Chapter 4

Salivary Glands

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Additional information is available at the end of the chapter

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Abstract

Saliva is a fluid secreted by the salivary glands that keeps the oral cavity moist and also coats the teeth along with mucosa. The salivary gland possesses tubuloacinar units, and these are merocrine. The functional unit of the salivary glands is the terminal secretory piece called acini with a roughly spherical or tubular shape. It also consists of branched ducts for the passage of the saliva and also plays an important role in the production and modification of saliva. Each type of duct is lined by different types of epithelia, on the basis of its location. Myoepithelial cells are contractile cells with respect to intercalated and secretory endpieces. Parotid, submandibular, and sublingual glands are the major salivary glands. The minor salivary glands are labial and buccal gland, glossopalatine gland, and palatine and lingual glands. Saliva plays an important role in mastication, speech, protection, deglutition, digestion, excretion, tissue repair, etc. Secretion stimulated in response to sympathetic stimulation will differ in protein and electrolyte from that due to parasympathetic stimulation. The concentration of saliva depends only on the rate of flow and not on the nature of stimulus. Saliva guides the clinician toward the optimal mode of treatment and guides the patient toward ultimate prognosis.

Keywords: saliva, serous gland, mucous gland, myoepithelial cells, acini, striated duct

1. Introduction

The human salivary glands are a group of compound exocrine glands that produce saliva, an important fluid required for lubrication, immunity, mastication, deglutition, taste, speech, etc. The salivary glands consist of a series of branched ducts which terminate in a spherical or tubular endpieces or acini; a correlation can be made to a bunch of grapes, with the stems analogous to the ducts and the grapes indicating the secretory endpieces. Serous and mucous cells (**Figure 1**) are the two main types of secretory cells present in salivary

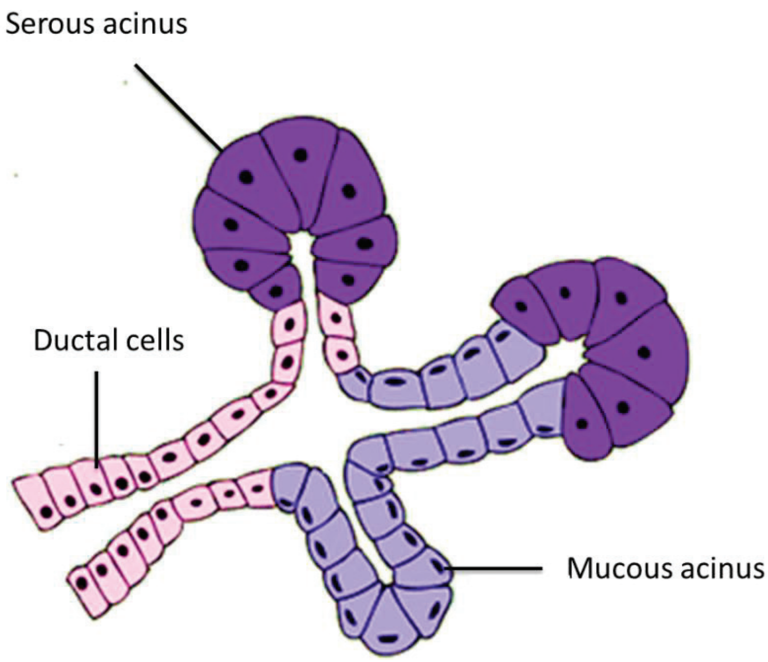

Figure 1. Structural organization of salivary gland [3].

gland and divided into two main groups. The major salivary glands include the paired parotid, submandibular, and sublingual glands. Additionally, the mucosa of the upper aerodigestive tract is lined by hundreds of small, minor salivary glands. The connective tissue forms a capsule around the gland and extends into it, dividing groups of secretory units and ducts into lobes and lobules. Blood vessels, lymphatic vessels and nerves that supply the gland, are present within the capsule [1].

The salivary glands are compound glands as they have more than one tubule entering the main duct, and the architectural arrangement is tubuloacinar, where acini are secretory units. These secretory units are merocrine as they release only the secretion of the cell from the secreting units. Myoepithelial cells are contractile cells associated with the secretory end-pieces and intercalated ducts of the salivary gland [2].

2. Classification, structure, and anatomy of salivary glands

- On the basis of size and location, salivary glands are classified as [1, 2]:

  a. Major salivary glands

    - Parotid
    - Submandibular
    - Sublingual

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b. Minor salivary glands

- Labial and buccal
- Glossopalatine
- Palatine
- Lingual
  - **i.** Anterior lingual gland (glands of Blandin and Nuhn)
  - **ii.** Posterior lingual serous gland (von Ebner's glands)
  - **iii.** Posterior lingual mucous gland

- On the basis of secretion [3], they are classified as:
  - Serous
  - Mucous

2.1. Major salivary glands

These are the largest, bilaterally paired, and situated extraorally, but their secretion reaches the oral cavity by variable long ducts.

2.1.1. Parotid gland

The parotid gland is the largest of all the salivary glands and weighs about 15–30 g. It is located below the external acoustic meatus between the ramus of the mandible and the sternocleidomastoid. It is divided by facial nerve into a superficial and deep lobe. The superficial lobe, overlying the lateral surface of the masseter, is defined as the part of the gland lateral to the facial nerve. The deep lobe is medial to the facial nerve and located between the mastoid process of the temporal bone and the ramus of the mandible. An accessory parotid gland may also be present lying anteriorly over the masseter muscle between the parotid duct and zygomatic arch [4].

The parotid duct, also known as Stensen's duct, secretes serous saliva and opens into the vestibule of the mouth (gingiva-buccal vestibule) opposite the crown of the upper second molar tooth [2].

2.1.2. Submandibular gland

It is the second largest salivary gland, also known as submaxillary salivary gland, weighs about 7–16 g and is almost the size of a walnut. It is situated in the submandibular triangle, which has a superior boundary formed by the inferior edge of the mandible and inferior boundaries formed by the anterior and posterior bellies of the digastric muscle. The gland is approximately J-shaped being indented by the posterior border of the mylohyoid which divides into a larger part superficial to the muscle and a smaller part lying deep to the muscle [4]. The submandibular gland duct, also known as Wharton's duct, is thin-walled, about 5 cm long, and runs forward above the mylohyoid muscle lying just below the mucosa of the floor of the mouth in its terminal portion. The duct opens on the floor of the mouth, on the summit of the sublingual papilla also called the caruncula sublingualis, lateral to the lingual frenulum [2].

2.1.3. Sublingual gland

It is the smallest of all the three major salivary glands that is almond shaped and weighs about 3–4 g. The gland lies above the mylohyoid, below the mucosa of the floor of the mouth, medial to the sublingual fossa of the mandible, and lateral to the genioglossus [4]. It comprises of one main gland duct with various small ducts. The main duct, Bartholin's duct, opens with or near the submandibular duct. Several smaller ducts, duct of Rivinus, open independently along the sublingual fold [2].

2.2. Minor salivary glands

The minor salivary glands are placed below the epithelium in almost all parts of the oral cavity. These glands comprise numerous small groups of secretory units opening via short ducts directly into the mouth. They lack a distinct capsule, instead mixing with the connective tissue of the submucosa or muscle fibers of the tongue or cheeks [2].

2.2.1. Labial and buccal glands

These glands are present on the lips and cheeks and comprise of mucous tubules with serous demilunes [1, 2].

2.2.2. Glossopalatine glands

These are located to the region of the isthmus in the glossopalatine fold but may extend from the posterior extension of the sublingual gland to the glands of the soft palate [1, 2].

2.2.3. Palatine glands

These are located in the glandular aggregates present in the lamina propria of the posterolateral aspect of the hard palate and in the submucosa of the soft palate and uvula [1, 2].

2.2.4. Lingual glands

The glands of the tongue can be divided into various groups [1, 2]. The anterior lingual glands (glands of Blandin and Nuhn) are present near the apex of the tongue. The ducts open on the ventral surface of the tongue near the lingual frenulum. The posterior lingual mucous glands are present lateral and posterior to vallate papillae and in association with lingual tonsil. The ducts of these glands open on the dorsal surface of the tongue. The posterior lingual serous glands (von Ebner's glands) are located between the muscle fibers of the tongue below the vallate papillae, and the ducts open into the trough of circumvallate papillae and at the rudimentary folate papillae on the sides of the tongue.

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3. Development of the salivary glands

The development of the glandular tissue involves the interaction of the epithelium with the underlying mesenchyme to form the functional part of the tissue [5, 6]. These epithelial-mesenchymal interactions are also known as secondary induction in which the mesenchyme is in close proximity with the epithelium and is required for the normal development of the epithelium. For example, epithelial-mesenchymal interactions regulate both the initiation and growth of the glandular tissue and the eventual cytodifferentiation of cells within the salivary glands. The mesenchyme, therefore, is required for normal development as well as formation of the supporting part of the adult gland.

All salivary glands follow a similar development pattern. The functional glandular tissue (parenchyma) develops as an epithelial outgrowth (glandular bud) of the buccal epithelium that invades the underlying mesenchyme. The connective tissue stroma (capsule and septa) and blood vessels form from the mesenchyme. The mesenchyme is composed of cells derived from neural crest and is important for the normal differentiation of the salivary glands.

As the bud formation begins during development, the portion of the bud closest to the stomodeum eventually differentiates into the main excretory duct of the gland, while the most distal portion of the bud forms the secretory endpieces or acini. The origin of the epithelial buds is believed to be ectodermal in the parotid and minor salivary glands but endodermal in origin in the submandibular and sublingual glands. The parotid gland originates near the corners of the primitive oral cavity by the sixth week of prenatal life. The submandibular glands arise from the floor of the mouth at the end of the sixth or the beginning of the seventh week in utero. The sublingual gland forms lateral to the submandibular primordium at about eighth week. All the minor salivary glands bud from buccal epithelium but start after their 12th prenatal week.

Stages of development [5, 6]

I. **Bud formation, i.e., induction of oral epithelium by underlying mesenchyme:** The mesenchyme underlying the oral epithelium induces the proliferation in the epithelium which results in tissue thickening and bud formation.

II. **Formation and growth of epithelial cord:** A solid cord of cells forms from the epithelial bud through cell proliferation. Condensation and proliferation occur in the surrounding mesenchyme which is closely associated with the epithelial cord. The basal lamina plays a role in influencing morphogenesis and differentiation of the salivary glands throughout the development.

III. **Initiation of branching in terminal parts of epithelial cord and continuation of glandular differentiation:** The epithelial cord proliferates rapidly and branches into terminal bulbs.

IV. **Dichotomous branching of epithelial cord and lobule formation:** The branching continues at the terminal portion of the cord forming an extension treelike system of bulbs. As branching occurs, the connective tissue differentiates around the branches, eventually producing extensive lobulation. The glandular capsule forms from mesenchyme and surrounds the entire glandular parenchyma.

V. **Canalization of presumptive ducts:** Canalization of the epithelial cord, with the formation of a hollow tube or duct, usually occurs by the sixth month in all the major salivary glands.

The two main theories to explain the mechanism of canalization are:

- Different rates of cell proliferation between the outer and inner layers of the epithelial cord.
- Fluid secretion by the duct cells which increases the hydrostatic pressure and produces a lumen within the cord. Further branching of the duct and structure and growth of the connective tissue septa continues at this stage of development.

VI. **Cytodifferentiation:** The final stage of salivary gland development is the histodifferentiation of the functional acini and intercalated ducts. Myoepithelial cells arise from the epithelial stem cells in the terminal tubules and develop in concert with acinar cytodifferentiation.

Parasympathetic nerves play an important role in epithelial tubulogenesis in the developing salivary gland which involve epithelial-mesenchymal interaction. The neurotransmitter, i.e., vasoactive intestinal peptide (VIP) and its receptor VIPR1, regulates various steps like epithelial proliferation, duct elongation, and lumen formation through cAMP or protein kinase A (PKA) pathway, thus linking epithelial tubulogenesis with parasympathetic neuronal function. Neurotrophic factor neurturin (NRTN), secreted by the buds, binds its receptor GFR alpha 2 and promotes functional nerve outgrowths to ensure parallel development of nerves and epithelium. Cystic fibrosis transmembrane conductance regulator (CFTR) causes lumen expansion during development [7].

4. Structure

4.1. Terminal secretory units

The functional unit of a salivary gland is the terminal secretory unit called acini [1, 2]. Regardless of size and location, the terminal secretory unit is made up of epithelial secretory cells, namely, serous and mucous acini. The serous and mucous cells along with myoepithelial cells are arranged in an acinus or acini with a roughly spherical or tubular shape and a central lumen.

Serous cells: They are pyramidal in shape with a broad base on the basement membrane, and the apex faces the lumen. The serous cells have a spherical nucleus placed at the basal region of the cell along with numerous secretory granules in which macromolecule components of saliva are stored and are present in the apical cytoplasm. The granules are zymogen granules and are formed by glycosylated proteins which are released into a vacuole. The serous cells show acid phosphates, esterases, glucuronidase, glucosidase, and galactoside activity. The central lumen usually has fingerlike extensions located between adjacent cells called intercellular canaliculi that increase the size of the luminal surface of the cells [2].

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Mucous cells: The secretory endpieces that are composed of mucous cells typically have a tubular configuration; when cut in cross section, these tubules appear as round profiles with mucous cells surrounding central lumen of larger size than that of serous endpieces. The nucleus is oval or flattened in shape and located above the basal plasma membrane. Sometimes, mucous cells have bonnet- or crescent-shaped appearance, which is made up of serous cells and are also known as demilunes first described by Giuseppe Oronzo Giannuzzi in 1865. The presence of demilunes is not clearly known, but these demilunes occur as a result of artifact during tissue preparation. Nowadays, recent studies like rapid freezing, freeze substitution, and three-dimensional reconstruction techniques have shown that serous cells align with mucous cells to surround a common lumen. The mucous cells show accumulation of large amounts of secretory product that pushes the nucleus and endoplasmic reticulum against the basal cell membrane.

The mucous secretion differs from secretion of serous in two important aspects:

- The secretion of mucous cells has little or no enzymatic activity and is responsible mainly for lubrication and protection of the oral tissues.
- The ratio of carbohydrates to protein is greater, and large amount of sialic acid and occasionally sulfated sugars are present [2].

  In routine histological sections, the secretion of mucous cell appears unstained, and they are strongly stained when special stains like PAS, alcian blue, mucicarmine, etc. are used [1].

4.2. Myoepithelial cells

These are the contractile cells associated with secretory endpiece and intercalated duct of the salivary glands. These cells are present between the basal lamina and the secretory or duct cells and are joined to the cells by desmosomes. They appear similar to smooth muscle but are derived from the epithelium. They are also known as basket cells or octopus sitting on a rock. The myoepithelial cells located around the secretory endpieces have stellate-shaped, numerous branching processes with a flattened nucleus and scanty perinuclear cytoplasm, but the cells associated with intercalated ducts have more fusiform shape and are elongated with fewer processes. These cells accelerate the initial flow of saliva from the acini, reduce luminal volume, support the underlying parenchyma, reduce the back permeation of fluid, and also help to maintain the patency. They maintain the cell polarity and structural organization of cells. They secrete various tumor suppressor proteins such as protease inhibitors and antiangiogenesis factors which provide a barrier against invasive epithelial neoplasm.

4.3. Ducts

It consists of hollow tubes that connect initially with the acinus, i.e., secretory endpieces, and extends to the oral cavity. It is not a pipeline or conduit for the passageway for the saliva, but it actively participates in the production and modification of saliva.

On the basis of location, ducts are of two types:

- **Intralobular ducts**: Those ducts which are within the lobule. The intercalated and striated ducts are intralobular ducts.

- **Interlobular ducts**: Those ducts which lie within the connective tissue within the lobules of the gland. The excretory ducts are interlobular ducts.

4.3.1. Intercalated duct

These are lined by single layer of cuboidal epithelium and are surrounded by myoepithelial cell bodies, and their processes typically are found along the basal surface of the duct. Under the light microscope, the intercalated ducts are difficult to identify as they are compressed between the secretory units. Under the electron microscope, the intercalated ducts have centrally placed nuclei and a small amount of cytoplasm containing some rough endoplasmic reticulum and a small Golgi complex. A few secretory granules may be found in the apical cytoplasm, especially in the cells located near the endpieces. The apical cell surface has a few short microvilli projecting into the lumen, and lateral surfaces are joined by junctional complexes. The macromolecule components, i.e., lysozyme and lactoferrin, are stored in the secretory granules of the intercalated duct and contribute to the saliva.

4.3.2. Striated ducts

The striated ducts receive the primary saliva from the intercalated ducts which constitute the largest portion of the duct system and are lined by columnar cells with a centrally placed large, spherical nucleus and pale, acidophilic cytoplasm. Under the electron microscope, the basal cytoplasm of the striated duct cells is partitioned by deep infoldings of the plasma membrane producing numerous sheetlike folds that extend beyond the lateral boundaries of the cell and interdigitate with similar folds of adjacent cells. Between the membrane infoldings, a large amount of radially oriented mitochondria are located in the portion of the cytoplasm. The combination of infoldings and mitochondria accounts for the striations seen in the light microscope. These ducts are involved in active transport and are considered as site of electrolyte reabsorption especially of sodium and chloride and secretion of potassium and bicarbonate. They also synthesize and secrete glycoproteins such as kallikrein and epidermal growth factor.

4.3.3. Excretory ducts

These ducts are located in the connective tissue septa between the lobules of the gland and are larger in diameter than striated duct. These ducts are lined by pseudostratified epithelium with columnar cells extending from the basal lamina to the ductal lumen and small basal cells that sit on the basal lamina. As the smaller ducts join to form large excretory ducts, the number of basal cell increases, and scattered mucous (goblet) cells may be present. The main excretory duct may become stratified near the oral opening. Tuft or brush cells with long stiff microvilli and apical vesicles are seen and are considered as receptor cells as they show nerve endings adjacent to the basal portion of the cell. Dendritic cells are also seen and play an important role in immune surveillance.

4.4. Connective tissue elements

The cells that are found in the connective tissue of the salivary glands are similar to those in other connective tissues of the body and include fibroblasts, macrophages, mast cells,

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occasional leukocytes, fat cells, and plasma cells. Collagen and reticular fibers are also embedded in a ground substance which is composed of proteoglycans and glycoproteins. It consists of a surrounding capsule that delineates the gland from the adjacent structures. Blood vessels and nerves are also present that supply the parenchymal components, i.e., glandular components and excretory ducts. The plasma cells present in the connective tissue produce immunoglobulins that are secreted into saliva by transcytosis.

5. Histology

5.1. Major salivary glands

- **Parotid glands:** The parotid gland is a purely serous gland, and all the acinar cells are similar in structure to the serous cells (**Figures 2** and **3**). Under the electron microscope, serous granules may have a dense central core, and the intercalated ducts are long branching along with pale-staining striated ducts, are numerous, and stand out evidently against the more densely stained acini. The connective tissue septa contain numerous fat cells which increase in number with age and leave an empty space in histologic sections.
- **Submandibular glands:** The submandibular gland is a mixed gland with both serous and mucous secretory units, but the serous units predominate. The mucous terminal portions are capped by demilunes of serous cells. Under the electron microscope, the intercalated ducts appear shorter in submandibular gland than those of the parotid, whereas the striated ducts are usually longer.
- **Sublingual glands:** The sublingual gland is also a mixed gland, but the mucous secretory units predominate. The mucous cells are present in tubular pattern along with serous

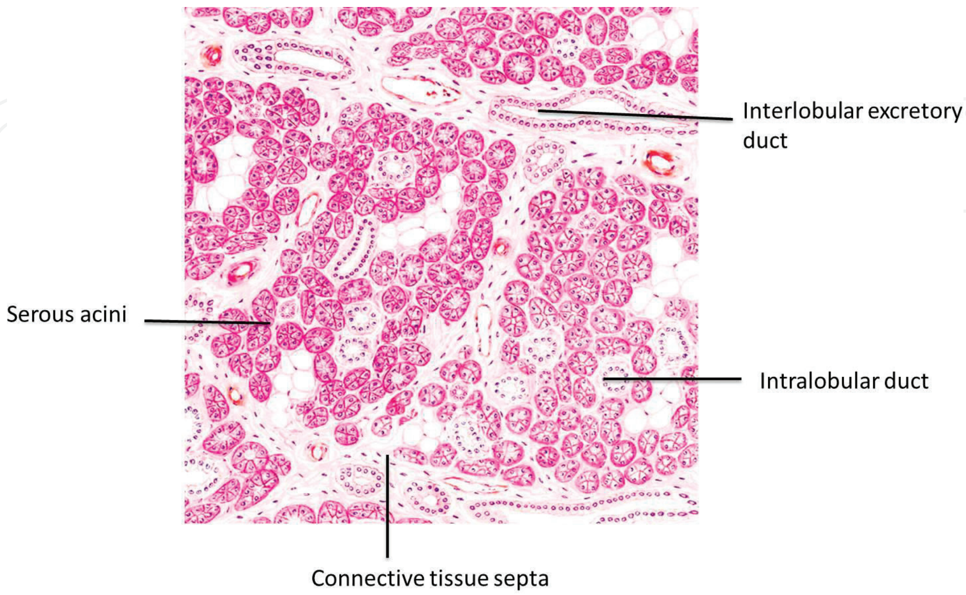

Figure 2. Histology of serous gland [3].

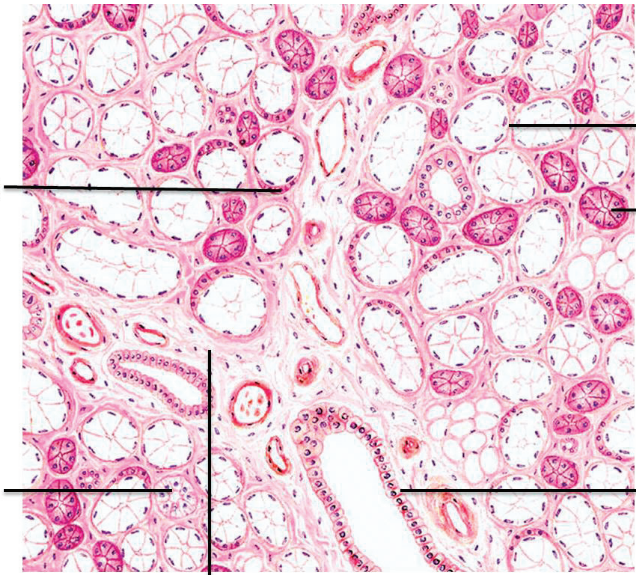

Figure 3. Histology of mixed gland [3].

demilunes and may be present at the blind ends of the tubules. The intercalated and striated ducts are poorly developed, and mucous tubules open directly into ducts lined with cuboidal or columnar cells without typical basal striations.

5.2. Minor salivary glands

- **Labial and buccal glands:** The glands of the lips and cheeks are a mixed gland consisting of mucous tubules with serous demilunes. The intercalated ducts appear variable in length, and the intralobular ducts possess only a few cells with basal striations.
- **Glossopalatine glands:** The glands present in the region of isthmus in the glossopalatine fold are purely mucous gland.
- **Palatine glands:** Palatine glands are a purely mucous gland, and the excretory ducts may have an irregular contour with large distensions as they course through the lamina propria.
- **Lingual glands:** In anterior lingual glands, the anterior portion of the glands is chiefly mucous in nature, whereas the posterior portions are mixed. The posterior lingual glands are purely mucous glands, but von Ebner's glands are purely serous gland.

6. Formation, secretion, and function of saliva

The oral cavity is kept moist by a film of fluid called saliva, which constantly coats its inner surfaces and occupies the space between the lining oral mucosa and the teeth [1, 2, 8–11]. It is a complex fluid, produced by the salivary gland, whose important role is maintaining the

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well-being of mouth. The whole saliva that bathes the oral cavity is primarily a mixture of secretions from the paired major (parotid, submandibular, sublingual) glands and the numerous minor (labial, buccal, palatine, and lingual) glands. The formation of saliva occurs in two stages:

1. **Formation of macromolecular components:** The structure of acinar cells consists of abundant RER, prominent Golgi complexes, and numerous secretory vesicles. Synthesis of secretory proteins begins with gene transcription and manufacture of mRNA to carry the sequence information from the nucleus to ribosome in the cytoplasm. Protein synthesized in the RER is settled to the Golgi complexes in transport vesicles. After fusion of their unit membrane with surface cell membrane, they rupture and they are released to the external environment. Rupture and rearrangement of the lipid layer of both permit the continuity of the granule membrane and cell membrane.

2. **Formation of fluid components:** After appropriate stimulation it is thought that the free Ca^{++} is released from storage site within the endoplasmic reticulum. Free cytoplasmic Ca^{2+} concentration can increase five- to tenfold in a second after such a stimulation which brings out significant compensatory changes that include the opening of the two membrane ion channels for passage of K^+ and Cl^-. When K^+ is released from the cell, a compensatory uptake of Na^+ and Cl^- occurs. The Cl^- exits the cell between the channels at luminal surface, and Na^+ enters the lumen through the paracellular pathway. The result of these ionic relocations is a flux of water into the lumen via the osmotic coupling of NaCl and H_2O.

The functions of saliva are:

- **Protection:** The protective functions of saliva is expressed as:
  - **a.** Lubricant
  - **b.** Mechanical washing
- **Buffering:** This occurs in two ways:
  - **a.** Many bacteria need a specific pH for growth; saliva prevents potential pathogens from colonizing in the mouth by denying them optimal environmental conditions.
  - **b.** Plaque microorganisms can produce acids from sugars, which if not rapidly buffered and cleared by saliva can demineralize enamel.
- **Digestion:** It provides taste acuity, neutralizes esophageal contents, and forms the food bolus.
- **Taste:** It dissolves substances to be carried to taste buds and also contains a protein, called gustin, which is necessary for growth and maturation of taste buds.
- **Antimicrobial action:** This occurs in various ways as:
  - **a.** Lactoferrin binds free iron and in doing so deprives bacteria of its essential element.
  - **b.** Lysozyme hydrolyzes the cell wall.

c. Histatin proteins with antibacterial property.

d. Immunoglobulin, i.e., secretory IgA, clumps or agglutinates microorganisms.

- **Maintenance of tooth integrity:** Saliva is saturated with calcium and phosphate ions, and interaction with saliva results in postoperative maturation through diffusion of such ions. This maturation increases surface hardness, decreases permeability, and increases the resistance of enamel to caries.
- **Tissue repair:** The rate of wound contraction is significantly increased in saliva due to the presence of peptides and proteins present in saliva.

7. Clinical considerations

a. **Radiation caries:** Radiation caries is a rampant form of dental decay that may occur in individuals who receive a course of radiotherapy that include exposure of salivary glands [1, 2, 11].

- Etiology

  Carious lesions are produced due to the exposure of salivary glands and reduced flow of saliva, decreased pH, decreased buffering capacity, and increased viscosity.

- Signs

  Superficial lesions attack the buccal, occlusal, incisal, and lingual surfaces. It includes cementum and dentin in cervical lesions. Lesions progress around the teeth circumferentially and resulting in loss of the crown.

b. Sjogren's syndrome: It consists of keratoconjunctivitis, xerostomia, and rheumatoid arthritis. The cause of the disease can be genetic, autoimmunological, etc.

- Features include dry mouth and dry eyes due to hypofunction of lacrimal and salivary glands. Most patients are treated symptomatically; ocular lubricants and salivary substitutes are given.

c. Xerostomia (dry mouth): It is defined as a subjective complaint of dry mouth that may result from a decrease in the production of saliva. It is not a disease but a symptom caused by many factors.

- Etiology
  - Sjogren's syndrome
  - Therapeutic radiation of head and neck
  - Surgical removal of salivary glands
  - Diabetes mellitus

- Acute viral infections involving salivary glands result in temporary xerostomia
- Anxiety, mental stress, and depression may temporarily decrease salivary flow

- Symptoms
  - Oral dryness (most common)
  - Halitosis
  - Burning sensation
  - Loss of sense of taste or bizarre taste
  - Difficulty in swallowing
  - Tongue tends to stick to the palate
  - Decreased retention of denture
- Signs
  - Saliva pool disappears
  - Mucosa becomes dry
  - Tongue shows glossitis and fissured with papilla atrophy
  - Angular cheilitis
  - Rampant caries at the cervical or cusp tip
  - Periodontitis
  - Candidiasis

8. Conclusion

Salivary glands are compound, exocrine, and tubuloacinar in nature secreting saliva which keeps the oral cavity moist. The secretory units are acini, and saliva reached the oral cavity through ducts. Saliva is of great importance to diagnostic and prognostic pathology.

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