Physiology of the salivary glands

Gábor Varga

Abstract

Salivary gland products are essential for oral health. Saliva is produced by three pairs of major glands, the parotid, the submandibular and sublingual glands, and by numerous minor glands scattered around the oral cavity. Salivary water and electrolyte secretion is an energy-consuming active two-stage process. First the acini secrete primary isotonic saliva into the luminal terminal end pieces of the gland parenchyma. This saliva is then modified by electrolyte reabsorption to form a hypotonic secretion in the ductal systems. Salivary proteins are continuously synthesized, and stored in secretory granules within the cell. Both electrolyte and protein secretions are highly regulated processes. Electrolyte secretion is primarily stimulated by parasympathetic stimulation while protein secretion is preferentially activated by sympathetic stimulation, but there is a considerable cross-talk and synergy between the two regulatory pathways. Approximately 1.0–1.5 litres of saliva is secreted by healthy persons each day; consisting of water, electrolytes, lubricants, antimicrobial compounds, enzymes and growth factors. These components of saliva facilitate speech, mastication and swallowing, and initiate food digestion. In addition, they protect the oral mucosa and the teeth. Thus, saliva secreted into the oral cavity is essential to maintain physiological conditions in the mouth.

Keywords Defence; electrolyte; molecular mechanism; parasympathetic; protein; regulation; saliva; salivary gland; secretion; sympathetic; water transport

Salivary gland development and structure

In humans there are three major pairs of salivary glands (Figure 1). The parotid glands are the largest, situated in front of the ear and behind the lower jaw. These glands deliver the saliva through ducts penetrating the buccal mucosa near the second upper molar. The submandibular glands can be found in the posterior part of the floor of the mouth close to the inner aspect of the mandible. The excretory ducts of these glands reach the oral cavity underneath the tongue lateral to the lingual fraenulum. The smallest major glands, the sublingual glands are situated in the floor of the mouth. Their secretion enters the oral cavity through a series of small ducts opening under the tongue. These three pairs of glands produce the largest part, about 92–95% of the total saliva volume. The remaining amount of saliva originates from the minor salivary glands. The minor salivary glands are located in the buccal, labial, palatal and lingual regions, including the base of the tongue (namely, the von Ebner's glands). In humans their number is between 600 and 1200. The regions of the mouth in which no minor glands can be found are the gingiva and the anterior part of the hard palate.

Salivary glands are made up of three major types of cells: acinar cells, ductal cells and myoepithelial cells. Parotid glands are composed of serous acini and secrete a watery saliva; sublingual glands have mucous acini with serous demilunes and secrete a very viscous saliva; whereas submandibular glands have mostly serous acini and some mucous acini attached to serous demilunes, and secrete moderately viscous saliva. In both glands pyramidal shaped acinar cells form glandular end pieces called acini. Acini drain into intercalated, striated and excretory ducts (Figure 2). Myoepithelial cells surround the acini and intercalated ducts to further facilitate saliva secretion. These cells contract rhythmically to compress the lumen to push saliva into the larger ducts and then into the oral cavity. Intercalated ducts consist of cuboidal cells arranged in a single layer. The striated and excretory ducts are formed by columnar cells with deep basolateral invaginations and intercellular interdigitations of the plasma membrane accompanied by numerous large, elongated mitochondria. Large excretory ducts consist of either stratified or pseudostratified columnar epithelium surrounded by basal cells (Figure 2). The ducts, composed of duct cells, are arranged in branching networks which not only conduct the saliva to the oral cavity but also modify its content.

Salivary gland water, electrolyte and protein secretion

Saliva is about 98% water; this is the most abundant and probably the most important component of it. The rest is composed of electrolytes including potassium, bicarbonate, calcium, sodium, chloride, phosphates and organic molecules such as proteins, glycoproteins, lipids, glucose and urea. Salivary water and electrolyte secretion is a two-step process: first acinar cells produce an isotonic secretory product, then, in the second stage, this fluid is modified while passing through the ductal tree, resulting in a highly hypotonic solution (Figure 3).

Primary saliva formation by acini

Transport of water may occur in two principally distinct ways through epithelia. Water can either be transported through the plasma membranes by a process known as transcellular transport, or it can be moved through the barrier formed by the tight junction complex in a process called paracellular transport. Studies attempting to determine the exact ratio of paracellular to transcellular water transport in salivary glands led to conflicting results but it is clear that these two processes are both involved in fluid movement. The transcellular transport pathway in the salivary glands primarily depends on aquaporin 5 (AQP5) water channels, localized to the luminal surface of acinar cells. Studies with parotid acinar cells obtained from AQP5-deficient mice revealed that the lack of AQP5 decreases transport not only through the plasma membrane but also through the tight junction complex. The absence of this water channel leads to decreased expression of tight junction proteins such as claudins and occludin, which regulate paracellular permeability. However, it is important to note that the basolateral-to-apical water secretion by acini is not an active process, but is rather due to osmotic gradient initiated by electrolyte secretion and accumulation at the apical/luminal side. In other words, water follows

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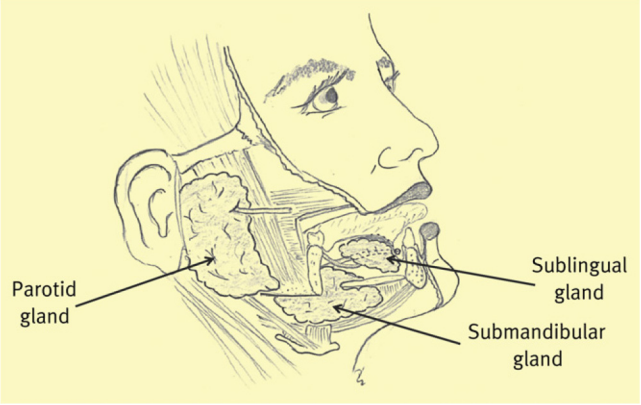

Figure 1 Anatomical arrangement of the human salivary glands: the parotid, the submandibular and the sublingual gland. The ducts of each salivary gland reach the oral cavity delivering saliva into the mouth.

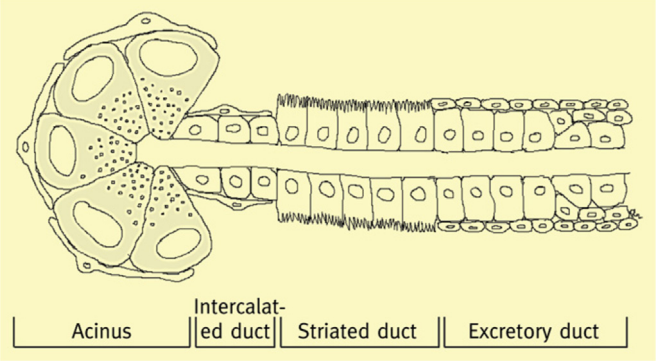

Figure 2 Salivary gland structure: Acini are surrounded by myoepithelial cells. The ductal tree consists of three principal elements: intercalated ducts, striated ducts and excretory ducts.

passively the actively transported electrolytes during acinar fluid secretion. The result of this process is an isotonic primary secretory fluid in the lumen of acini.

Water movement in salivary glands is primarily driven by active transcellular Cl^- secretion but the process is much more complicated than a simple vectorial movement of a particular ion. The energy for moving Cl^- across the cell actually comes from the highly active Na^+/K^+ ATPase pump. This pump uses ATP to extrude 3 Na^+ and to allow entry of 2 K^+ into the cell, forming a very high Na^+ concentration difference between the extracellular and the intracellular space, and also a somewhat lower, but still considerable difference in K^+ concentrations. At the expense of the great Na^+ concentration gradient, the Na^+ K^+ 2 Cl^- cotransporter (NKCC1) undergoes three cotransport cycles, allowing the entry of 3 Na^+, 3 K^+ and 6 Cl^- ions into the acinar cell from the interstitium. As a consequence of the coordinated NKCC1 and the Na^+/K^+ ATPase activities, K^+ and Cl^- are concentrated in the intracellular space well above their equilibrium potential.

When autonomic nerve stimulation results in the activation of the M3 muscarinic receptors, an intracellular second messenger, Ca^{2+} is released, and, as a consequence, Ca^{2+}-activated potassium channels at the basolateral membrane release K^+ into the interstitium, whereas Cl^- ions are released into the acinar lumen by Ca^{2+}-activated chloride channels at the apical membrane. As an additional event, from the interstitium Na^+ is driven through tight junctions into the luminal side due to the accumulation of Cl^- in the lumen.

The identity of K^+ and Cl^- channels participating in the above process has been recently described. Two different K^+ channels with somewhat different characteristics were suspected to be located at the basolateral membrane of salivary acinar cells. One of these is a Ca^{2+}-activated K^+ channel of intermediate single channel conductance commonly named IK1 or SK4. The second K^+ channel is both Ca^{2+}- and voltage-activated with a large single channel conductance. It is named maxi K or Slo. Initial experiments indicated that salivary gland fluid secretion was not affected in mice lacking either the IK1 channel or the Slo channels individually. In contrast, fluid secretion was severely impaired in mice lacking both IK1 and Slo channels, indicating that either type of K^+ channel can independently support K^+ release from the cell. These basolateral K^+ channels recycle K^+ ions to the extracellular space and their opening hyperpolarizes the membrane, thus increasing the driving force for Cl^- exit on the opposite side through TMEM16A calcium-activated chloride channels. The NaCl accumulation in the lumen results in an osmotic gradient which draws water through the acinar epithelia. In this way the water component of saliva is obtained through an active electrolyte secretory pathway.

The above described mechanism explains isotonic primary saliva secretion to a great degree, but not completely. When the NKCC1 cotransporter is knocked down or fully inhibited by pharmacological blockers or by genetically knocking out the transporter gene, fluid secretion is diminished by about 70%. The residual 30% of fluid secretion observed during NKCC elimination is HCO_3^--dependent, suggesting that there is a second Cl^- concentrating mechanism. This alternative Cl^- uptake mechanism depends on the coordinated activities of Na^+/H^+ and Cl^-/HCO_3^- exchangers located in the basolateral membrane of acini. Plasma CO_2 can diffuse through the basolateral membrane of the cell and enter the cytosol. Within the cell carbonic anhydrase catalyses the production of H^+ and HCO_3^- from H_2O and CO_2. The newly produced HCO_3^- can be exchanged to Cl^- by the Cl^-/HCO_3^- exchanger and cells eliminate unnecessary H^+ by the Na^+/H^+ exchanger. As a result, cells accumulate intracellular Cl^- which then can be secreted apically upon muscarinic stimulation. The anion secretory process can be maintained at low level even under Cl^--free conditions, since an apical anion conductance still persists, probably in the form of HCO_3^- exit through the channels which are not fully selective for Cl^- but at a lower level may also let HCO_3^- pass through.

Secondary saliva modifications by ductal cells

As a result of modifications by the ductal system, the final ionic composition of saliva is quite different from the primary isotonic secretion produced by the acini. Salivary gland ducts are composed of different cell types. There are three main types of ductal cells in salivary glands: intercalated, striated and excretory ducts. Intercalated and striated ducts are intralobular and excretory ducts are primarily extralobular. A comparison of the ion composition and osmolality of the saliva collected from intralobular or extralobular ducts suggests that NaCl reabsorption is accomplished by both intra- and extralobular ductal