Secretory functions of the gastrointestinal tract

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Abstract

The alimentary tract is an organ of functional diversity. The absorption of water, nutrients, minerals, and vitamins is made possible through the coordinated action of the salivary glands, intestine, stomach, exocrine pancreas and hepatobiliary system.

Keywords Gastric secretion; GI-tract; luminal nutrient sensing; regulation; secretory mechanisms

Introduction

As food stuff passes through the alimentary canal it is manipulated, via endocrine, paracrine, and neural elements. The cephalic phase of digestion is mainly under neural control mechanisms whereas hormonal mechanisms dominate the gastric and intestinal. The process whereby the release of such hormones is controlled is termed luminal nutrient sensing (LNS; Figure 1).

Oral secretions

Food stuffs entering the oral cavity are purposefully mixed with saliva by chewing and tongue movements, to provide effective lubrication and first-degree mechanical degradation of its nutritional content. This is achieved by the action of teeth, salivary mucus and serous secretions entering the mouth from multiple bilateral salivary glands.

The different salivary glands

The major salivary glands are compound tubular alveolar glands, the parotid, sublingual and submandibular salivary glands, which are positioned symmetrically on both sides in the upper cheeks, under the tongue and mandible, respectively. There are also many smaller glands scattered in the submucosa, the oral cavity having a mucin-secreting and taste-facilitating function by the secretion of locally acting lipases. The parotid gland secretion is mainly serous and also the largest responder to elevated salivary secretion requirements, the submucosal secretions are all mucus, and the sublingual and submandibular glands are mixed in content. The latter mainly serve to maintain baseline secretory rates.[3]

Salivary composition

Saliva is made up of 99% water, assuming different properties due to the relative content of different proteins and ions. Ions and proteins are secreted by acinar cells deep in the ducts and the flow rate determines the concentration in the delivered saliva since an increased flow rate minimizes time for salt reuptake from the cells lining the ducts. At low flow rates, most of secreted 145–160 mM Na^+ and 120–130 mM Cl^- is taken up by active transport in the ducts, rendering the saliva hypotonic, whereas HCO_3^- remains in the secreted portion alongside of a ductal cell added K^+ secretion. At high flow rates, where there is less time for tubular exchange mechanisms to operate, the final salivary composition more closely resembles the initial acinar secretion and is plasma-like in composition. The amount of HCO_3^- depends on the level of adrenergic stimulation, and the pH of secreted saliva is usually in the alkaline range of about 7.5, protecting against acidic enamel erosion.[3,4]

There are several different proteins secreted in saliva. Some are secreted by all glands, such as bacteriostatic immunoglobulin A (IgA), whereas others are secreted to higher extent by certain glands. Amylase is the most abundantly secreted protein and is secreted by the parotid gland upon food intake, whereas mucins are secreted by the submandibular, sublingual and submucosal smaller glands.

Amylase's function as a carbohydrate-digesting agent needed for nutritional uptake is debated as it quickly loses its effect reaching the acidic environment of the stomach. It has, however, been postulated to be effective in clearing the oral cavity of food remnants after intake, reducing substrate levels for bacterial growth. The mucins are high-molecular-weight proteins rich in glycosylated amino acid residues which add visco-elasticity to the saliva, facilitating bolus formation and safe swallowing. The statherin group of proteins is secreted by both parotid and submandibular/sublingual glands, important for dental health as it lubricates and protects the integrity of the enamel. As statherins form part of enamel as well as bind Ca^{2+}, they prevent enamel hydroxyapatite degradation and excessive calcium-based callus formation on teeth.[3]

Mechanism of secretion

A total of 1 litre of saliva is produced in the oral cavity per day. As touched upon briefly, two major glandular cell types are involved in secretion and modification of the salivary contents: the deep acinar cells, and the epithelial duct cells lining the glandular crypts. The structure of these exocrine glands is similar to those of the exocrine pancreas, discussed later in this article. The acinar cells secrete isotonic fluid with Na^+, Cl^- and K^+, along with proteins in secretory granules from the basal membrane of the cells.

Acinar cell ion homeostasis relies on the activity of the Na^+/K^+-ATPase, which exports three Na^+ ions from the cell in exchange for $2K^+$ ions. Diffusion of these two ions down the gradients generated by the ATPase establishes the resting membrane potential and powers secondary active transporters. The $Na^+/K^+/2Cl^-$ co-transporter (NKCC1) is situated in the basolateral

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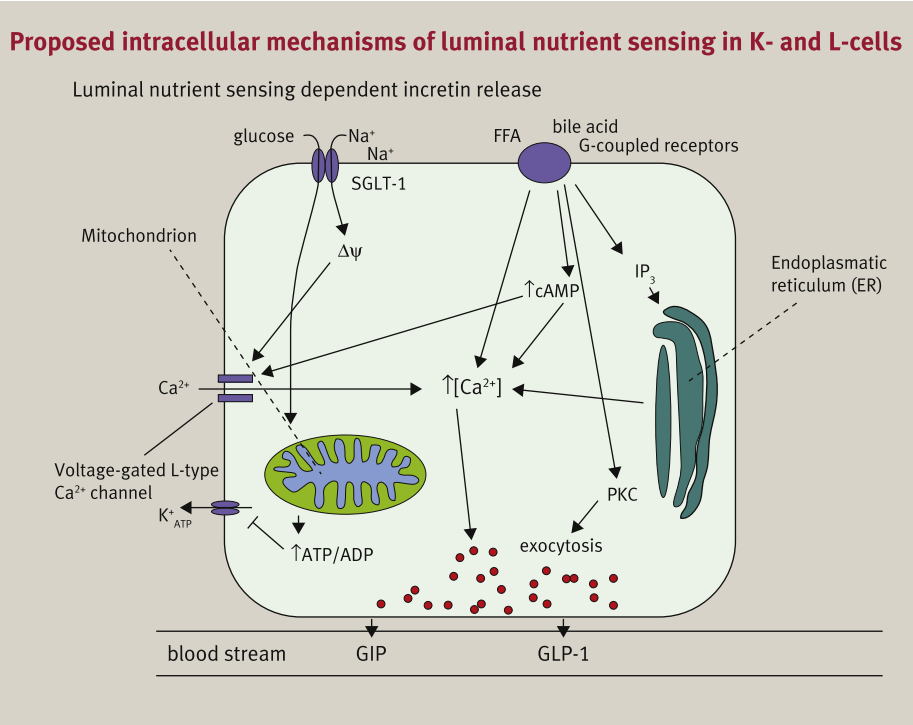

Figure 1 Secretion of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) through exocytosis is dependent on a rise in $[Ca^{2+}]_i$. Glucose is absorbed through sodium-coupled glucose transporters (SGLT-1). The rise in $[glucose]_i$ increases the ATP level which inhibits the activity of the ATP-sensitive K^+ channel (K^+ -ATP). Na^+ influx as well as decreased K^+ efflux depolarizes the cell membrane which increases the opening probability of the voltage-sensitive L-type Ca^{2+} channels, causing an influx of Ca^{2+}. Free fatty acids (FFA) and bile acids bind G-protein coupled receptors which activate intracellular pathways raising levels of cAMP. Their downstream activating pathways cause a rise in cAMP which results in increased opening probability of voltage gated Ca^{2+} channels, and also protein kinase C (PKC) and inositol(1,4,5)-trisphosphate (IP3) causing Ca^{2+} -release from intracellular stores to initiate exocytosis.[1,2]

cell membrane of the acinar cells and mediates the major influx of said ions down their electrochemical gradient. Two other crucial ion channels in the same membrane are the non-electrogenic exchangers: Na^+/H^+ exchanger (NHE1), and Cl^-/HCO_3^- exchanger (AE2). The NHE1 is activated by a reduction in intracellular pH, and the AE2 by an increase, which therefore, in concert, serve to regulate intracellular pH. There is also a single ion K^+ channel in the basolateral membrane. In the apical, or luminal membrane are the Ca^{2+} activated Cl^- channels (TMEM16A/ANO1) and the water aquaporin channel. The key step in initiating electrolyte secretion is an increase in intracellular Ca^{2+} which activates the apical membrane Cl^- channels and aquaporins. The efflux of water and Cl^- causes cell shrinkage and a negative charge increase in the glandular lumen. The former initiates a feedback system to activate the basolateral transport systems and the latter causes Na^+ to diffuse along a paracellular route from the interstitial to the luminal space along with further water.[4]

In the duct cells the primary saliva is modified through absorption of Na^+ via the ENaC channel, and Cl^- reabsorption and HCO_3^- secretion. This is achieved through a Cl^-/HCO_3^- exchange channel as well the HCO_3^-/Cl^- co-transporter: cystic fibrosis transductance regulator (CFTR). The CFTR favours Cl^- transport to HCO_3^-. Like in acinary cells the Na/K-ATPase establishes the membrane potential which fuels accumulation of HCO_3^- in the cytosol across the basolateral membrane through a Na^+/HCO_3^- co-transporter channel. Luminal K^+ channels carry K^+ along the electrochemical gradient into the lumen of the ducts.[4] Unlike in the acini, the ductal paracellular route is 'tight' to water.[3]

Most work done to understand the secretion mechanisms of protein in saliva has been performed on parotid cells even though these are believed to be largely shared also by the other salivary gland cells. About 80–90% of parotid acinary cell protein secretion, amylase included, occurs through stimulated exocytosis of secretory granules over the apical membrane into the deep glandular ducts. This can be achieved by adrenergic pharmacologic agents, such as isoproterenol as well as parasympathetic mediators. In-between meals, as β-adrenergic stimulation is low, there is a constitutive secretion level that originates, also from secretory granules, but independent of stimulation. About one-third of acinary cell volume is made up from secretory granules; 85% of these are subjected to storage and maturation, whereas only 15% are released without storage. Which granules that are selected for either, and if this is a passive or controlled process, is hitherto under debate. The secretory granules in both instances are generated from the trans-Golgi network after which they undergo a maturing process in which the concentration of protein increases through membrane removal and volume reduction.[5] Acinary cell secretion upon stimulation, is not only a fusion of secretory granulae with apical membrane but also that of separate secretory granules with each other so as to facilitate the immediate release of large quantities of protein.

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