Gastric mammalian target of rapamycin signaling, hormone production and energy metabolism

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Abstract
The obesity epidemic imposes a significant health burden on human beings. Current understanding of the mechanisms underlying the development of obesity is incomplete and contemporary treatment is often ineffective. Gastrointestinal hormones are important regulators of food intake and energy metabolism. Previous studies indicate that the mammalian target of rapamycin signaling pathway in the gastric mucosa is crucially involved in fuel sensing in the gastrointestinal tract and plays a critical role in the coordination of nutrient availability and ingestive behavior via the production of gastric hormones. As an important component of the brain-gut axis regulating food intake and energy homeostasis, energy sensing in the gastrointestinal tract may provide a novel insight into our understanding of the precise coordination between the organism and cellular energy state.

Key words: Gastric mammalian target of rapamycin; Hormones; Energy metabolism

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INTRODUCTION
Food intake and energy metabolism are regulated by the reciprocal actions of a group of anorexigenic peptides, which include leptin, insulin, cholecystokinin, peptide YY and glucagon-like peptide, and by the actions of a group of orexigenic peptides, including ghrelin. The majority of these hormones are secreted by endocrine cells scattered throughout the gastrointestinal tract[1]. All these hormones are proposed to modulate the activity of the energy metabolism center within the hypothalamus, ultimately leading to a change in feeding behavior and the control of metabolic homeostasis[2]. While many studies reveal that nutrient sensing molecules within the hypothalamic neurons are critical in the control of energy homeostasis[3] and defects in fuel sensing at the hypothalamic cellular level may lead to energy imbalance at the organism level and to the development of obesity[4], a recent study suggests that there also exists a fuel sensing mechanism in the gastric mucosa[5]. This finding suggests that the
interaction between peripheral and central fuel sensing mechanisms is a crucial feature of feeding behavior and energy homeostasis[9]. The peripheral fuel sensing mechanism in the gastric mucosa may function to regulate the production of gastric hormones and therefore contribute to the modulation of energy metabolism.

**FUEL SENSING MECHANISM**

Obesity is defined as the condition in which energy intake consistently outpaces energy expenditure leading to the accumulation of excess fat to an extent that health is negatively affected. The development of obesity is linked to small but cumulative discrepancies between caloric intake and energy expenditure[8]. Under normal conditions, balance in energy metabolism is maintained by a precise regulation of cellular activity in multiple organs that matches nutrient supply at the organism level[6]. The link between the energy status of individual cells and the overall energy balance of the entire organism is complex and remains largely unknown. Many studies have identified the hypothalamus as a critical organ for integrating intracellular metabolic processes with energy homeostasis at the organism level[7], adjusting food intake to match the level of overall cellular activity. Recent investigations have identified 5’ AMP-activated protein kinase (AMPK) as key fuel sensors in hypothalamic neurons. AMPK is a serine-threonine protein kinase which serves as a cellular fuel sensor to protect cell viability in response to ATP depletion[9]. AMPK is tightly regulated, monitoring changes in the cellular ratio of adenosine monophosphate (AMP) and adenosine triphosphate (ATP). Recent studies have suggested that AMPK in the hypothalamus regulates energy metabolism by integrating inputs from multiple peptide hormones, neurotransmitters and nutrients. Alteration of hypothalamic AMPK activity leads to changes in food intake and body weight[11-13]. mTOR, a highly conserved serine-threonine kinase, has been reported to serve as an intracellular ATP sensor. In vitro studies have demonstrated that cellular levels of ATP regulate mTOR signaling[14]. Aberrant mTOR activity is linked to the development of cancer, diabetes and obesity[13]. Significant elevation of mTOR signaling has been observed in liver and skeletal muscle of insulin-resistant obese rats maintained on a high fat diet[10]. In contrast, absence of the mTOR downstream target, S6 kinase 1, protects against diet-induced obesity and improves insulin sensitivity in mice[17]. mTOR signaling in hypothalamic neurons is involved in neural sensing of nutrient availability and regulates food intake and energy balance[9]. These observations suggest that mTOR plays an important role in central neuronal control of nutrient intake and energy balance. Further studies indicate that mTOR signaling is a potential downstream pathway for food intake regulation in response to hypothalamic AMPK[8], likely through the mediation of tuberous sclerosis complex 2, a known inhibitor of mTOR signaling[9]. Thus, food intake and nutrient metabolism may be coordinately regulated by linking AMPK and mTOR signaling pathways in the hypothalamus. These observations have motivated extensive studies of hypothalamic fuel sensing mechanisms and hypothalamic regulation of energy metabolism[7]. In contrast, virtually no attention has been focused on fuel sensing by the gastrointestinal tract, despite its critical role in the regulation of food intake.

**GASTRIC mTOR IS A FUEL SENSOR**

**INTEGRATING FUEL SUPPLY WITH HORMONE PRODUCTION**

A series of studies have identified mTOR as a potential candidate of fuel sensor in the gastric mucosa because of its expression in a distinct group of the gastric endocrine cells, its reciprocal relationship with energy status and its role in the regulation of gastric hormone production[6,15,20].

**Co-localization of mTOR signaling molecules in gastric neuroendocrine cells**

Chromogranin A is a widely recognized marker of neuroendocrine cells, including those of the stomach, large and small intestine, adrenal medulla and pancreatic islets[21]. It is also an excellent marker for neuroendocrine tumors[22]. In the gastric fundus, the active forms of mTOR signaling molecules express in cells located in the basal one third of the gastric mucosa. One third of chromogranin A-immunoreactive cells express phospho-S6K1, the downstream target of mTOR. The majority of the mTOR positive endocrine cells are ghrelin positive with a small fraction of cells stained positive for gastrin immunoreactivity. No mTOR signaling molecule is located within somatostatin immunoreactive cells[23]. These studies suggest that mTOR signaling may selectively influence the function of a subpopulation of gastric endocrine cells.

**A reciprocal relationship between gastric mTOR signaling and energy status at the organism level**

Gastric mTOR signaling also senses the body energy status. Gastric mTOR activity decreases in 48 h fasted mice relative to fed animals. In contrast, there is a significant increase in gastric phospho-mTOR (Ser2448) and phospho-S6 (Ser235/236) expression in obese mice relative to lean animals[16]. Gastric mTOR signaling is therefore reciprocally related with the short- and long-term changes in nutritional status at the organism level.

**Gastric mTOR and hormone production**

Numerous peptides are synthesized and released from distinct populations of secretory neuroendocrine cells throughout the gastrointestinal tract[24]. Their roles in the regulation of gastrointestinal function have been well characterized for many years and it is now becoming evident that they also modulate feeding behavior and energy metabolism via distinct mechanisms. Major neuroendocrine products have been identified as gastrin in G
cells, histamine and uroguanylin in enterochromaffin-like (ECL) cells, somatostatin in D cells, serotonin in EC cells and ghrelin in X/A-like cells[23,24]. Hormones secreted from gastric endocrine cells bind to receptors located in the hypothalamus to regulate food intake and energy metabolism[25]. The fuel sensing mechanism is critical for the regulation of gastrointestinal hormone synthesis and secretion and therefore provides a fine tuning for the peripheral and central control of feeding behavior and energy homeostasis.

**Ghrelin:** In 1999, ghrelin was isolated from the human and rat stomach as the endogenous ligand for the growth hormone secretagogue-receptor (GHS-R)[26]; it is synthesized mainly by X/A-like cells in the gastric mucosa and secreted into the circulation[27]. Several molecular forms of ghrelin are found in the stomach and circulation: the 28 amino acid ghrelin with n-octanoylated serine in position 3; des-acyl ghrelin, an identical peptide in which the third amino acid serine is not acylated; and the 27 amino acid des-gluatnine 14 ghrelin produced by alternative splicing of the ghrelin gene[28]. Another putative proghrelin peptide, termed “obestatin”, has been proposed[29] but biochemical and functional evidence supporting its existence has not been forthcoming. Octanoylation is necessary for ghrelin to bind with its receptor, GHS-R. Ghrelin-O-acyltransferase, the enzyme responsible for ghrelin acylation, has been recently characterized as a member of the Membrane Bound O-Acyltransferases family[29,30]. Ghrelin has been reported to exercise a broad array of functions including control of food intake[31] and glucose metabolism[32]. Exogenous ghrelin induces adiposity in rodents by stimulating an acute increase in food intake, as well as a reduction in fat utilization[33]. Blocking the action of ghrelin by either its receptor antagonism[34] or interfering with its availability for its receptor by neutralizing antibodies[35] or Spiegelmer RNA[36] have been reported to show some effects on reduction of food intake and body weight, although the immunization against ghrelin fails to cause long-term body weight reduction. Ghrelin exerts its orexigenic effect via a mechanism involving the central nervous system; at least part of the orexigenic effect of ghrelin is mediated by up-regulating the genes encoding orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP)[36] in the hypothalamus. During fasting, ghrelin secretion increases[37]. Conversely, plasma ghrelin concentration decreases in most obese subjects[38] except in Prader-Willi syndrome[39]. Ghrelin and its receptor are expressed in human and rat pancreatic islets[40]. Ghrelin inhibits glucose stimulated insulin secretion in a dose-dependent manner in vitro[41]. Intravenous ghrelin injection decreases plasma insulin and increases plasma glucose levels, likely by inhibition of insulin secretion[41]. Absence of ghrelin in ob/ob mice lowers blood glucose substantially even though it does not decrease food intake or body weight[42].

The secretion of ghrelin is tightly coupled to the fasting or fed state[43]. While it is presumed that precise control in the production and secretion of ghrelin is critical for the maintenance of energy balance, the molecular mechanisms by which ghrelin producing cells modulate transcription and translation of ghrelin to match overall energy status remain largely unknown. A recent study has demonstrated that gastric mTOR is a critical molecule coordinating the ghrelin production with energy supply levels. In gastric mucosa, mTOR signaling molecules are located mainly in the ghrelin-positive cells. More than 90% of ghrelin-positive cells stain positively for mTOR signaling molecules. There exists a reciprocal relationship between gastric mTOR signaling and the expression and secretion of ghrelin during changes in energy status. Inhibition of gastric mTOR signaling increases expression of gastric ghrelin and circulating ghrelin. Conversely, activation of gastric mTOR signaling attenuates the expression and secretion of ghrelin. All these data support the concept that gastric mTOR activity is reciprocally linked to the production of ghrelin[44].

**Gastrin:** Gastrin is an acid secretagogue peptide discovered by Edkins[45] in 1906. Gastrin stimulation of ECL cells results in the increased synthesis and release of histamine, which then induces acid secretion by binding to the H receptors located on parietal cells[46]. Other major physiological functions of gastrin on the gastrointestinal tract includes functioning as a growth/differentiation factor[47]. Gastrin release is stimulated by vagal impulses during the cephalic phase and by intramural neural reflexes as well as by the presence of food constituent in the gastric lumen during the gastric phase of acid secretion[48]. Increased production of hydrochloric acid lowers intragastric pH and inhibits further secretion of gastrin[49]. Gastric mTOR signaling may be involved in the regulation of gastrin synthesis and secretion in a proportion of gastric G cells. Only 1/3 of gastrin cells contain mTOR signaling molecules, suggesting that regulation of gastrin synthesis and secretion may involve multiple mechanisms[50].

**Somatostatin:** Somatostatin was originally isolated as a hypothalamic somatotropin-release inhibiting factor[51] and was soon found to potently inhibit the secretion of multiple hormones, including gastrin[52]. However, production of somatostatin appears not to be affected by gastric mTOR. No mTOR activity is detected in somatostatin positive cells. Furthermore, inhibition of gastric mTOR signaling by rapamycin demonstrates no effect on the synthesis and secretion of somatostatin[53].

All of this evidence supports that mTOR signaling selectively modulates the production of gastric hormones. The differential regulation of gastric hormones by mTOR signaling may provide an alternative strategy for the development of novel therapeutics for obesity and other disorders of energy metabolism.

**GASTRIC FUEL SENSING AND ENERGY METABOLISM**

In the central nervous system, fuel substrates such as glu-
cose, fatty acids and amino acids, or hormones including leptin and insulin, act on the hypothalamic neurons to inform the energy metabolism regulating center of the energy status\textsuperscript{[8]}. Specific populations of “glucosesensing” neurons have been identified\textsuperscript{[31]}. In the hypothalamic arcuate nucleus, pro-opiomelanocortin neuron is the glucose-excited neuron, while NPY neuron is inhibited by glucose. These neurons form the neuronal circuits to monitor and integrate the quantitative and temporal changes in glucose concentration\textsuperscript{[31]}. By regulating their activity and neurotransmitter release, these neurons coordinate the central glucose level with the peripheral glucose production and utilization to maintain the glucose homeostasis\textsuperscript{[31,32]}.

How hypothalamic neurons sense the energy supply is being actively explored. Studies by Cota et al\textsuperscript{[9]} strongly support the notion that mTOR is a critical intracellular molecule within hypothalamic neurons to coordinate the energy supply with food intake and energy metabolism. Although mTOR and S6K1 are widely expressed in a variety of tissues within the CNS, the phosphorylated form of these two kinases is abundantly localized in the hypothalamus, particularly in the NPY/AgRP neurons. Activity of the mTOR pathway in the hypothalamus is tightly linked with energy supply. mTOR activity decreases during fasting and its activity conversely increases during re-feeding. Central administration of leucine, a branch chained amino acid, decreases food intake and body weight by activation of the hypothalamic mTOR signaling. Leptin stimulates hypothalamic mTOR activity and inhibition of mTOR signaling blunts the anorectic effect of leptin\textsuperscript{[33]}. Hypothalamic specific expression of dominant negative S6K results in an increase in food intake, whereas expression of constitutively active S6K decreases food intake\textsuperscript{[34]}. These observations suggest that mTOR is a critical fuel sensor in the hypothalamus.

Inhibition of mTOR signaling by rapamycin has been demonstrated to increase food intake. Such an orexigenic effect of rapamycin may be mediated by ghrelin. Intraperitoneal injection of rapamycin stimulates ghrelin secretion and expression. Ghrelin receptor antagonist D-Lys-3-GH-releasing peptide-6 or ghrelin receptor deletion abolishes the rapamycin-induced increment in food intake despite that plasma ghrelin remains elevated\textsuperscript{[35]}. Together with the observation that mTOR is selectively expressed in a subpopulation of gastric endocrine cells and its activity is reciprocally related with the energy level, we propose that gastric mTOR is a peripheral fuel sensor integrating the energy supply with the food intake and energy metabolism by alteration of ghrelin production. Defining the mTOR signaling pathway to inhibit the production of acyl ghrelin, the active form of ghrelin, would shift therapeutic focus to gastric targets.

CONCLUSION
The fuel sensing mechanism in the central nervous system is critical for energy homeostasis. However, the anatomical structure and location of the hypothalamus pose significant hurdles for therapy targeting this organ. Searching for peripheral targets is appealing. Novel evidence suggests that mTOR is a critical regulatory molecule in gastric ghrelin cells and that its activity is linked to energy supply through modulation of the production of acyl ghrelin. Further studies will aim to advance our understanding of intracellular processes in the production of ghrelin and to provide new information on the integration of cellular activities of gastric endocrine cells with overall nutrient availability. Results of these new investigations will yield new insights relevant to treatment strategies for human obesity.

REFERENCES
1. Cummings DE, Overduin J. Gastrointestinal regulation of food intake. J Clin Invest 2007; 117: 13-23
2. Havel PJ. Peripheral signals conveying metabolic information to the brain short-term and long-term regulation of food intake and energy homeostasis. Exp Biol Med (Maywood) 2001; 226: 963-977
3. Cota D, Prouls K, Seeley RJ. The role of CNS fuel sensing in energy and glucose regulation. Gastroenterology 2007; 132: 2158-2168
4. Mori H, Inoki K, Münzberg H, Opland D, Faouzi M, Villanueva EC, Benoue T, Kwiatkowski D, MacDougald OA, Myers MG, Guan KL. Critical role for hypothalamic mTOR activity in energy balance. Cell Metab 2009; 9: 362-374
5. Xu G, Li Y, An W, Li S, Guan Y, Wang N, Tang C, Wang X, Zhu Y, Li X, Mulholland MW, Zhang W. Gastric mammalian target of rapamycin signaling regulates ghrelin production and food intake. Endocrinology 2009; 150: 3637-3644
6. Hill JO, Wyatt HR, Reed GW, Peters JC. Obesity and the environment: where do we go from here? Science 2003; 299: 853-855
7. Sandoval D, Cota D, Seeley RJ. The integral role of CNS fuel-sensing mechanisms in energy balance and glucose regulation. Annu Rev Physiol 2008; 70: 513-535
8. Clare M, Smith MA, Battenham RL, Selman C, Choudhury AI, Fryer LG, Clements M, Al-Qassab H, Heffron H, Xu AW, Speakman JR, Barsh GS, Violet B, Vaulont S, Ashford ML, Carling D, Withers DJ. AMPK is essential for energy homeostasis regulation and glucose sensing by POMC and AgRP neurons. J Clin Invest 2007; 117: 2325-2336
9. Cota D, Prouls K, Smith KA, Kozma SC, Thomas G, Woods SC, Seeley RJ. Hypothalamic mTOR signaling regulates food intake. Science 2006; 312: 927-930
10. Saha AK, Persons K, Safer JD, Luo Z, Holick MF, Ruderman NB. AMPK regulation of the growth of cultured human keratinocytes. Biochem Biophys Res Commun 2006; 349: 519-524
11. Minokoshi Y, Shiuchi T, Lee S, Suzuki A, Okamoto S. Role of hypothalamic AMP-kinase in food intake regulation. Nutrition 2008; 24: 786-790
12. Minokoshi Y, Alquier T, Furukawa N, Kim YB, Lee A, Xue B, Mu J, Foujelle F, Ferré P, Birnbaum MJ, Stuck BJ, Kahn BB. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. Nature 2004; 429: 569-574
13. Andersson U, Filipsson K, Abbott CR, Woods A, Smith K, Bloom SR, Carling D, Small CJ. AMP-activated protein kinase plays a role in the control of food intake. J Biol Chem 2004; 279: 12005-12008
14. Dennis PB, Jaeschke A, Saitoh M, Fowler B, Kozma SC, Thomas G. Mammalian TOR: a homeostatic ATP sensor. Science 2001; 294: 1102-1105
15. Inoki K, Corradetti MN, Guan KL. Dysregulation of the
Xu GY et al. mTOR and gastric hormones

TSC-mTOR pathway in human disease. Nat Genet 2005; 37: 19-24

Khamzina L, Veilleux A, Bergeron S, Marette A. Increased activation of the mammalian target of rapamycin pathway in liver and skeletal muscle of obese rats: possible involvement in obesity-linked insulin resistance. Endocrinology 2005; 146: 1473-1481

Um SH, Frigerio F, Watanabe M, Picard F, Joaquin M, Sticker M, Fumagalli S, Allegretti PR, Kozma SC, Auwerx J, Thomas G. Absence of S6K1 protects against age- and diet-induced obesity while enhancing insulin sensitivity. Nature 2004; 431: 200-205

Blanin Martínez de Morentín P, González CR, Saha AK, Martins L, Díezuez C, Vidal-Puig A, Tena-Sempere M, López M. Hypothalamic AMP-activated protein kinase as a mediator of whole body energy balance. Rev Endocr Metab Disord 2011; 12: 127-140

Inoki K, Zhu T, Guan KL. TSC2 mediates cellular energy response to control cell growth and survival. Cell 2003; 115: 577-590

Xie G, Li Y, An W, Zhao J, Xiang X, Ding L, Li Z, Guan Y, Wang X, Tang C, Zhu Y, Wang N, Li X, Mullolland H, Zhang W. Regulation of gastric hormones by systemic rapamycin. Peptides 2010; 31: 2185-2192

Wilson BS, Lloyd RV. Detection of chromogranin in neuroendocrine cells with a monoclonal antibody. Ann J Pathol 1984; 115: 458-468

Bajetta E, Ferrari L, Martinetti A, Celio L, Procopio G, Artale S, Zilembo N, Di Bartolomeo S, Serenig E, Bombardieri E. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer 1999; 86: 858-865

Dockray GJ, Varro A, Dimaline R. Gastric endocrine cells: gene expression, processing, and targeting of active products. Physiol Rev 1996; 76: 767-798

Kojima M, Kangawa K. Ghrelin: structure and function. Physiol Rev 2005; 85: 495-522

Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999; 402: 656-660

Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, Nakazato M. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology 2000; 141: 4255-4261

Zhang J, Ren PG, Asvian-Kretchmer O, Luo CW, Rauch M, Klein C, Hsueh AJ. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin’s effects on food intake. Science 2005; 310: 996-999

Yang J, Brown MS, Liang G, Grishin NV, Goldstein JL. Identification of the acyltransferase that octanoylates ghrelin, an appetit-stimulating peptide hormone. Cell 2008; 132: 387-396

Gutierrez JA, Solenberg PJ, Perkins DR, Willency JA, Knierman MD, Jin Z, Witcher DR, Luo S, Onyia JE, Hale JE. Ghrelin octanoylation mediated by an orphan lipid transferase. Proc Natl Acad Sci USA 2008; 105: 6320-6325

Gil-Campos M, Aguilera CM, Cañete R, Gil A. Ghrelin: a hormone regulating food intake and energy homeostasis. Br J Nutr 2006; 96: 201-226

Heppner KM, Tong J, Kirchner H, Nass R, Tschöp MH. The ghrelin O-acyltransferase-ghrelin system: a novel regulator of glucose metabolism. Curr Opin Endocrinol Diabetes Obes 2011; 18: 50-55

Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, Matsukura S. A role for ghrelin in the central regulation of feeding. Nature 2001; 409: 194-198

Asakawa A, Inui A, Kaga T, Katsuura G, Fujimiy A, Fujino MA, Kasuga M. Antagonism of ghrelin receptor reduces food intake and body weight gain in mice. Gait 2003; 52: 947-952

Carlson MJ, Cummings DE. Prospects for an anti-ghrelin vaccine to treat obesity. Mol Interact 2006; 6: 249-252

Helming S, Maasch C, Eulberg D, Buchner K, Schröder W, Lange C, Vonhoff S, Wlortzka B, Tschöp MH, Rosewicz S, Klussmann S. Inhibition of ghrelin action in vitro and in vivo by an RNA-Spiegelmer. Proc Natl Acad Sci USA 2004; 101: 13174-13179

Chen HY, Trumbauer ME, Chen AS, Weingarth DT, Adams JR, Frazier EC, Shen Z, Marsh DJ, Feighner SD, Guan XM, Ye Z, Nargund RP, Smith RG, Van der Ploeg LH, Howard AD, MacNeil DJ, Qian S. Orexigenic action of peripheral ghrelin is mediated by neuropeptide Y and agouti-related protein. Endocrinology 2004; 145: 2607-2612

Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 2001; 50: 1714-1719

Tschoëp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML. Circulating ghrelin levels are decreased in human obesity. Diabetes 2001; 50: 707-709

Cummings DE, Clement K, Purnell JQ, Vaisse C, Foster KE, Frayo RS, Schwartz MW, Basdevant A, Weigle DS. Elevated plasma ghrelin levels in Prader Willi syndrome. Nat Med 2002; 8: 643-644

Date Y, Nakazato M, Hashiguchi S, Dezaki K, Mondal MS, Hosoda H, Kojima M, Kangawa K, Arima T, Matsuo H, Yada T, Matsukura S. Ghrelin is present in pancreatic alpha-cells of humans and rats and stimulates insulin secretion. Diabetes 2002; 51: 124-129

Dezaki K, Hosoda H, Kakei M, Hashiguchi S, Watanabe M, Kangawa K, Yada T. Endogenous ghrelin in pancreatic islets restricts insulin release by attenuating Ca2+ signaling in beta-cells: implication in the glycemic control in rodents. Diabetes 2003; 52: 3142-3151

Sun Y, Asnicar M, Saha PK, Chan L, Smith RG. Ablation of ghrelin improves the diabetic but not obese phenotype of ob/ob mice. Cell Metab 2006; 3: 379-386

Kim MS, Yoon CY, Park KH, Shin CS, Park KS, Kim SY, Cho BY, Lee HK. Changes in ghrelin and ghrelin receptor expression according to feeding status. Neuroreport 2003; 14: 1317-1320

Edkins JS. The chemical mechanism of gastric secretion. J Physiol 1906; 34: 133-144

SMITH AN. Gastrin and histamine release. J Physiol 1954; 123: 71P-72P

Ekudanyo AA, Lee CY, Goodlad RA. Gastrin and the growth of the gastrointestinal tract. Gait 1995; 36: 203-208

Sachs G, Zeng N, Prinz C. Physiology of isolated gastric endocrine cells. Annu Rev Physiol 1997; 59: 243-256

Uvnäs-Wallenstein K, Uvnäs B, Nilsson G. Quantitative aspects of the vagal control of gastric release in cats. Acta Physiol Scand 1976; 96: 19-28

Ling N, Burgus R, Rivier J, Vale W, Brazaupe P. The use of mass spectrometry in deducing the sequence of somatostatin—a hypothyamic polypeptide that inhibits the secretion of growth hormone. Biochem Biophys Res Commun 1973; 50: 127-133

Raptis S, Dollinger HC, von Berger L, Schlegel W, Schröder KE, Pfeiffer EF. Effects of somatostatin on gastric secretion and gastric release in man. Digestion 1975; 13: 15-26

Levin BE, Roith VH, Kang L, Sanders NM, Dunn-Meynell AA. Neuronal glucosensing: what do we know after 50 years? Diabetics 2004; 53: 2521-2528

Blouet C, Ono H, Schwartz GJ. Medibosial hypothalamic p70 S6 kinase 1 modulates the control of energy homeostasis. Cell Metab 2008; 8: 459-467

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