*Nature Reviews Neuroscience* | AOP, published online 8 August 2012; doi:10.1038/nrn3322

METABOLISM

# Why high-protein diets work

PHOTODISC

> peptides derived from dietary proteins act as antagonists on μ-opioid receptors

Protein-rich diets are known to suppress appetite. Mithieux and colleagues now provide a mechanism for this well-known phenomenon by showing that peptides derived from dietary proteins act as antagonists on μ-opioid receptors (MORs) on neurons in the wall of the portal vein. The resulting signal to the brain promotes gluconeogenesis in the gut, which acts as a satiety signal to reduce food intake.

The authors had previously shown, in rodents, that the consumption of a protein-rich diet induces intestinal gluconeogenesis and that this phenomenon is required for the appetite-reducing effect of such a diet. In the new study, rats in which afferent nerves from the gut were inactivated through local periportal application of capsaicin showed no induction of the gluconeogenic enzymes glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) on a protein-rich diet, indicating that gut–brain communication is involved in the regulation of appetite by protein diets.

The authors assessed whether MORs are involved in this gut–brain communication because MORs are highly expressed in the small intestine and, in humans, MOR agonists and antagonists increase and decrease food intake, respectively. Infusion of MOR agonists and antagonists into the mesenteric vein of rats increased and decreased, respectively, intestinal G6Pase activity and PEPCK expression, but the infusions had no effects in rats in which the portal vein was denervated. MOR antagonist infusion induced expression of cFOS (a marker of neural activation) in the dorsal vagal complex (DVC) and parabrachial nucleus (PBN) — which receive input from the vagal nerve and spinal cord afferents, respectively — and in brain nuclei that receive input from these areas. There was no increase in cFOS expression in rats whose portal vein afferents had been inactivated with capsaicin or had received an MOR agonist. Thus, MOR antagonism in the portal vein activates brain areas via two neural pathways.

Does a protein-rich diet induce MOR antagonism? This possibility was suggested by the finding that infusion of an MOR agonist reversed the protein-rich-diet-induced increase in G6Pase and PEPCK expression in the gut. Dietary proteins are digested into oligopeptides, and infusion of a proteolytic digest or selected oligopeptides into the portal vein increased G6Pase activity in the gut. Furthermore, infusion of the oligopeptide Tyr-Ala induced cFOS expression in the DVC, PBN and their target areas. These effects were abolished after denervation of the periportal area. More direct evidence that oligopeptides act as MOR antagonists was provided in experiments in a neuroblastoma cell line. Here, Tyr-Ala and Gly-Gly competed with the synthetic MOR agonist DAMGO for binding to MORs. The authors further found that MOR agonists decreased and MOR antagonists increased cyclic AMP levels in the cells.

Lastly, the authors showed that infusion of oligopeptides or a proteolytic digest induced G6Pase activity in the jejunum in wild-type mice but not in mice lacking MOR. In addition, unlike wild-type mice, MOR-knockout mice did not permanently reduce their food intake after switching from a starch-enriched to a protein-rich diet. Moreover, wild-type mice infused with the MOR antagonist naloxone reduced their food intake by 15%, and this effect did not occur in mutant mice lacking intestinal G6Pase.

Thus, antagonism of intestinal MORs by food protein products activates gut–brain neural pathways and thereby induces intestinal gluconeogenesis — a process that underlies the satiating effects of food proteins.

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**ORIGINAL RESEARCH PAPER**
Duraffourd, C. *et al.* Mu-opioid receptors and dietary protein stimulate a gut-brain neural circuitry limiting food intake. *Cell* **150**, 377–388 (2012)