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Review

Leptin secretion by white adipose tissue and gastric mucosa

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Summary. Leptin is a hormone that plays a central role in the regulation of food intake and energy expenditure. Originally discovered in mature white adipocytes, it was subsequently isolated from the gastric mucosa. This tissue contains a large number of epithelial endocrine and exocrine cells secreting leptin in the blood stream and in the gastric lumen, respectively. Light and electron microscopy have shown that adipocytes and gastric epithelial cells contain leptin along their rough endoplasmic reticulum-Golgi-granules secretory pathway. Both tissues synthesize a soluble form of the leptin receptor that is secreted bound to leptin in the blood and into the gastric juice. This soluble receptor protect leptin and enhances its half-life. Despite the similarities in the mechanisms of leptin secretion by adipocytes and gastric epithelial cells, they are in fact radically different. In gastric cells leptin follows a rapid regulated secretion pathway whereas adipocytes secrete leptin in a constitutive slow fashion. These differences can be explained by the specific roles play by leptin originating from these two different tissues. Gastric leptin is involved in the short-term regulation of digestion, including delay of gastric emptying, absorption of nutrients by the intestinal wall and secretion of gastric, intestinal and pancreatic hormones. On the other hand, leptin secreted by white adipocytes acts primarily on the hypothalamus for the long-term regulation of food intake. Therefore, the coordination of adipose and gastric leptins ensures the proper management of food processing and energy storage.

Key words: Leptin, Gastric mucosa, Adipocyte, Secretion, Energy storage

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Introduction

In the 1950s, parasymbiosis experiments were carried out by Jackson Laboratories on two species of genetically obese rodents, the ob/ob and db/db mice. Results suggested the existence of lipostatic factors, hormones produced by white adipose tissue, that act on the brain to regulate food intake and energy expenditure (Kennedy, 1953; Hervey, 1959). This theory was validated in 1994, when the team conducted by Jeffrey Friedman identified the ob gene in rodent adipose tissue. Its product, leptin, was named after the greek "leptos" meaning "thin" (Zhang et al., 1994). Following this discovery, specific leptin receptors were identified and localized in areas of the hypothalamus involved in the regulation of food intake and energy expenditure (Tartaglia et al., 1995). The role of leptin as a lipostatic factor was confirmed with the treatment of leptin-deficient ob/ob mice that completely reversed their hyperphagy and obesity, and increased their energy expenditure. Further studies demonstrated that leptin is also involved in a pleiotropic physiological phenomenom, ranging from reproduction to immunity (Himms-Hagen, 1999; Considine, 2005).

Structurally, leptin is a small non-glycosylated peptide of 167 amino acids (146 without the signal peptide). It possesses 4 α-helixes but is not classified as a cytokine. It was rather included in the recently created "adipokines" family that groups the wide variety of peptides and hormones secreted by the white adipose tissue. The leptin receptor belongs to the family of the gp130 receptors (Tartaglia et al., 1995). Six isoforms have been identified so far. Five of them are membrane-bound and are expressed ubiquitously, OB-Ra and OB-Rb being the most widespread. OB-Re is a soluble form corresponding to the extracellular part of the receptor, that binds leptin in circulation to enhance its half-life (Huang et al., 2001; Lammer et al., 2001). All receptors possess the same extracellular domain and the same affinity for leptin, but differ by the size and amino acid sequence of their transmembrane and cytoplasmic domains (Liu et al., 1997). Each membrane-bound receptor may therefore activate a different pattern of

intracellular pathways, including STAT (Signal Transducers and Activator of Transcription), JAK (Janus Kinases), PI3K (PhosphoInositide 3-Kinase) and MAPK (Mitogen-Activated Protein Kinase) (Ghilardi et al., 1996; Vaisse et al., 1996; Fruhbeck, 2006).

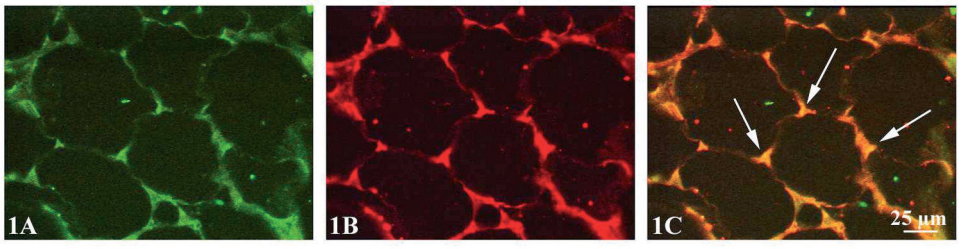
White adipose tissue is not the only tissue secreting leptin. Among others, the gastric mucosa has been shown to contain numerous endocrine and exocrine cells secreting leptin (Bado et al., 1998; Cinti et al., 2000; Cammisotto et al., 2005a, b). Typical endocrine cells are located in the gastric mucosa while epithelial Chief cells do secrete leptin through an exocrine pathway into the gastric lumen. These two secretions have fundamental roles within the digestive tract, as membrane-bound leptin receptors are present on apical and basal membranes of intestinal enterocytes (Cammisotto et al., 2005b).

White adipocytes and gastric epithelial cells are two cell types the metabolism of which is closely linked to food intake and energy storage. However, these two cell types present different morphological characteristics, different leptin secretory pathways and respond to different stimuli. These characteristics are important for the coordinated control of food intake and nutrient absorption.

Leptin secretion by white adipocytes

White adipose tissue is disseminated inside the body. Under basal conditions, each fat pad releases different amounts of leptin (Zheng et al., 1996). In rat, epididymal adipose tissue produces the highest quantities of leptin (about 10 ng/million cells) whereas in human the subcutaneous one displays these properties (Arner, 2001). Therefore, most work on leptin secretion in rodents is based on epididymal adipocytes, but the results were found qualitatively valid for the other fat pads. When epididymal adipose tissue is examined by light microscopy, leptin immunostaining is present in the cytoplasm, around the nuclei and along the thin rim surrouding the central lipid droplet (Fig. 1A) (Cammisotto et al., 2006b). Adipocytes synthesize several membrane-bound and soluble isoforms of leptin receptor (Gallardo et al., 2005) and leptin is released bound to its protective soluble receptor which is also involved in interactions of leptin with other tissues membrane bound-receptors (Yang et al., 2004). The soluble isoform of the receptor is synthesized directly from its specific mRNA, or may originate from the proteolytic cleavage of the membrane bound receptors OB-Ra (Gallardo et al., 2005). Expression of leptin receptor (all isoforms) displays a cellular distribution similar to that of leptin (Fig. 1B). Co-localization of both proteins becomes evident by double immuno-labeling experiments (Fig. 1C), which is particularly clear at the level of the Golgi apparatus of the adipocytes (Fig. 1D).

Further examination of epididymal adipocytes by electron microscopy using the immuno-gold labeling



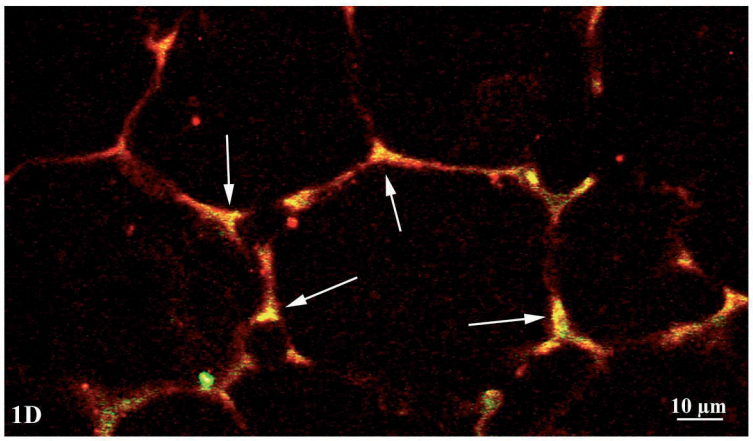


Fig. 1. Immunohistochemical staining of leptin and its receptor in epididymal white adipose tissue. Tissue sections (5 µm) were incubated with a rabbit anti-leptin and goat anti-leptin receptor antibodies, and revealed respectively with an anti-rabbit FITC- and an anti-goat TRITC-conjugated secondary antibodies. Areas close to the nucleus and the thin rim surrounding the lipid droplets show positive staining for leptin (**A**, green fluorescence) and for its receptor (**B**, red fluorescence). Colocalization becomes evident in figure **C** upon fusion of the pictures (orange-yellow fluorescence). Arrows point to brighter yellow areas which could represent Golgi apparatus (**D**).

approach (Bendayan, 1995) unravels the cellular structures containing leptin (Fig. 2A-C) and its receptor (Fig. 2D,E), namely the rough endoplasmic reticulum, the Golgi apparatus and the numerous small vesicles located close to the plasma membrane. Quantification of immuno-gold labeling demonstrates an increasing gradient of concentration for leptin along the RER–Golgi-secretory vesicles pathway (Table 1) which reflects processing and concentration of the protein before its release.

Leptin secretion by the gastric mucosa

Early studies have found leptin mRNA in the gastric mucosa, in human as well as in rodents (Bado et al., 1998; Schneider et al., 2001). Light microscopy revealed that cells on the lower half of the gastric mucosa fundus are positive for leptin (Fig. 3A). This coincides with the region of pepsinogen secreting cells (Fig. 3B) (Bado et al., 1998; Cammisotto et al., 2005b). A closer examination revealed the existence of two populations of

Table 1. Quantitation of leptin immunolabeling in cellular compartments of gastric epithelial Chief cells and white epididymal adipocytes.

	RER	Golgi	Secretory vesicles
Gastric mucosa Chief Cells	17.21±3.59*	27.95±3.36	69.64±5.70
Epididymal white adipocytes	7.44±1.69	14.39±3.65	47.37±5.78
Control of specificity**	0.38±0.17	1.36±0.41	2.59±0.18

*: Labeling densities expressed as gold particles per µm2 (Mean values ± SEM). **: Control were carried out by using an antigen-adsorbed antibody on Chief Cells.

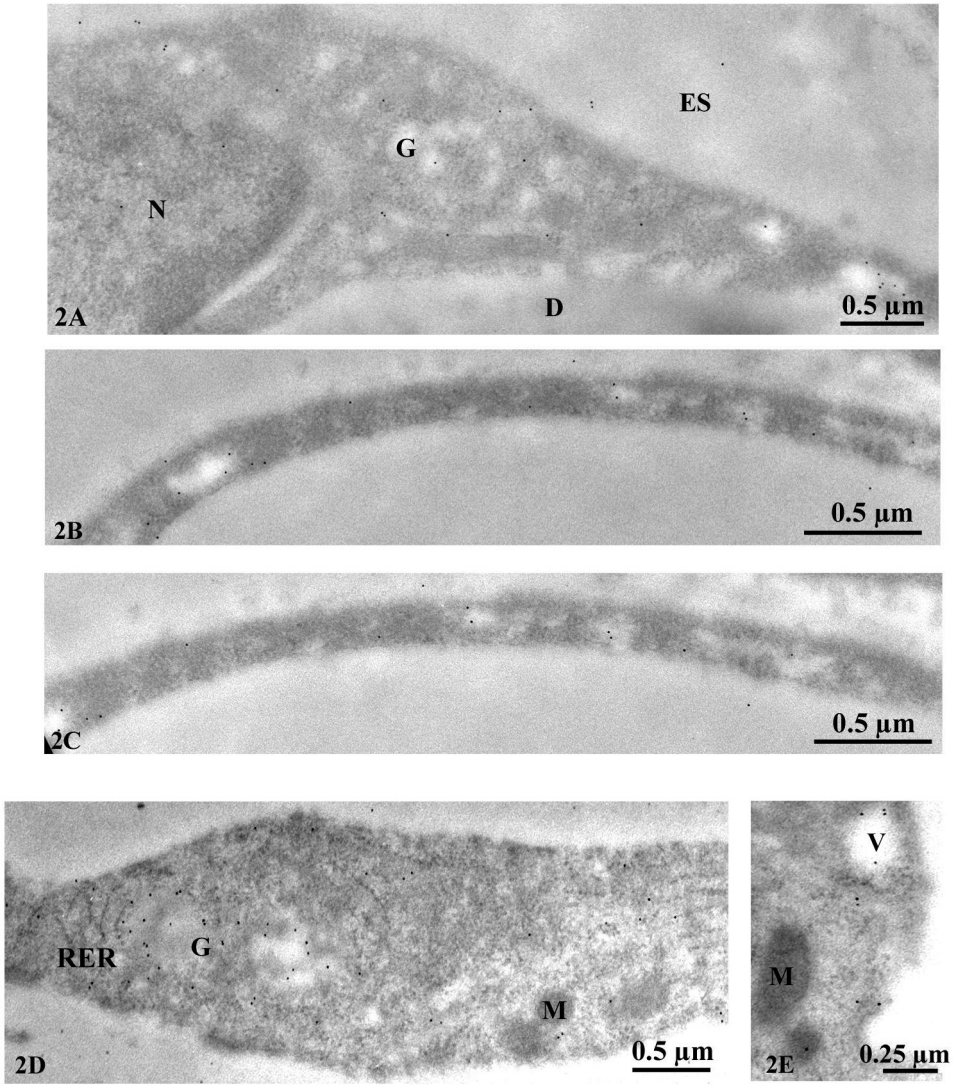


Fig. 2. Ultrastructural localization of leptin and of leptin receptor in white adipocytes. Immunogold labeling was carried out on ultra-thin sections of epididymal adipose tissue. Gold particles (10 nm in size) revealing the presence of leptin (**A-C**) and of its receptors (**D, E**) are located over the rough endoplasmic reticulum (RER), the Golgi apparatus (G) and numerous vesicles close to the membrane. No labeling is present over the lipid droplets (L), extracellular space (ES), mitochondria (M) or nucleus (N).

gastric leptin containing cells: the Chief epithelial cells that also secrete pepsinogen, and specific small endocrine cells scattered between the gastric pits (Fig. 3C, D). Double immunolabelings of leptin and pepsinogen, confirm the simultaneous secretion of pepsinogen and leptin by the Chief epithelial cells (Fig. 3E). Electron microscopy revealed that leptin and pepsinogen are simultaneously present in the rough endoplasmic reticulum, the Golgi apparatus (Fig. 4A, B) (Cammisotto et al., 2005b) and the secretory granules of the Chief cells (Fig. 4C). On the other hand, the small leptin endocrine cells located close to the blood capillaries of the gastric mucosa, are negative for pepsinogen, leptin being located along their RER-Golgi-granules secretory pathway (Fig. 4D) (Cinti et al., 2001; Cammisotto et al., 2005b). Similarly to white adipocytes, quantification of gold particles in gastric epithelial cells shows an increase in leptin labeling density from the rough endoplasmic reticulum to the secretory granules along a classical RER-Golgi-granules secretory pathway (Table 1). Furthermore, quantitation performed under control conditions demonstrates levels of background labeling speaking in favor of the specificity of the results (Table 1).

By western blot analysis, the presence of leptin in the gastric mucosa and gastric juice was confirmed (Cammisotto et al., 2006a) (Fig. 5A). This observation raises however the serious concern of how such a small peptide resists the harsh conditions of the gastric juice? Indeed, leptin does display a remarkable resistance to

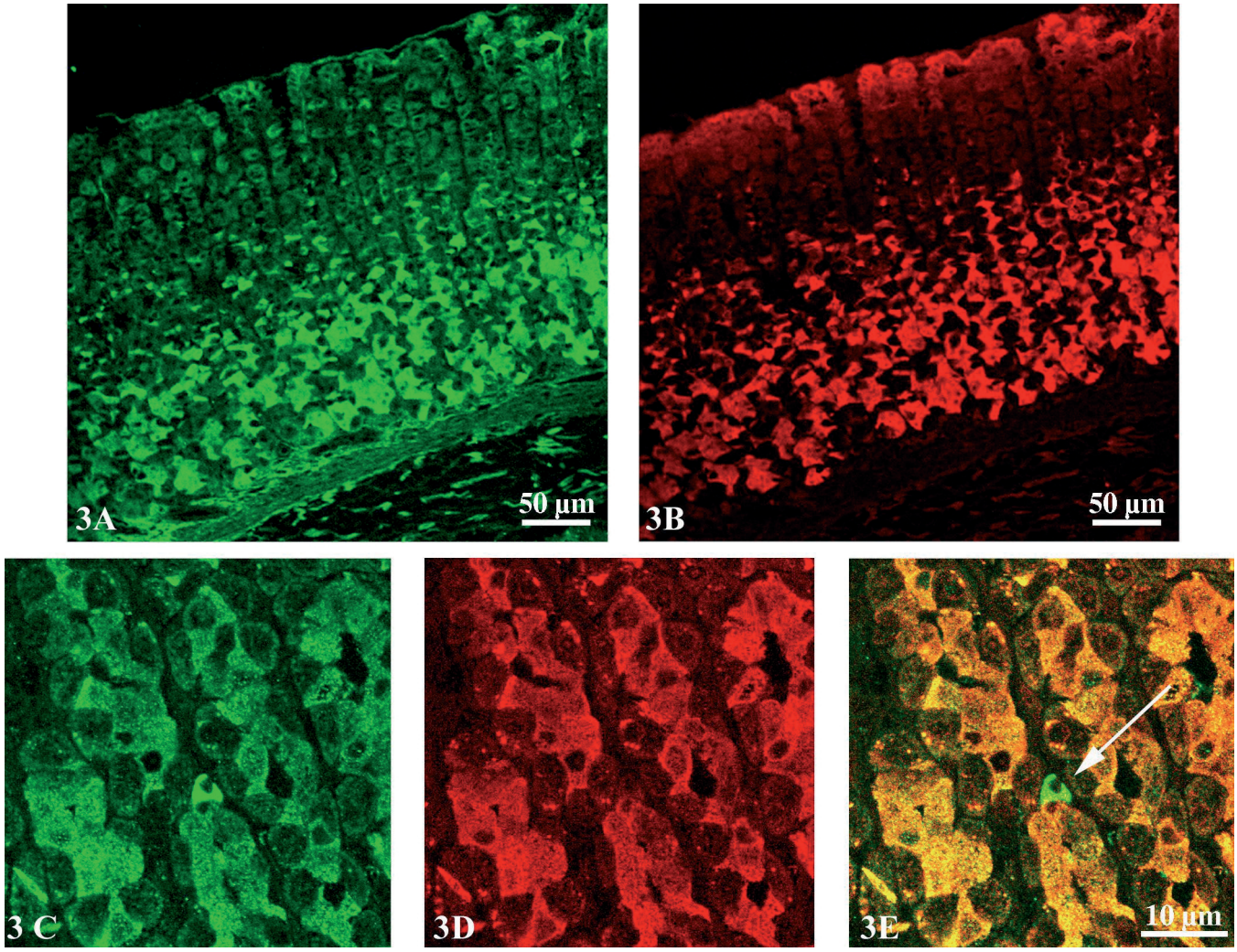


Fig. 3. Localization of leptin and pepsinogen in the gastric mucosa. Tissue sections were incubated with rabbit anti-leptin **(A)** or goat anti-pepsinogen **(B)** antibodies. Leptin antibodies were revealed with FITC-conjugated anti-rabbit IgG (green fluorescence) and pepsinogen antibodies with a TRITC-conjugated anti-goat IgG (red fluorescence) secondary antibodies. Exocrine Chief cells are positive for both leptin and pepsinogen **(C-E)**. Endocrine cells are positive only for leptin (arrow) **(E)**.

proteolytic conditions such as those found in the gastric juice and duodenal fluid (Sobhani et al., 2002). Part of the answer was provided when it was shown that gastric leptin is bound to a protein of high molecular weight that seems to play a protective role (Guilmeau et al., 2003). We have recently identified this binding protein as the soluble isoform of the leptin receptor that is released upon proteolytic cleavage of the membrane-bound isoform (Cammisotto et al., 2006a). Its structure and molecular weight are similar to the soluble leptin

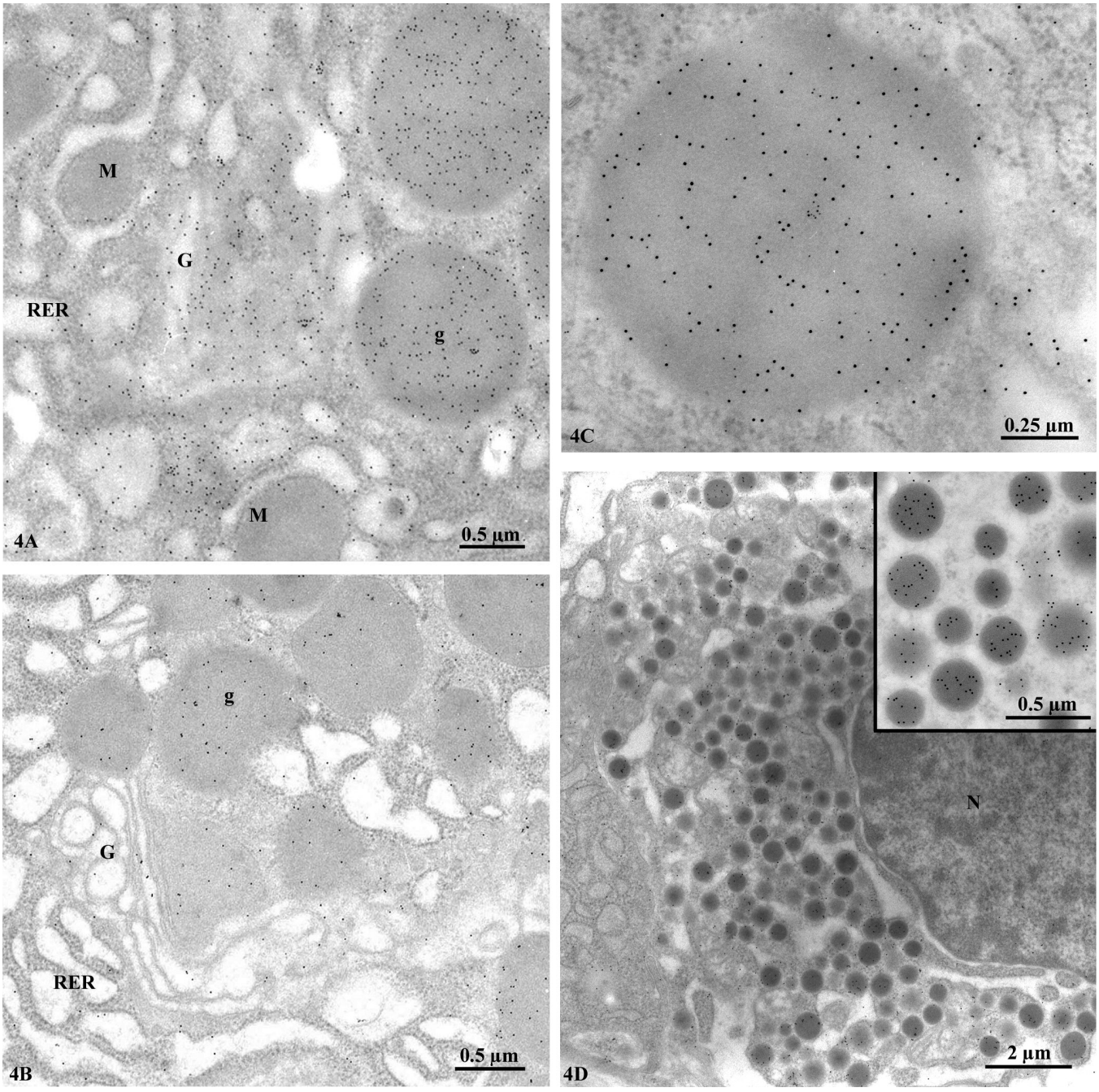


Fig. 4. Ultrastructural localization of leptin and pepsinogen in the gastric mucosa. Ultra-thin sections were incubated with antibodies against leptin or pepsinogen. Protein A-gold (10 nm) or anti-goat IgG gold (10 nm) were used. Pepsinogen **(A)** and leptin **(B)** were found within the granules of the exocrine Chief cells. Double labeling demonstrates pepsinogen and leptin in the same granules, 10 nm gold particles revealing pepsinogen and 5 nm gold particles revealing leptin **(C)**. Endocrine cell secretory granules are positive only for leptin **(D)**.

receptor molecule present in blood. The presence of leptin bound to its soluble receptor in secretory exocrine and endocrine cells was revealed by immunocytochemistry (Figs. 6A-C) and electron microscopy confirmed the presence of this leptin receptor in endocrine and exocrine granules (Fig. 6D). Interestingly, a closer examination revealed the presence of the leptin receptor bound to the membrane of the immature granules in exocrine cells. This membrane-bound receptor gets distached from the membrane of the immature granules by proteolytic cleavage as the granule matures (Fig. 7A). Several proteases were revealed in these granules, particularly the Proprotein Convertase 7. The membrane-bound leptin receptor molecule possesses several PC7-specific cleavage sites making it a good target for this convertase (Cammisotto et al., 2006a). Once released from the membrane, the extracellular portion of the leptin receptor appears to bind leptin inside exocrine Chief cell secretory granules before release into the gastric juice (Fig. 7B). Similar

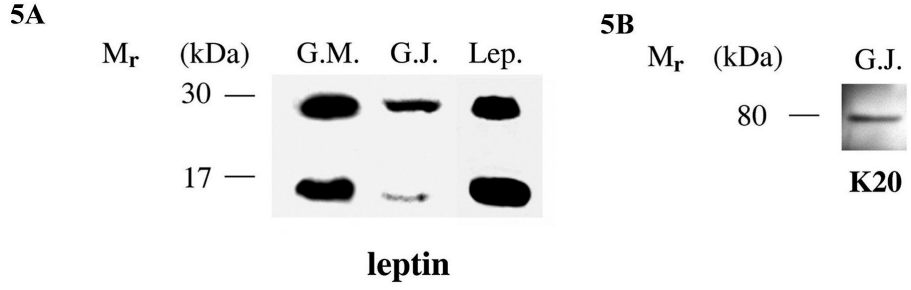


Fig. 5. Immunoblot for leptin. Gastric mucosa extract (G.M), gastric juice (G.J) and recombinant leptin were separated on a 10% acrylamide gel, transferred and revealed with the anti-leptin antibody. Gastric mucosa and juice display monomers (16 kDa) and dimmers (32 kDa) of leptin. Recombinant leptin yields similar bands (**A**). Soluble leptin receptor (MW around 80 kDa) was found in the gastric juice of the same samples using an antibody (K20) directed against the extracellular portion of the receptor (**B**).

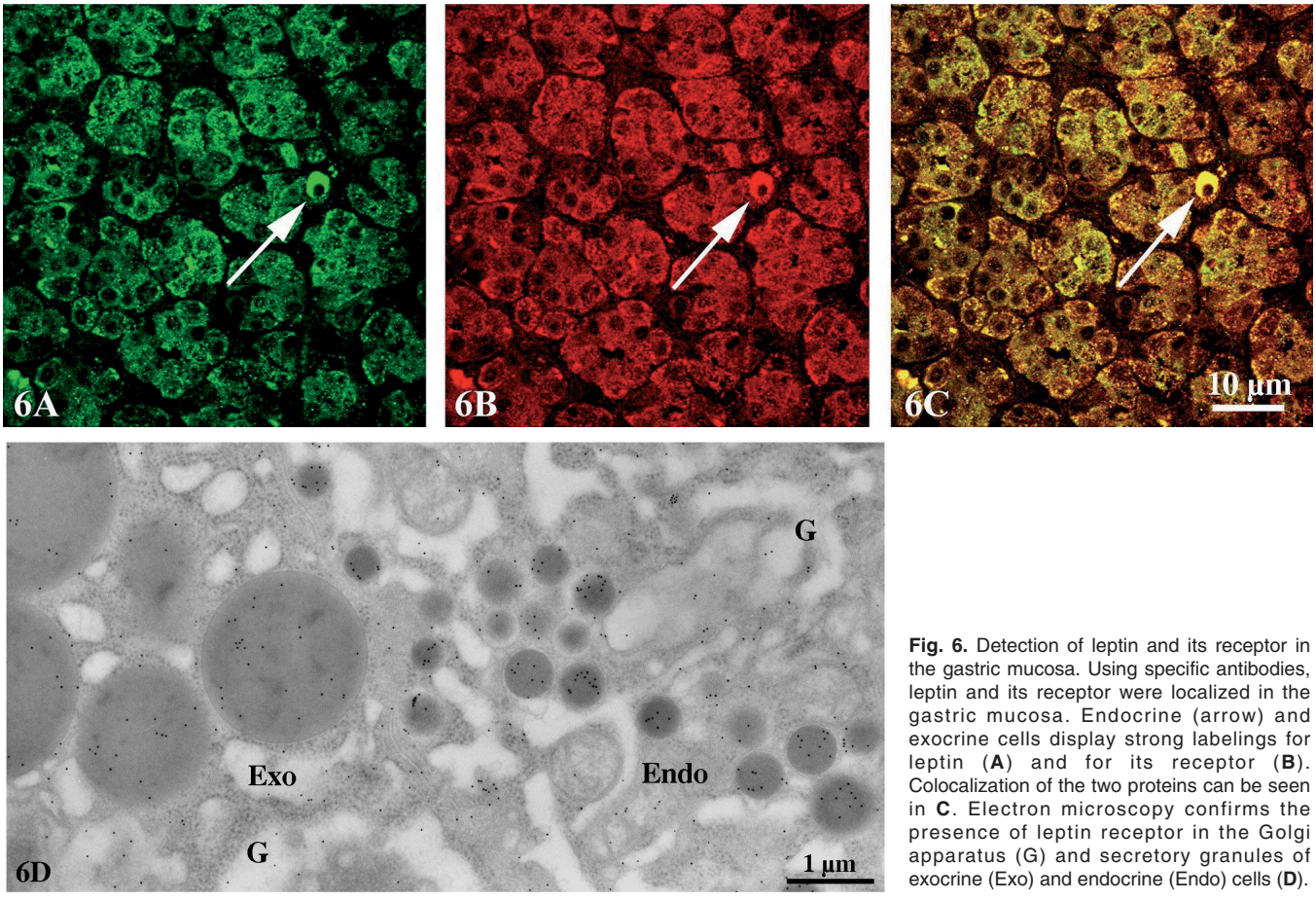
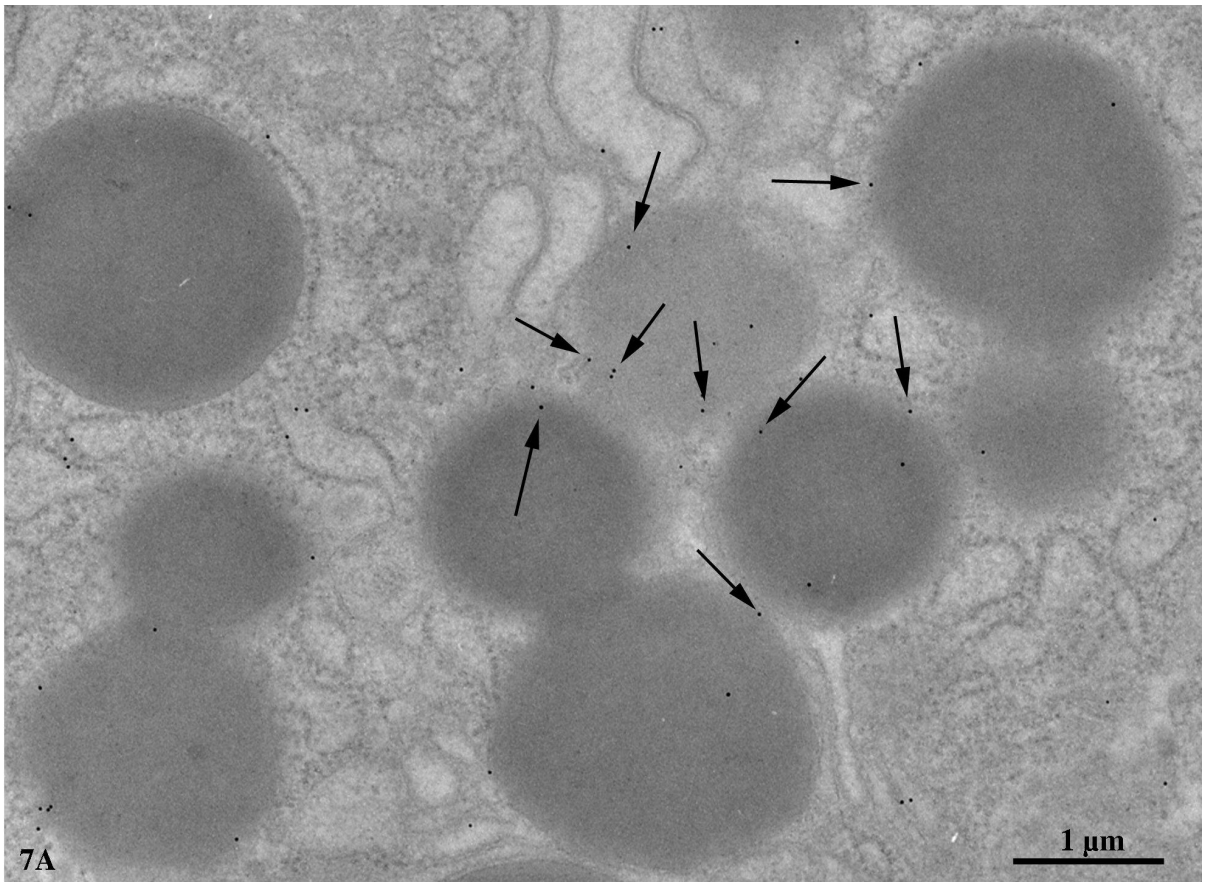


Fig. 6. Detection of leptin and its receptor in the gastric mucosa. Using specific antibodies, leptin and its receptor were localized in the gastric mucosa. Endocrine (arrow) and exocrine cells display strong labelings for leptin (**A**) and for its receptor (**B**). Colocalization of the two proteins can be seen in **C**. Electron microscopy confirms the presence of leptin receptor in the Golgi apparatus (G) and secretory granules of exocrine (Exo) and endocrine (Endo) cells (**D**).



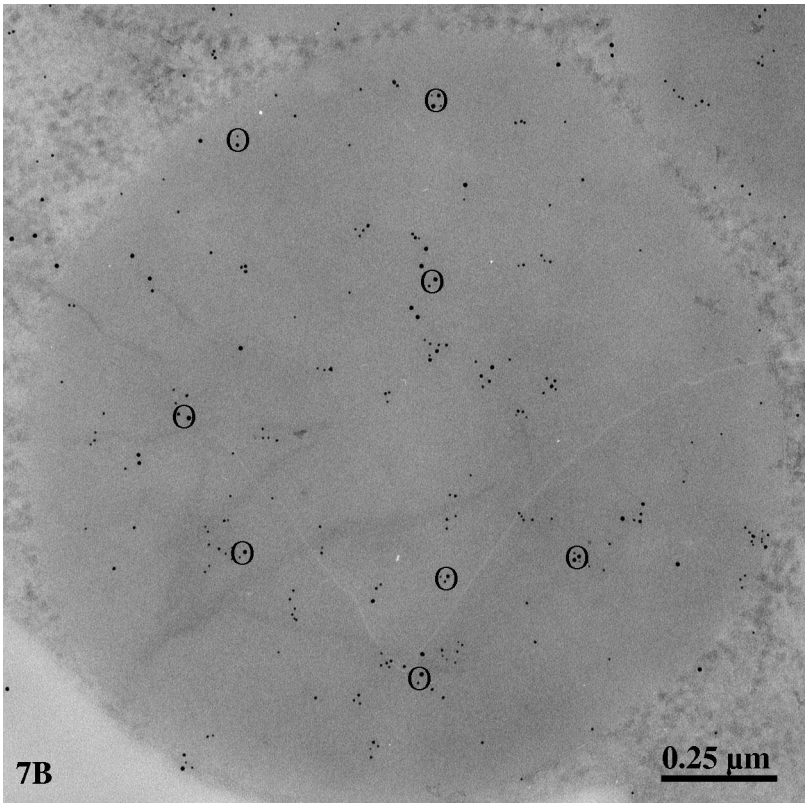


Fig. 7. Electron microscopy of leptin receptor in the gastric mucosa. Labeling for membrane bound leptin receptors is found associated to the limiting membrane of light grey immature and dark grey mature secretory granules in exocrine cells (arrows). Labeling is markedly reduced in mature dark grey granules **(A)**. In mature granules, labeling for leptin is found associated with the labeling of its soluble receptor (Circles), as shown respectively by small (5 nm) and large (10 nm) gold particles **(B)**.

observations were made for endocrine cells, the leptin-leptin receptor complex being in this case secreted into the interstitial space.

Secretory pathways

Cytochemistry has demonstrated that white adipocytes as well as gastric Chief cells and gastric endocrine cells secrete leptin and its receptors along the RER-Golgi apparatus- secretory granules pathway.

Leptin secreted by adipocytes

The morphological approach has demonstrated the presence of leptin-containing vesicles close to the plasma membrane. On the other hand, in vitro studies on isolated white adipocytes revealed the dynamics of leptin secretion. In non-stimulated conditions, adipocytes continuously synthesize and secrete leptin, so that the intracellular leptin content remains constant at all times. In the presence of stimulating agents, leptin intracellular content and secretion increase in parallel and become significantly different from basal values but this occurs only one hour after stimulation (Cammisotto et al., 2006b). No sudden release of leptin is observed upon stimulation. De novo leptin synthesis is required to observe the increase in discharge that occurs upon stimulation. This was demonstrated by the drastic inhibitory effects of cycloheximide and brefeldin A on protein synthesis and secretion. Such observations go along with the characteristics of a constitutive secretory pathway.

Another support for the constitutive secretion of leptin by adipocytes comes from a study on the role of calcium on leptin secretion (Cammisotto and Bukowiecki, 2004). In the classic model of regulated secretion, sudden and potent entry of calcium triggers fusion of secretory vesicles with the plasma membrane followed by the immediate release of their content (Lang, 1999). Stimulating leptin secretion from white adipocytes does not require calcium entry (Cammisotto and Bukowiecki, 2004). In fact, calcium has a permissive role on leptin secretion, through its role on glucose uptake. Indeed, glucose is needed as an energy source for leptin synthesis (Whitehead et al., 2001; Cammisotto and Bukowiecki, 2004). Moreover, forcing calcium entry with ionophores does not stimulate leptin release; on the contrary, it tends to inhibit stimulated leptin secretion (Cammisotto and Bukowiecki, 2004).

Leptin secretion is stimulated by a wide range of factors, particularly food intake which leads to an increase in energetic substrates in the blood (such as glucose, amino acids and fatty acids) and triggers the release of several hormones including insulin (Havel, 1972). Glucose, at physiological concentrations, is required to maintain basal leptin secretion but is not sufficient to increase leptin secretion from white adipocytes (Cammisotto et al., 2005b). On the other hand, insulin is a potent stimulus for leptin synthesis and secretion, with a half-effective concentration of about 1 nM, which is in the range of physiological concentrations (Cammisotto and Bukowiecki, 2002; Cammisotto et al., 2003). Most interestingly, amino acids per se stimulate leptin synthesis and secretion, and the addition of insulin further enhances this secretion (Cammisotto et al., 2005a) indicating that insulin and amino acids stimulation of leptin secretion are mediated by different pathways. Plasma free fatty acids on the other hand do not influence leptin secretion. However, the release of intracellular fatty acids by stimulation of lipolysis potently inhibits stimulated leptin secretion, suggesting that endogenous free fatty acids in a situation of stress (physical activity, lack of food) inhibits leptin secretion (Cammisotto et al., 2003).

Secretion of gastric leptin

In contrast to leptin secretion by adipocytes, leptin release by the gastric mucosa epithelial cells follows a classic regulatory secretory pathway. In rats fasted for 18 hrs, onset of food intake triggers a rapid release of leptin into the gastric lumen together with pepsinogen, while leptin stores get almost completely depleted (Bado et al., 1998; Pico et al., 2002). In parallel, plasma leptin increases three fold (Bado et al., 1998). Feeding stimulates leptin mRNA expression along with increase of leptin synthesis followed by leptin secretion that takes place upon depletion of leptin stores (Cinti et al., 2000). Results have been found to be similar in rat and human (Cinti et al., 2000).

Similarly to white adipocytes, food composition plays a major role in the secretion of gastric leptin. Leptin mRNA expression in rat gastric mucosa is up-regulated by sucrose-rich but not by fat-rich diets (Lindqvist et al., 2005). Fasted rats refed with a carbohydrate-rich diet have their gastric leptin synthesis increased (Sanchez et al., 2004). Many hormones such as cholecystokinin are involved in the secretion of gastric leptin (Bado et al., 1998). Intravenous infusions of pentagastrin or secretin cause an increase in circulating leptin levels and leptin release into the gastric juice (Sobhani et al., 2000, 2002). Insulin also triggers a release of gastric leptin but this effect is dependent on the integrity of the vagal nerve system (Sohbani et al., 2002). Finally, leptin seems to downregulate its own production in the stomach, as Zucker fa/fa rats with no functional leptin receptor are characterized by an upregulation of gastric leptin mRNA and gastric leptin content (Pico et al., 2002).

Roles of adipocyte and gastric leptins

Leptins from adipocytes and gastric mucosa are released at different times after the onset of food intake. While the gastric mucosa secretes leptin within minutes after the beginning of food intake, adipocytes need several hours to release significant amounts of leptin. These two pools of leptin serve different purposes.

Gastric leptin is involved in the short-term regulation of food absorption mostly at the level of the intestinal mucosa, whereas leptin from white adipose tissue controls satiety and energy storage at the long term.

Roles of adipocyte leptin

Leptin is a pleiotropic hormone, we will therefore limit this section to its role on food intake and energy expenditure. Leptin secreted by adipocytes is vehiculated by the blood stream, and crosses the blood-brain barrier by means of a saturable transporter (Koistinen et al., 1998; Kastin et al., 1999). Its main site of action is located in the hypothalamus particularly in the arcuate nucleus which plays a central role in the regulation of food intake (Mercer et al., 1996; Elmquist et al., 1998; Schwartz et al., 2000). This nucleus contains two populations of neurons expressing leptin receptors. One contains the orexigen peptides NPY (Neuro-Peptide Y) and AgRP (Agouti Related Protein) and leptin decreases their expression (Kuhar and Vecchia, 1999). The other population of neurons synthesizes the anorexigen CART peptides (Cocaine Amphetamine Related Transcript) and α-MSH (Melanocortin-Stimulating-Hormone derivatives of POMC, Pro-Opio-Melano-Cortin) and leptin increases their expression (Hillebrand et al., 2002; Ellacott and Cone, 2004). Neurons in the arcuate nucleus project towards the paraventricular, lateral hypothalamic, ventromedial and dorsomedial nuclei. These in turn project into the brainstem and the dorsomotor nucleus of the vagus nerves and activate the nervous system endings in several tissues (Minokoshi et al., 1999; Satoh et al., 1999). The overall effect is a feeling of satiety, an increase in energy expenditure and an activation of the sympathetic nervous system in different tissues.

Roles of gastric leptin

Gastric leptin exerts its function first on the digestive tract. Leptin receptors mRNA are expressed by the human gastric mucosa (Mix et al., 2000), and receptors were reported on gastric mucosa cell membranes (Morton et al., 1998; Breidert et al., 1999). Our team found a precursor of the soluble receptor isoform along the RER-Golgi-granules secretory pathway of the cells (Cammisotto et al., 2006a). On the other hand, duodenal, jejunal, and ileal enterocytes do express membrane-bound leptin receptors on their apical microvilli and baso-lateral membranes (Morton et al., 1998; Barrenexte et al., 2002; Cammisotto et al., 2005b). The functional long isoform leptin receptor (Ob-Rb) was also detected in human colon at the apical plasma membrane of colonocytes (Buyse et al., 2001). Thus, gastric exocrine and endocrine secretions of leptin constitute a gastro-enteric axis that coordinates the role played by leptin on the digestive tract (Cammisotto et al., 2005b).

Exocrine luminal leptin has been shown to act directly on intestinal cells through their specific receptors present on enterocyte microvilli. It regulates the transport of nutrients, enhances di- and tripeptides uptake by increasing the number of PepT1 transporters on microvilli (Buyse et al., 2001) and increases the uptake of glucose while decreasing transport of galactose (Lostao et al., 1998). Leptin also regulates intestinal lipid transport (Morton et al., 1998; Buyse et al., 2001; Doi et al., 2001; Stan et al., 2001). On the other hand, luminal leptin administration to fasted rats increases pancreatic enzyme secretion including amylase (Nawrot-Porabka et al., 2004). Endocrine leptin also regulates the secretion of several gastro-enteric hormones; leptin inhibits dose-dependently the secretion of the orexigenic gastric peptide ghrelin (Kojima et al., 1999; Barazzoni et al., 2003; Kamegai et al., 2004).

Gastric leptin participates in satiety by acting on the stomach. It potentiates the effect of cholecystokinin by slowing gastric emptying and promoting gastric distension (Moran and McHugh, 1982) without affecting the central nervous system (Wang et al., 2000). Also, leptin stimulates the production of Glucagon-like Peptides 1 and 2 (GLP1 and GLP2) that inhibit gastric emptying (Nauck et al., 1997; Naveilhan et al., 1999).

Pathologies

Systemic leptin has been shown to have a central role in obesity, diabetes, cardiovascular and gastrointestinal diseases. In obese patients, subcutaneous and visceral adipose tissue overexpress leptin mRNA (Lonnqvist et al., 1995). In long term, hyperleptinemia results in central and peripheric leptin resistance. Central resistance leads to hyperhagia (Munzberg and Myers, 2005) while peripheral leptin resistance has been linked to a decrease in glucose uptake, decrease in glycogen synthesis and accumulation of intracellular lipids leading to peripheric insulin resistance (Liu et al., 1997; Unger, 2004). Leptin is also involved in hypertension, arteriosclerosis, cancer and eating disorders (Ramos et al., 2004; Chan and Mantzoros, 2005; Luo et al., 2005; Singhal, 2005).

Gastric leptin is involved in immunity and inflammation of the digestive tract. Helicobacter pylori, the major cause of chronic gastritis and peptic ulcer diseases (Blaser, 1990), increases the expression of leptin mRNA and leptin secretion by the gastric mucosa. In turn, leptin could stimulate monocytes to produce proinflammatory cytokines like IL-1, IL-6 and tumour necrosis factor α (TNF-α) (Santos-Alvarez et al., 1999; Nishi et al., 2005). In the intestinal mucosa, leptin modulates the activation and proliferation of T lymphocytes and redirects cytokine responses towards a T helper 1 phenotype by enhancing production of IL-2 and interferon (Lord et al., 2002). This seems particularly important in inflammatory bowel diseases that are characterized by hyperleptinemia and over-activation of the immune system. Indeed, mesenteric adipose tissue gets hypertrophied in Crohn's disease and releases large amounts of leptin into the blood enteric

circulation (Karmiris et al., 2005; Otero et al., 2005). In ulcerative colitis, a certain population of colonic cells differentiates into leptin-secreting cells which have been shown to be involved in colonic inflammation (Siegmund et al., 2004).

Perspectives

Alteration in leptin plasma levels and intracellular signalling in obesity and diabetes have been extensively studied. The role of leptin on gastric and intestinal function is starting to be the focus of many studies related to gut inflammation and dysfunction. In particular, intestinal mucosa from diabetic patients is characterized by increased glucose uptake, decreased amino acids absorption and over production of lipoproteins and lipogenesis (Haidari et al., 2002; Zoltowska et al., 2003). Several diabetic rodents, including the leptin deficient mouse ob/ob model, present the same symptoms (Mayer and Yannoni, 1956; Jiao et al., 1991). On the other hand, the increased production of leptin by mesenteric white adipose tissue in patients with Crohn's disease and by colonic cells in patients with ulcerative colitis point out an important role for leptin in these pathologies (Sitaraman et al., 2004; Karmiris et al., 2005). The near future will probably see the development of extensive research on the effects of mesenteric and gastric leptin on the gastro-intestinal functions.

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