

Gastric leptin- An exocrine secretion regulating food intake

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Leptin plays important roles on the nutritional and energy status of the organism. It is secreted in an endocrine way by the adipose tissue and in an exocrine way by the gastric mucosa. Gastric epithelial chief cells express and secrete leptin into the gastric lumen through their RER-Golgi-secretory granules regulated pathway together with classical gastric enzymes such as lipase and pepsinogen. Upon food intake, the content of the granules is released into the gastric lumen. Leptin resists the drastic proteolytic conditions of the gastric juice thanks to its binding to the soluble isoform of the leptin receptor. The formation of the leptin-leptin receptor complex takes place in the secretory granule prior release. Once secreted, this complex crosses the pyloric sphincter reaching the duodenal lumen. Transmembrane leptin receptors lining the intestinal cells apical microvilli bind the luminal leptin and internalize it through clathrin-coated vesicles. Leptin regulates absorption of nutrients and participates in the intestinal mucosa integrity. However some of the internalized leptin is transported through transcytosis to the baso-lateral membrane to be released into the interstitial space to reach the blood circulation and the hypothalamic target cells. Since leptin is normally present in the gastric lumen and reaches the circulation through transcytosis across the intestinal cells, we designed an oral formulation of leptin that by using the same pathway can reach the blood circulation. Such an oral formulation of leptin is able to control food intake by various normal animal models and restores leptin levels in animal models expressing leptin deficiency.

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