Prouroguanylin is a gastrointestinal paracrine signal and prohormone that is secreted after nutrient ingestion. In this issue of the *JCI*, Valentino et al. show that prouroguanylin is converted to uroguanylin in the CNS, which can activate guanylyl cyclase 2C (GUCY2C) receptors in the brain to reduce food intake in mice. This 16–amino acid residue peptide is a novel component of the gut-brain axis that represents a new and unique opportunity to manipulate gut-brain signaling for therapeutic intervention in obesity.
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Guanylin and uroguanylin: new gut hormones

Guanylin and uroguanylin are peptides of 15– and 16–amino acids in length, respectively. They are both secreted by intestinal epithelial cells as prohormones, which require enzymatic conversion into active hormones. To date, their function has been thought to be largely paracrine. Upon secretion into the lumen of the GI tract, they act on guanylyl cyclase 2C (GUCY2C) receptors on intestinal epithelial cells, increasing intracellular cyclic GMP (cGMP). Interestingly, GUCY2C receptors also are the target for heat-stable enterotoxins and upon activation can decrease intestinal fluid absorption, which can lead to diarrhea (6, 7).

cGMP, however, has also been implicated in the regulation of nutrient intake in invertebrate models (8). Therefore, Valentino and colleagues hypothesized that uroguanylin or guanylin might act as part of the gut-brain axis that regulates ingestion, energy homeostasis, and body weight (5). Consistent with this hypothesis, they found that mice engineered to globally lack the GUCY2C receptor carried more body fat as a direct result of increased food intake. These observations were further corroborated when they observed that systemic administration of a GUCY2C agonist reduced food intake in wild-type mice but not GUCY2C-deficient mice.

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resulted in a reduction of food intake (5), providing tangible proof for a unique new component of the gut-brain signaling axis that controls metabolic homeostasis.

**Uroguanylin: a GI hormone different than others?**

Several GI hormones depend on unique posttranslational modifications as critical determinants of their actions. For example, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) have a very short half-life, due to inactivation by the relatively ubiquitous protease dipeptidyl-peptidase 4 (DPP-4) (9). On the flip side of the DPP-4 equation is peptide YY (PYY). PYY is secreted as a 36–amino acid residue peptide and rapidly cleaved by DPP-4 into PYY3-36, which has been reported to control energy metabolism beyond classic endocrine mechanisms, such as modulating hormone secretion and receptor expression. It implies that, for reasons that are not obvious, it was advantageous for survival to find multiple alternative ways to fine tune the potency and the kinetics by which a complex array of endocrine signals could control energy balance.

**A road to new therapies?**

The bottom line of the work of Valentino et al. (5) is that it looks like uroguanylin should be added to the long list of hormones that appear to be part of how the gut convinces us to put our forks down and end a meal. A number of important questions will have to be answered by future studies, including whether the here reported functions of this hormone system are relevant in humans. It would also be important to find out whether there are particular nutrients that specifically trigger this pathway and whether its actions are modulated by bariatric surgery. Given the unique biology of uroguanylin, it may offer a number of potential possibilities for therapeutic intervention to help obese individuals lose weight. GUCY2C agonists could be developed that would suppress food intake, and one could design pharmacological strategies to increase the secretion of prouroguanylin or promote the conversion of the prohormone into uroguanylin within the key target regions in the CNS. Finally, we could take a page out of the uroguanylin playbook we have just been given by making prodrugs that are cleaved into GUCY2C agonists by the same enzymes that cleave prouroguanylin. Such a strategy would provide a method to directly deliver the drug to the key target tissue, while hopefully limiting the potential side effects associated with activating GUCY2C receptors in the GI tract. Successful targeting of this pathway for the development of novel therapeutics for obesity would likely depend to a considerable extent on the ability of the therapeutics to divorce the beneficial effects in the hypothalamus from an undesired impact on intestinal fluid absorption.

While the results of Valentino et al. (5) are extremely exciting and clinically significant, it is still too soon to declare victory in the fight to limit the obesity epidemic. There are several examples in which intriguing reports on novel peptide processing seemed to promise rapid breakthroughs.
The enteric nervous system (ENS) controls the gastrointestinal system. Enteric glia have long been regarded as the essential “glue” of the ENS. Now, however, two independent reports in this issue of the JCI provide compelling evidence that mouse enteric glia can also be neuronal precursors. These reports show that enteric glia give rise to neurons in vitro and that neurogenesis can be experimentally induced to occur in vivo in the adult mouse ENS. Unfortunately, glia do not constitutively replace neurons, and neurogenesis is not easily provoked. Although these new observations make it clear that clinical trials using glia to replace enteric neurons are more than premature, they are enticing for future research.

Behind an enteric neuron there may lie a glial cell

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It controls the gastrointestinal (GI) system and comprises a large number of neurons and glia that are organized into complex networks of interconnected ganglia distributed throughout the gut wall. Enteric neurons cluster into two plexi: the myenteric plexus, which is situated between the inner circular and outer longitudinal layers of the muscularis externa; and the submucosal plexus, which is located within the dense connective tissue between the muscularis externa and the mucosa.

One of the many functions of the GI system controlled by the ENS is motility, and thereby GI transit. As a result, aganglionosis of the bowel, whether congenital (as in Hirschsprung disease) or acquired (as in Chagas disease), leads to intestinal obstruction (2, 3). Nerve bundles, however, are present in the aganglionic segments of colon in individuals with Hirschsprung disease, meaning that nerves are not, by themselves, sufficient for GI transit (4). Nerve cell bodies and the complex microcircuits of the ENS, which uniquely enable it to control GI motility and secretion in the absence of CNS input, are required for normal GI tran-