Nutritional hormones and the entero-osseous axis

C.M. Isales and M. Hamrick

Departments of Orthopedic Surgery and Cell Biology, Medical College of Georgia, Augusta, GA, USA

Keywords: GIP, GLP-2, Incretin, Osteoblast, Osteoclast

Enteric hormones represent the mechanism by which ingested nutrients are distributed to the various tissues in the body, so as to maximize their utilization. These hormones play a key role in regulating the energy balance. Nutritional hormones are also known to be important in bone turnover as evidenced by the fact that as soon as a meal is ingested, bone breakdown is suppressed1,3. Many nutrition-related hormones have been shown to have effects on bone turnover through in vitro or in vivo studies including: (A) Intestinal Hormones: (1) Glucose-dependent insulinotropic peptide (GIP); (2) Ghrelin and (3) Glucagon-like peptide (GLP) 2; (B) Pancreatic Hormones: (1) Insulin (2) Amylin (3) Adrenomedullin and (4) Preptin (C) Adipocyte-secreted Hormones: (1) Leptin (2) Adiponectin and (3) Resistin, as recently reviewed by Clowes et al.4 and Reid et al.5.

As a group however, the incretin hormones (GLP-1; GLP-2 and GIP) have the strongest evidence for affecting post-prandial bone turnover. GLP-1 is a 37-amino-acid peptide secreted from L-cells in the small intestine in response to nutrients and potentiates insulin secretion. We have previously demonstrated that GLP-1 receptors are not present in either osteoblasts or osteoclasts. This finding has been confirmed by others; although recently, GLP-1 receptor knockout mice have been shown to have increased bone breakdown suggesting that GLP-1 can also indirectly modulate bone turnover4.

GLP-2 is a 33 amino acid peptide expressed mainly in the L-cells of the small intestine. GLP-2 is secreted in response to nutrient ingestion and its physiologic function appears to be to regulate intestinal motility and stimulate intestinal cell growth, and it is also anti-apoptotic7. GLP-2 receptors are expressed in osteoclasts and administration of GLP-2 to human subjects inhibits bone resorption and increases bone mass3,8,9. GIP was first identified in the 1970s as a hormone secreted by cells in the enteric endocrine system. Because this 42-amino-acid peptide was found to inhibit gastric acid secretion, it was initially named gastric-inhibitory peptide (GIP)10. Subsequently, GIP was shown in the presence of glucose to stimulate insulin secretion from pancreatic β cells11. Because of GIP’s role in the regulation of insulin secretion, its name was changed to glucose-dependent insulinotropic peptide (GIP)12-16. GIP is secreted from endocrine cells (K cells) in the proximal small intestine 17. GIP secretion from the enteroendocrine cells appears to be regulated both by enteric neurons in the small intestine (bombesin) and direct stimulation by nutrients18.

Since multiple enteric hormones have been shown to affect bone turnover, we first screened osteoblast and osteoclast cell lines for the presence of all the members of the seven transmembrane domain G-protein coupled family of receptors (GPCR).

An osteoblastic cell lines (MC3T3, a mouse osteoblast cell line) and an osteoclastic cell line (RAW 264.7, a mouse macrophage cell line) were screened for expression of all 15 members of this receptor family including: (A) Intestinal Hormones: (1) Glucose-dependent insulinotropic peptide (GIP); (2) Ghrelin and (3) Glucagon-like peptide (GLP) 2; (B) Pancreatic Hormones: (1) Insulin (2) Amylin (3) Adrenomedullin and (4) Preptin (C) Adipocyte-secreted Hormones: (1) Leptin (2) Adiponectin and (3) Resistin, as recently reviewed by Clowes et al.4 and Reid et al.5.

The authors have no conflict of interest.

Corresponding author: Carlos Isales, M.D., Department of Internal Medicine, Medical College of Georgia, 1120 15th Street, Augusta, GA 30912, USA
E-mail: cisales@mcg.edu
Accepted 11 August 2008
PTH do not rise after a meal) and act within the time period observed for suppression of the markers of bone breakdown (i.e., calcitonin rises only in response to calcium in diet), only the receptors for GIP and GLP-2 are expressed in osteoclasts. These data would suggest that GLP-2 acts mainly as an antiresorptive hormone while GIP can act both as an antiresorptive and anabolic hormone.

Data from our laboratory has shown that GIP is in fact involved in normal bone turnover. Specifically, our GIP data in vitro demonstrates: (1) GIP receptors are present in both osteoblasts and osteoclasts; (2) in osteoblasts, GIP increases collagen type I synthesis and increases alkaline phosphatase activity; (3) in osteoblasts, GIP stimulates proliferation and actions as an anti-apoptotic agent; and (4) in osteoclasts, GIP inhibits PTH-induced long bone resorption and decreases osteoclastic resorption pit depth. In vivo studies, (5) GIP receptor knockout mice have a lower bone mass, decreased serum markers of bone formation and increased markers of bone breakdown and (6) GIP-overexpressing transgenic mice have increased bone mass.

Taken together, data from our studies and those of other investigators suggest that the intestine (and the hormones produced there) is a major regulator/co-ordinator of nutrient delivery to the bone, and this gut-bone cross-talk (which we have called the "entero-osseous axis") is an important determinant, and is a reflection of, the body's energy balance.

References

Peptides 2003;24:611-6.


