pathways that is believed to balance numerous homeostatic and behavioral processes (*1*, *2*). In this context, our stomach does not just collect, process, and transport ingested food, but it also represents a multileveled conversational partner of the central nervous system. A key element of this communication process is the hunger-inducing hormone ghrelin, which is believed to convey information about nutrient availability from the stomach to the brain (*3*, *4*).

Zhang and colleagues (*5*) now report on page 996 of this issue that ghrelin not only has a sibling derived from the same peptide precursor (preproghrelin), but also that this new ghrelin-associated peptide behaves as a physiological opponent of ghrelin. Guided by bioinformatics-based predictions for typical enzymatic cleavage sites, they identified a 23–amino acid region of preproghrelin that is highly conserved across species, suggesting a relevant biological function. The authors purified a secreted peptide of the predicted size and sequence from rat stomach tissue and also detected it in rat blood. Similar to ghrelin, which requires posttranslational modification close to its amino terminus by acylation (*6*), the biological activity of the ghrelin-associated peptide also depends on modification, but by much more common amidation at its carboxyl terminus.

The surprising finding is the pharmacological effects of the newly identified peptide in comparison with the known actions of ghrelin. Whereas ghrelin increases food intake and body weight (*7*), the ghrelin-associated peptide decreases food intake and body weight gain in rodents. Moreover, Zhang *et al.* observed that the new peptide decelerates gastric emptying and decreases intestinal contractility in mice, both of which counteract the well-defined effects of ghrelin (*8*). Through a targeted screen of mammalian orphan receptors and subsequent analyses in cultured mammalian cells, Zhang *et al.* show that the ghrelin-associated peptide binds to and activates the orphan receptor GPR39 (*9*). This G protein–coupled receptor has been mapped to human chromosome 2 and is expressed in multiple tissues, including the stomach, intestine, and hypothalamus. This localization is consistent with a role in energy balance regulation (*10*). GPR39 is a member of a family that includes the receptors for ghrelin and motilin, another gastrointestinal hormone that stimulates food intake, gastric emptying, and gut motility (*9*, *11*). These facts support a somewhat counterintuitive, but nevertheless intriguing, relationship between ghrelin and the ghrelin-associated peptide.

To denote its anorexigenic actions, Zhang and colleagues named this new gastric hormone obestatin (from the Latin term *obedere*, meaning to "devour").

THE GHRELIN–MOTILIN RECEPTOR FAMILY MODULATES APPETITE AND GASTROINTESTINAL MOTILITY

Ligands	Receptors	Food intake	Gastric emptying
Motilin	Motilin-R (GPR38)	↑	↑
Neuromedin U	Neuromedin-R1 (GPR66), -R2	↓	↓
Neurotensin	Neurotensin-R1, -R2, -R3	↓	↓
Ghrelin	GHS-R	↑	↑
Obestatin	GPR39	↓	↓

The ghrelin-motilin receptor family and their ligands. Each of these gastrointestinal hormones acts on a specific G protein–coupled receptor from the same family to affect food intake and gastrointestinal motility (*9*–*11*). Similar dual effects on satiety and gastrointestinal motility are known for glucagon-like peptide 1, cholecystokinine, or peptide YY. Collectively, these peptides may serve to couple meal termination with inhibition of upper gastrointestinal function to prevent malabsorption and postprandial metabolic disturbances (*1*, *2*, *8*).

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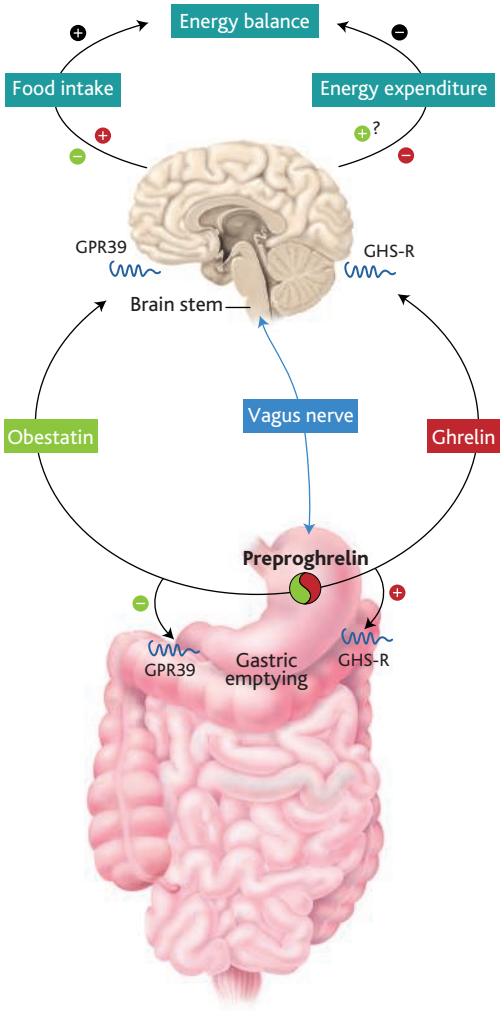
Inevitably, the terms "obesity" and "statins," a class of lipid-lowering drugs, come to mind. However, obestatin has not been tested in animal models of obesity and there is no evidence for a lipid-lowering effect. Furthermore, even its effect on body weight appears to be very subtle. The failure of obestatin treatment to decrease leptin levels in mice may indicate lack of lipolytic potency. Effects of obestatin on food intake regulation following administration to peripheral circulation or directly into the brain of mice suggest the typical action profile of a gastrointestinal satiety hormone. However, it is possible that obestatin may simply suppress appetite by triggering nausea or visceral illness. Recent examples have emphasized the importance of excluding nonspecific appetite suppression when examining anti-obesity drug candidates (*12*). Furthermore, despite sequence homologies between rodent and human obestatin (87%) and GPR39 (93%) sequences (*5*, *9*), data from rodents cannot always be translated to humans, where the effects of obestatin have yet to be determined.

Another concern regarding a role for obestatin in energy balance regulation arises from its quantification in blood. Although Zhang *et al*. confirmed earlier findings that the level of plasma ghrelin increases upon fasting and decreases following nutrient ingestion (*5*, *11*), they did not observe any changes in circulating obestatin upon fasting or feeding in rodents. Detection methods for differentiating between circulating amidated and nonamidated obestatin are not yet available, but could still reveal an association with nutrient availability. Nevertheless, total plasma obestatin generally appears to be a fraction of the level of plasma ghrelin. Should hormones derived from the same prepropeptide not circulate in an equimolar ratio?

Another peptide precursor that gives birth to antipodal regulators of food intake may provide some answers. The neuropeptide proopiomelanocortin is cleaved into several active fragments that include the appetite-suppressing α- and β melanocyte–stimulating hormones (α-, β-MSH) and the appetite-stimulating hormone β-endorphin (*13*). Tissue-specific enzymes determine which of these are generated. A similar scenario could determine how and where preproghrelin is fragmented into bioactive peptides. An earlier study postulated one other circulating preproghrelin fragment, a 13–amino acid peptide called C-ghrelin (*14*). In addition, turnover rates of ghrelin and obestatin may differ appreciably, according to their acylation or amidation rates, which again would be a parallel to the acetylation of the proopiomelanocortin derivative α-MSH (*15*). Dissecting the posttranslational cleavage, activation, or degradation processes of peptide hormones may reveal elegant enzymatic drug targets: Simultaneous activation of an agonist and deactivation of its endogenous functional antagonist could provide a powerful strategy for homeostatic control.

If obestatin lives up to its name as a circulating hormone with a physiologically relevant anorectic as well as an obesity-preventing function, the puzzling discrepancy between the very mild phenotype of mice lacking ghrelin (*16*, *17*) and the unsurpassed pharmacological effects of ghrelin on energy balance would receive an unexpected—but logical—explanation. The absence of an orexigenic hormone may be counterbalanced by the simultaneous deletion of an equally potent satiety factor. Targeted mouse mutagenesis is widely used as a strategy to unmask or validate the biological function of a gene product. An obvious abnormality of such a knockout mouse is usually interpreted as a reliable indicator of the target's physiological role. However, subtle or absent differences between gene-disrupted mice and their wild-type littermates are often regarded as evidence of negligible biological relevance. Such conclusions should be regarded with caution because developmental compensation may mask loss of function. However, rarely has such compensation been defined on a molecular level. The Zhang *et al*. findings caution against the interpretation of results based exclusively on gene disruption or messenger RNA quantification due to an additional level of complexity represented by posttranslational processing of proteins.

The discovery of obestatin leaves several questions unanswered. Why does a mouse that is deficient for the ghrelin receptor not exhibit an impressive phenotype? Should the absence of ghrelin action in the presence of an intact obestatin signaling pathway not generate a robust negative energy balance? Why does obestatin, unlike ghrelin, not affect growth hormone secretion from the pituitary gland, despite the presence of the obestatin receptor in this organ? Although the adversarial relationship between ghrelin and obestatin certainly is an important contribution to our understanding of body weight regulation, the search for a magic bullet against obesity is likely to continue—admittedly, a gut feeling.



The Yin and Yang personalities of ghrelin and obestatin. Both hormones derive from the same precursor protein and are predominantly secreted by the stomach and released into the blood. Each acts on a different receptor (GPR39 and GHS-R, as shown) and has an opposite effect on food intake, body weight, and gastrointestinal motility.

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