

Ghrelin: A Gastrointestinal and Hypothalamic Peptide Affecting Hormone Secretion and Fat Metabolism

Ghrelin, a 28 amino acid peptide synthesized by the gastrointestinal tracts and hypothalamic arcuate nuclei of rodents and humans, is the natural ligand for the GH secretagogue receptor (GHS-R). Since synthetic GH secretagogues increase weight in experimental animals, both groups of investigators studied the effect of ghrelin on feeding and weight gain in intact adult male rats.

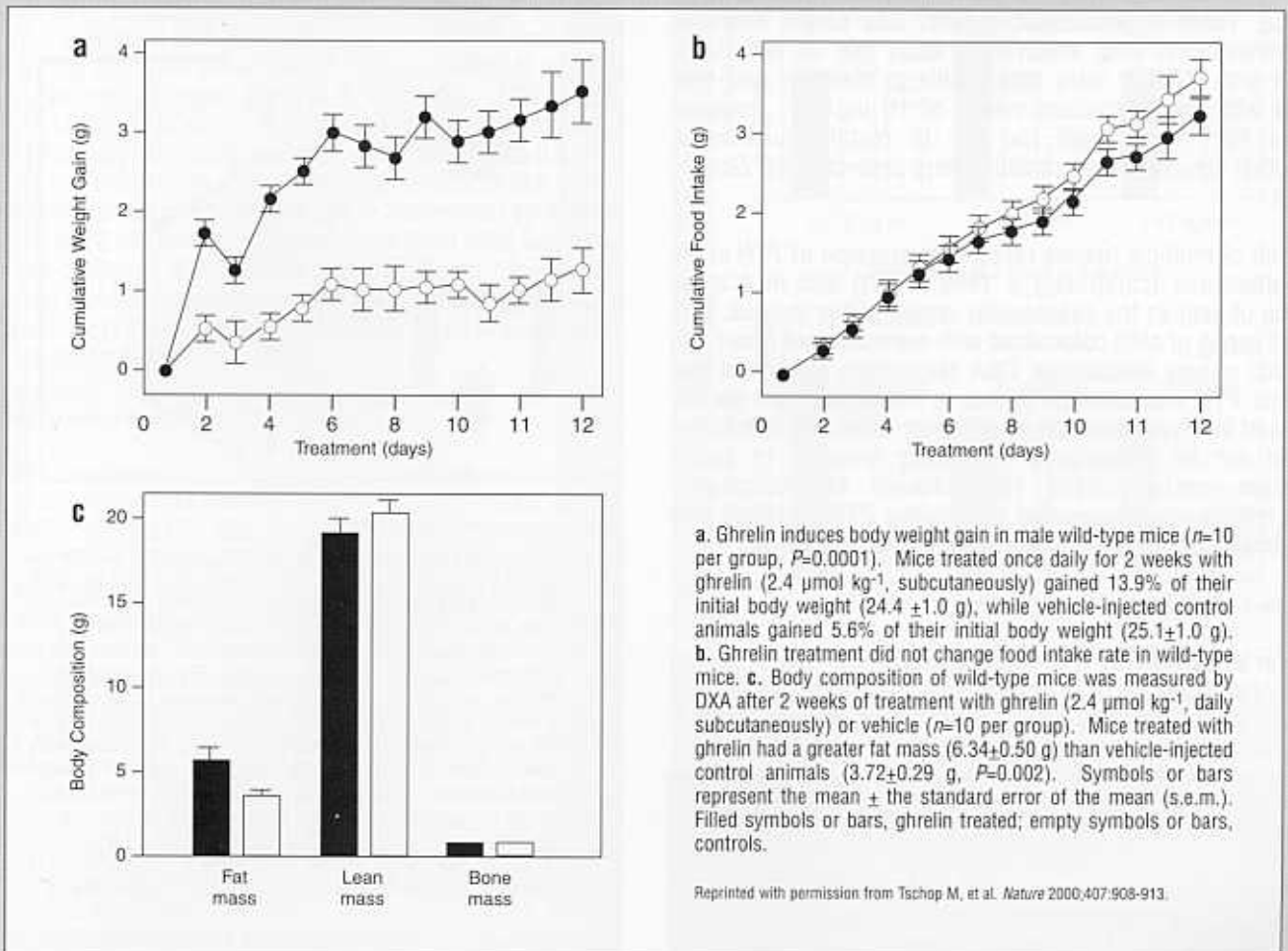
Tschop et al demonstrate that once-daily *subcutaneous administration* of synthetic rat ghrelin ($2.4 \mu\text{mol/kg/d}$; MW 3313.85) for 14 days doubled the rate of weight gain without inducing hyperphagia and increasing food intake; the increase in weight was due to accumulation of fat without alteration in lean body mass or bone density (see Figure). The isolated increase in fat was related to an increase in respiratory quotient (RQ) of ghrelin-treated rats, indicating that this peptide stimu-

lated carbohydrate utilization while decreasing the rate of fat utilization. Ghrelin did not increase the rate of energy expenditure or the motor activity of recipients. The mechanism by which ghrelin enhanced fat accumulation was not due to its GH-releasing effects as GH was lipolytic in control animals and was similarly effective in GH-deficient dwarf rats and wild-type animals. Its effect was not mediated by the orexigenic neuropeptide Y (NPY), as ghrelin stimulated fat accumulation in *NPY*^{-/-} animals. *Continuous intracerebroventricular (ICV) infusion* of ghrelin for 7 days enhanced weight gain in wild-type rats and increased their RQ and food intake. Tschop et al also observed that fasting increased and feeding decreased serum concentrations of ghrelin in these animals.

Wren et al report that *intraperitoneal administration* of ghrelin (3, 10, and 30 nmol) *acutely* increased food intake only in the

Figure

Ghrelin-Stimulated Adiposity in Mice



first hour after injection; its *ICV injection* (0.3, 1.0, and 3.0 nmol) acutely increased food intake, with maximum intake in the first hour after injection but with a duration of effect of 24 hours. *ICV ghrelin* increased serum concentrations of GH and corticotropin and decreased those of thyrotropin.

Tschop M, et al. Ghrelin induces adiposity in rodents. *Nature* 2000;407:908-913.

Wren AM, et al. The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. *Endocrinology* 2000;141:4325-4328.

Editor's comment: Ghrelin is now added to the complex of neuroendocrine and transcription factors that affect feeding behavior and energy metabolism, including peroxisome-proliferator-activated receptor γ 2, leptin, NPY, melanin-concentrating hormone, pro-opiomelanocortin and melanocortin, the agouti protein, and so forth, and provides another site at which weight-control pharmacologic therapeutics may be targeted. The mechanism by which ghrelin selectively spares fat metabolism, thus increasing its accumulation, is unknown at present. Increased RQ without an increase in energy intake might be due to decreased activity of the sympathetic nervous system or to hypothalamic stimulation. The bioeffects of ghrelin are uniquely suited to enhance the anabolic effects of GH, which is maximally effective in the well-nourished recipient.

Date et al have identified the rat and human gastrointestinal X/A-like cell of the oxyntic gland as the site of synthesis of ghrelin; these cells are located primarily in the fundus of the stomach. Apparently, more than 18 cell types that synthesize

endocrine-like hormones have been identified to date in the gastrointestinal tract. There are 4 distinct endocrine cells, each synthesizing a specific product in the oxyntic mucosa of the rat: ECL-histamine; D-somatostatin; enterochromaffin-serotonin; and X/A-like-ghrelin.

Allen W. Root, MD

Date Y, et al. Ghrelin, a novel growth hormone-releasing acetylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology* 2000;141:4255-4261.

Kojima M, et al. Ghrelin is a novel growth hormone-acetylated peptide from stomach. *Nature* 1999;402:656-660.

2nd Editor's comment: A third article, by Nakazato et al in (*Nature* 2001;409:194) supplements the above. Rats were injected with ghrelin in the cerebral ventricles, which produced significantly greater weight gain than was observed in controls infused with saline. The authors demonstrated that the increased eating observed was not related to GH secretion. However, ghrelin stimulates not only food intake but also GH secretion. These mechanisms are not interdependent. However, in the normal creature with the capability to respond in a dual manner to ghrelin, the growth action of GH may be enhanced by the increased food ingestion. These early reports are not necessarily synchronous. Confirming and additional studies are needed and undoubtedly clarification will occur.

Robert M. Blizzard, MD

Autosomal Dominant Hypophosphataemic Rickets Is Associated With Mutations in *FGF23*

Clinical and biochemical manifestations of autosomal dominant hypophosphatemic rickets (ADHR) are same as to those of X-linked hypophosphatemic rickets (XHR), ie, deformities of the lower extremities, short stature, rickets, hypophosphatemia. XHR has been attributed to loss-of-function mutations in *PHEX*, a gene encoding an endopeptidase that may serve to activate or degrade an as yet uncharacterized protein involved in phosphate transport termed "phosphatonin."

Studies of families with multiple members affected with ADHR by collaborating investigators of the ADHR Consortium linked this disorder to chromosome 12p13.3. Utilizing publicly available genomic sequences from chromosome 12p13, the authors found 37 genes in this region, 13 of which were previously unrecognized. With more discriminating linkage analysis, a segment of chromosome 12p13.3 encoding 11 genes was identified; screening of these genes for mutations revealed 1 with homology to those encoding the fibroblast growth factor (FGF) family that was mutated in patients with ADHR. Previously undescribed, *FGF23* has 3 exons with 1612 bp encoding a peptide with 251 amino acids that has a similar 3-dimensional configuration and 25% to 36% homology with other members of the FGF family; *FGF23* is the largest FGF described to date. In subjects with ADHR, mutations in *FGF23* that segregated with the disease include: NT 527G→A → Arg176Gln; NT 535C→T → Arg179Trp; and NT 536G→A → Arg179Gln.

These changes were not polymorphisms. No mutations of *FGF23* were detected in patients with hypophosphatemic bone disease or in subjects with apparent XHR with normal *PHEX* analyses. In normal human tissues, *FGF23* was expressed predominantly in heart, liver, and thyroid/parathyroid tissue. The physiologic function of *FGF23* was not identified in this report. The investigators speculate that it might be related to or perhaps even be the elusive phosphaturic substance "phosphatonin."

ADHR Consortium. *Nat Genet* 2000;26:345-348.

Editor's comment: This work illustrates the treasure trove of genetic data already available from the Human Genome Project waiting to be mined for relevance to human physiology and pathophysiology. *PHEX* is expressed by osteoblasts, and it has been hypothesized that "phosphatonin" also may be synthesized by these cells. In normal mouse embryos, the murine homologue *Fgf23* maps to chromosome 6. The present investigators were unable to demonstrate expression of *Fgf23* in the tibiae of embryonic mice, perhaps suggesting that *FGF23* is not "phosphatonin."

Allen W. Root, MD

Ecarot B, Desbarats M. 1,25-(OH)₂D₃ down-regulates expression of *PHEX*, a marker of the mature osteoblast. *Endocrinology* 1999;140:1192-1199.