Salivary Glands

6

Arthur R. Hand

Abbreviations

AQP5	Aquaporin-5
CFTR	Cystic fibrosis transmembrane regulator
CMV	Cytomegalovirus
Cyclic AMP	3′,5′-cyclic adenosine monophosphate
EB	Epstein-Barr virus
EGF	Epidermal growth factor
FGF-10	Fibroblast growth factor-10
FGFR2b	Fibroblast growth factor receptor-2b
HIV-1	Human immunodeficiency virus-1
IgG	Immunoglobulin G
IgG4-RD	Immunoglobulin G4-related disease
IgM	Immunoglobulin M
IP_3	Inositol trisphosphate
LADD	Lacrimo-auriculo-dento-digital syndrome
MMR	Measles-mumps-rubella vaccine
PKA	Protein kinase A
PKC	Protein kinase C
PRPs	Proline-rich proteins
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S-IgA	Secretory immunoglobulin A
SLPI	Secretory leukocyte protease inhibitor
SS	Sjögrens syndrome
TFF3	Trefoil factor 3
TGFα	Transforming growth factor alpha
TLRs	Toll-like receptors
VEGF	Vascular endothelial growth factor

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Introduction

The salivary glands are exocrine glands that secrete *saliva*, a watery fluid that contains electrolytes, proteins, mucins, and other substances that create and regulate the environment of the oral cavity and serve to protect the oral tissues and facilitate taste, mastication, swallowing, and speech. There are three *major salivary glands*—the *parotid*, *submandibular*, and *sublingual* glands—that are located bilaterally outside the oral cavity and have long ducts that convey the saliva to the mouth. Except for the gingivae, the anterior dorsum of the tongue, and some regions of the hard palate, the mucosal lining of the oral cavity also contains hundreds of small glandular aggregates, the *minor salivary glands*, with ducts that open individually onto the mucosal surface. Saliva secretion is regulated by both branches of the autonomic nervous system and stimulated mainly by activation of taste receptors and oral mechanoreceptors. The salivary glands can be affected by local and systemic conditions, including neoplasms. The most common patient complaint related to the salivary glands is a "dry mouth" due to reduced secretion of saliva as a result of damage to the glands by autoimmune diseases or radiation, or by the use of drugs that affect salivary function.

This chapter reviews the anatomy of the salivary glands, their histology and development, the secretion, composition and functions of saliva, and its potential role as a diagnostic fluid. Also discussed are some of the more common pathological conditions of the glands, including salivary hypofunction and its causes, duct obstruction, infections and inflammation, and neoplasms.

Anatomy

The largest salivary gland, the parotid gland, is located on the side of the face, anterior to the external ear and superficial to the masseter muscle (Fig. 6.1). A portion of the gland wraps around the posterior edge of the mandibular ramus

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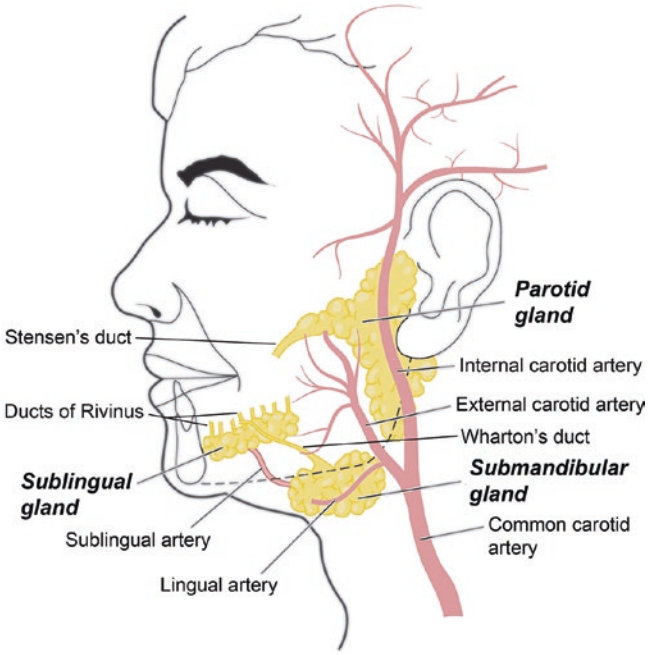

Fig. 6.1 Location of the major salivary glands. (Modified from Blamb/Shutterstock.com)

and neck. The main duct (*Stensen's duct*) extends anteriorly over the masseter muscle, then penetrates the buccinator muscle and opens at the parotid papilla on the buccal mucosa opposite the maxillary second molar. Branches of the facial nerve (cranial nerve VII) course through the gland, and branches of the carotid artery provide the blood supply. The parasympathetic secretory innervation is derived from the glossopharyngeal nerve (cranial nerve IX) via the otic ganglion and the auriculotemporal nerve. The sympathetic secretory innervation originates from the upper thoracic spinal cord, synapses in the superior cervical ganglion, and accompanies the blood vessels supplying the gland.

The submandibular gland is located in the submandibular space, inferior to the mylohyoid muscle (Fig. 6.1). A portion of the gland extends posterior and superior to the mylohyoid. The main duct (*Wharton's duct*) travels anteriorly below the floor of the mouth and opens at the sublingual caruncle by the lingual frenum. Branches of the lingual artery provide the blood supply of the gland. The parasympathetic secretory innervation travels via the facial (cranial nerve VII), chorda tympani, and lingual nerves, synapsing in the submandibular ganglion. Like the parotid, the sympathetic secretory innervation travels with the blood vessels supplying the gland.

The sublingual gland is located below the floor of the mouth (Fig. 6.1). The main duct (*Bartholin's duct*) opens with the submandibular duct at the sublingual caruncle, and several small ducts (*ducts of Rivinus*) open along the sublingual fold. The sublingual artery provides the blood supply of the gland. Similar to the submandibular gland, the sublingual gland receives its parasympathetic secretory innervation from the submandibular ganglion, and its sympathetic innervation accompanies the blood supply.

Histology

A fibrous connective tissue capsule encloses each of the major salivary glands [1]. Septa of connective tissue extend into the gland, dividing it into *lobes* and smaller *lobules* (Fig. 6.2). Blood vessels, nerves, lymphatic vessels, and excretory ducts are present in the septa. The parenchymal tissue within the lobules is organized into *secretory endpieces*, or *acini*, and a system of intralobular *ducts* that modify the secretory product of the acinar cells, primary saliva, and convey it to the interlobular excretory ducts (Fig. 6.2). The secretory endpieces consist of a roughly spherical or tubular arrangement of secretory cells around a central lumen that is confluent with the initial part of the duct system. The intralobular ducts consist of a simple cuboidal or columnar epithelium. All of the parenchymal components are surrounded by loose connective tissue within which reside fibroblasts, plasma cells, mast cells, macrophages, dendritic cells, and the occasional lymphocyte. The smallest branches of the vascular system, arterioles, capillaries, and venules, and the unmyelinated fibers of the autonomic nerves innervating the secretory and duct cells, also are found in the connective tissue between the individual parenchymal components.

There are two types of secretory cells found in salivary glands, *serous cells* and *mucous cells* (Fig. 6.3). Serous cells secrete a variety of proteins and glycoproteins, electrolytes, and water. Their structure is characterized by the presence of a spherical nucleus located in the basal cytoplasm, abundant rough endoplasmic reticulum, a prominent Golgi complex, and dense secretory granules stored in the apical cytoplasm (Fig. 6.4). The luminal surface of serous cells has a few small microvilli and is expanded by *intercellular canaliculi* that extend along the lateral surfaces between adjacent cells toward the basal surfaces of the cells. Junctional complexes, consisting of a tight junction, adhering junction, and one or more desmosomes, hold adjacent cells together and separate the luminal surface from the lateral and basal cell surfaces. Gap junctions involved in cell–cell communication are present on the lateral cell surfaces.

The main secretory product of mucous cells is mucin; only a few other organic substances have been identified as

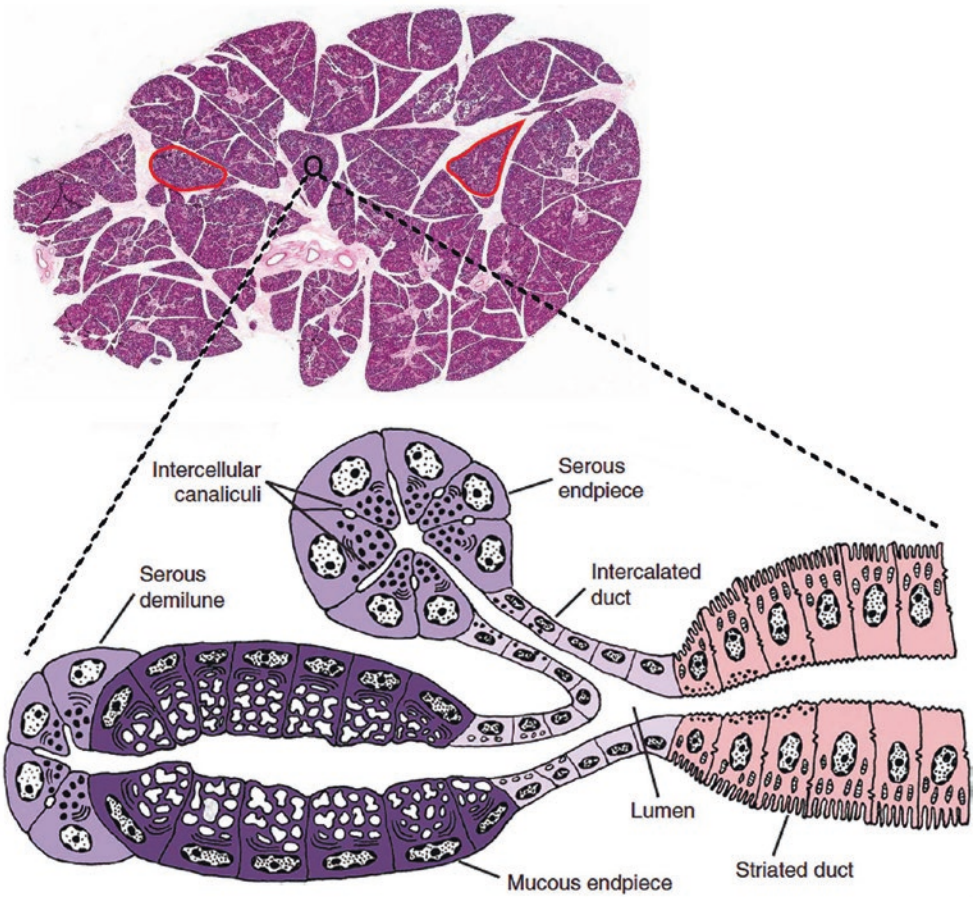

Fig. 6.2 Low-magnification view of human submandibular gland section with two lobules outlined in red. The diagram shows serous and mucous secretory endpieces and the intralobular components of the duct system. (Modified from [1]; reprinted with permission from Wiley-Blackwell)

mucous cell products. In typical histological preparations, mucous cells are characterized by a large apical mass of often fused, pale secretory granules; a flattened, dense nucleus; rough endoplasmic reticulum; and a large Golgi complex located in the basal cytoplasm (Fig. 6.5). However, this appearance has been shown to be an artifact of the chemical fixatives used to prepare tissue samples. In samples prepared by rapid cryofixation, mucous cell structure is similar to that of serous cells, with distinct, relatively compact secretory granules.

A third epithelial cell type present in the endpieces is the *myoepithelial cell* (Fig. 6.6). These are stellate-shaped contractile cells that are located between the basal lamina and the basal surfaces of the secretory cells. Processes originating from the cell body are filled with actin and myosin filaments and extend around the endpieces. The myoepithelial cells function to support the endpieces, and their contraction forces saliva from the endpiece lumen into and along the duct system. Myoepithelial cells also are located along the initial part of the duct system where they have a spindle shape and extend along the longitudinal axis of the duct. Their contraction serves to shorten and maintain the patency of the ducts.

The secretory endpieces are connected to the first part of the duct system, the *intercalated ducts* (Fig. 6.7). These ducts consist of small cuboidal cells that have a relatively simple structure with few organelles. In cross-section, the diameter of these ducts is always smaller than that of the secretory endpieces, and their lumina also have a small diameter. The cells nearest the endpieces may contain a few secretory granules in their apical cytoplasm; they contribute a few proteins and/or mucins to the saliva. The initial intercalated ducts usually join with other intercalated ducts, forming a larger intercalated duct, which may merge again before joining a striated duct.

The *striated ducts* form the main part of the intralobular duct system (Fig. 6.8). These ducts consist of a simple columnar epithelium surrounding a lumen larger than that of the intercalated ducts, and their overall diameter is as large as or larger than that of the secretory endpieces. The cells have a centrally placed nucleus, and at the light microscopic level the basal region appears to have vertical striations due to the

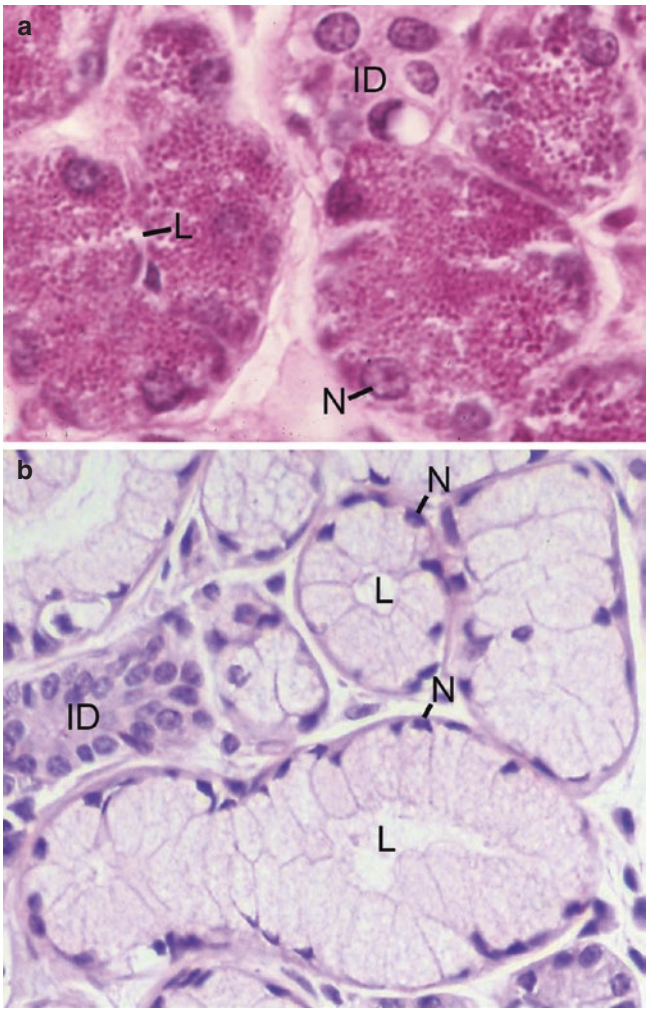

Fig. 6.3 (**a**) Serous cells: Three serous endpieces are seen, each consisting of several serous cells filled with densely stained secretory granules. A small lumen (L) is visible in the center of the endpiece at the left. Nuclei with prominent nucleoli are round to oval and located in the basal cytoplasm. (**b**) Mucous cells: Portions of several mucous endpieces, typically exhibiting a tubular configuration, are present. Lumina (L) are large and the lateral membranes of the mucous cells are distinct. The mucous cell cytoplasm is filled with pale mucous granules and their nuclei are dense and flattened against the basal cell surface. *ID* intercalated duct

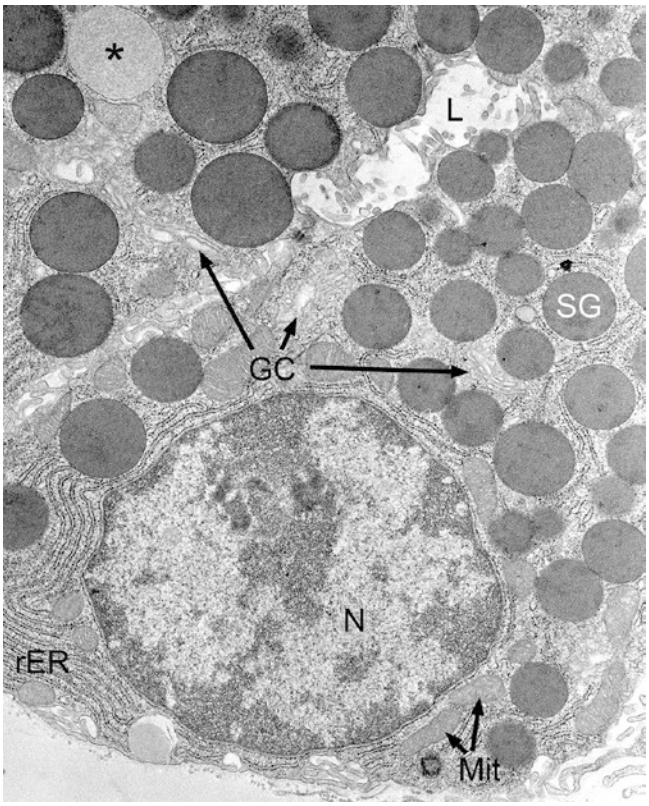

Fig. 6.4 Electron micrograph of a serous cell. The round nucleus (N) is located in the basal cytoplasm along with abundant rough endoplasmic reticulum (rER). The Golgi complex (GC) is in the supranuclear cytoplasm along with numerous dense secretory granules (SG). * immature secretory granule, *L* lumen, *Mit* mitochondria. (Modified from [1]; reprinted with permission of Wiley-Blackwell)

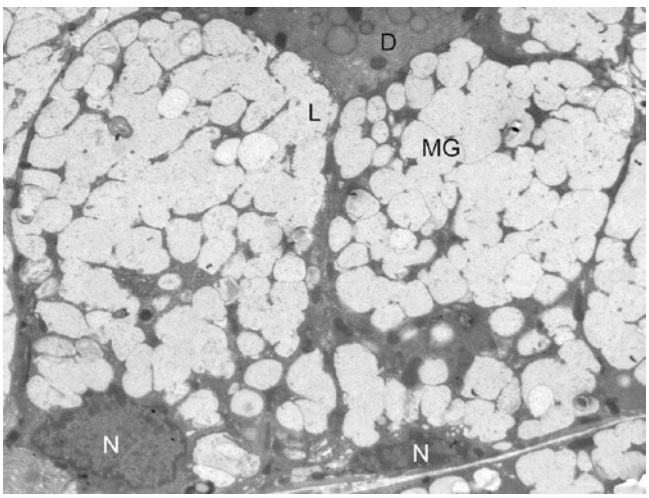

Fig. 6.5 Electron micrograph of two mucous cells. Their cytoplasm is filled with mucous granules (MG) with a light flocculent content. Most of the granules are fused with neighboring granules. The nuclei (N) are dense and located close to the basal cell membrane. A portion of a serous demilune cell (D) is visible at the top. *L* lumen

highly infolded basal cell membrane with numerous mitochondria aligned between the infoldings. The cytoplasm contains a few cisternae of rough endoplasmic reticulum, a small perinuclear Golgi complex, a few lysosomes and peroxisomes, and tubules of smooth endoplasmic reticulum and small vesicles in the apical cytoplasm. In some cells small dense secretory granules are present in the apical region. A few basal cells may be present in larger striated ducts, along with occasional dendritic cells. In addition to conveying the saliva toward the mouth, a significant function of the striated ducts (as well as the excretory ducts) is modification of the primary saliva secreted by the endpieces.

As the striated ducts leave the lobules and enter the interlobular connective tissue, they become *excretory* (or *interlobular*) *ducts* (Fig. 6.9). These ducts typically consist of a pseudostratified epithelium, with small basal cells and columnar cells that extend from the basal lamina to a large lumen. The columnar cells are similar in appearance to striated duct cells, but have fewer basal infoldings, and usually lack apical secretory granules. Occasional dendritic cells may be present, as well as mucous goblet cells in the larger ducts. Tuft cells with prominent microvilli that likely have chemosensory functions are scattered throughout the epithelium. As the excretory ducts merge and eventually form the *main excretory duct*, they increase in size and close to the oral cavity the epithelium may become stratified.

The parotid gland is a *pure serous gland with* all of its secretory endpieces consisting of serous cells (Fig. 6.10). The submandibular and sublingual glands are *mixed glands*, consisting of both serous and mucous cells. The submandibular gland consists predominantly of serous secretory endpieces, but also has mucous secretory endpieces arranged mainly in a tubular configuration (Fig. 6.11). The mucous tubules typically have a few serous cells attached to the end

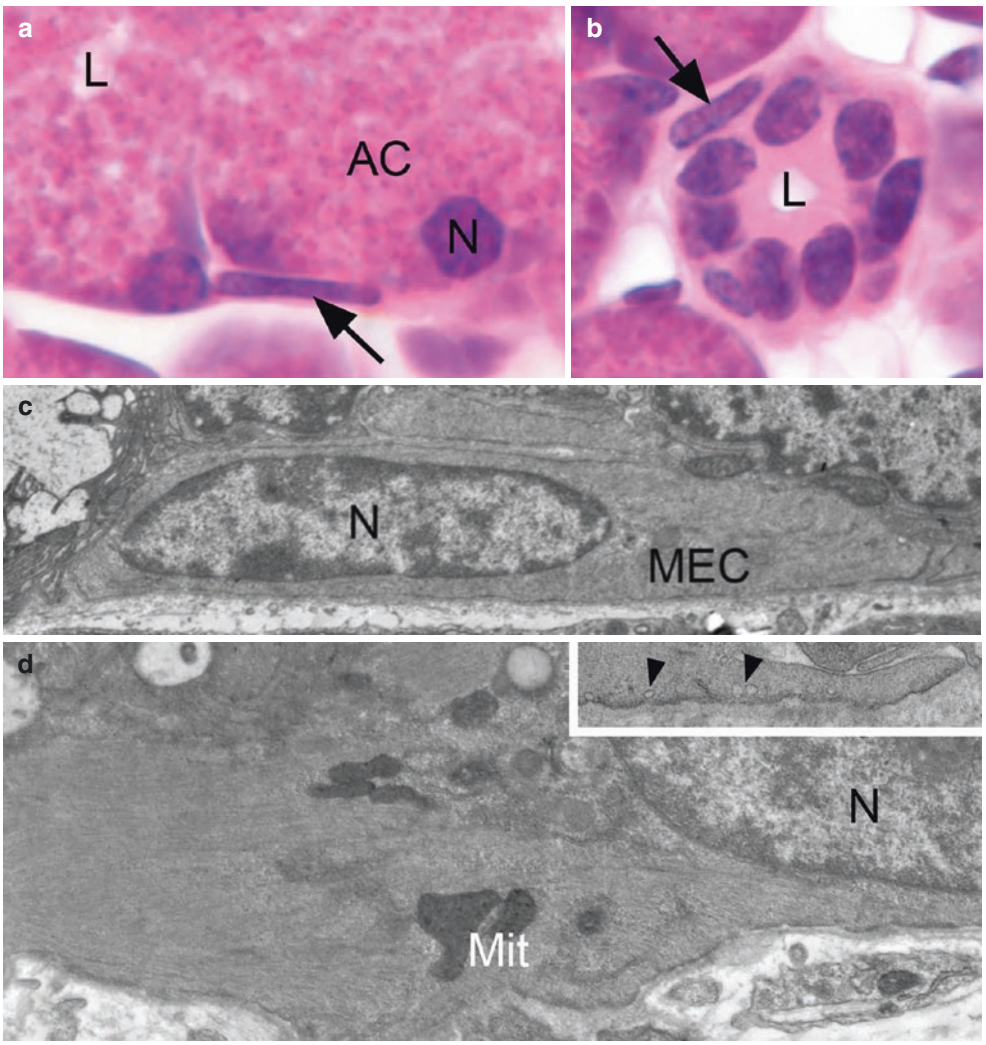

Fig. 6.6 Myoepithelial cells. (**a**) Myoepithelial cell (arrow) along the basal surface of serous acinar cells (AC). (**b**) Myoepithelial cell (arrow) associated with an intercalated duct. (**c**, **d**) Electron micrographs of myoepithelial cells (MEC) at the basal surfaces of mucous acini. The cytoplasm is filled with actin and myosin filaments. The inset in (**d**) shows caveolae (arrowheads) along the basal membrane of the myoepithelial cell. (Image courtesy of Dr. Zaki Hakami). *L* lumen, *Mit* mitochondria, *N* nucleus

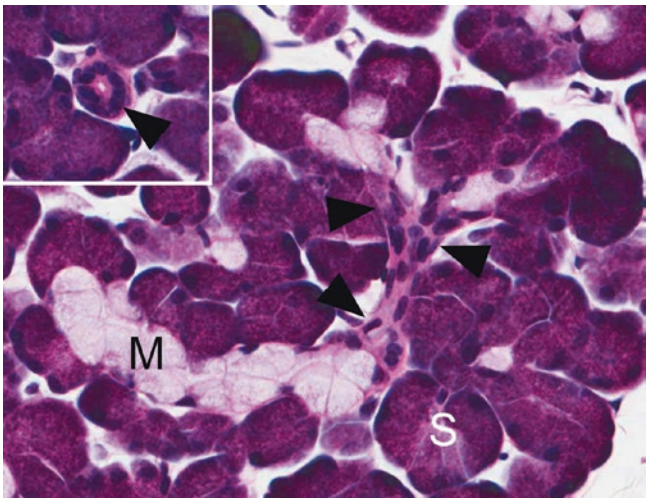

Fig. 6.7 Intercalated ducts. Longitudinal and cross (inset) sections of intercalated ducts (arrowheads). The ducts are smaller in diameter than the endpieces and consist of a simple cuboidal epithelium. A small lumen can be seen in the cross-sectioned duct. *M* mucous endpiece, *S* serous endpiece

of the tubule. This configuration is called a *serous demilune*. The products of the demilune cells reach the main lumen of the mucous tubule via intercellular canaliculi. The sublingual gland consists predominantly of mucous tubules with serous demilunes (Fig. 6.12); a few serous endpieces may be present. With age, an increase in the number of adipocytes present in the loose connective tissue occurs, especially in the parotid and submandibular glands. The main structural features of the major salivary glands are given in Table 6.1.

In addition to the three major glands, hundreds of small *minor salivary glands* are present in the mucosa throughout the oral cavity except for the gingivae, anterior dorsum of the tongue, and parts of the hard palate (Table 6.2) [1, 3]. These glands are located in the lamina propria or submucosa, or between muscle fibers of the tongue, and their ducts open directly onto the surface of the mucosa (Fig. 6.13). Most of the minor glands consist of mucous secretory endpieces; in some glands the mucous endpieces may have associated serous demilunes. An exception is the *lingual serous glands* (of *von Ebner*), associated with the circumvallate and foliate papillae on the posterior dorsal and lateral regions of the tongue (Fig. 6.13c). These are pure serous glands whose ducts open into the troughs of the papillae; they are thought to function in the taste process and maintenance of taste buds. The duct cells of the minor glands are similar to intercalated duct cells. Striated ducts usually are not present in these glands. The minor glands secrete continuously and play an important role in the moistening, lubrication, and protection of the oral mucosa.

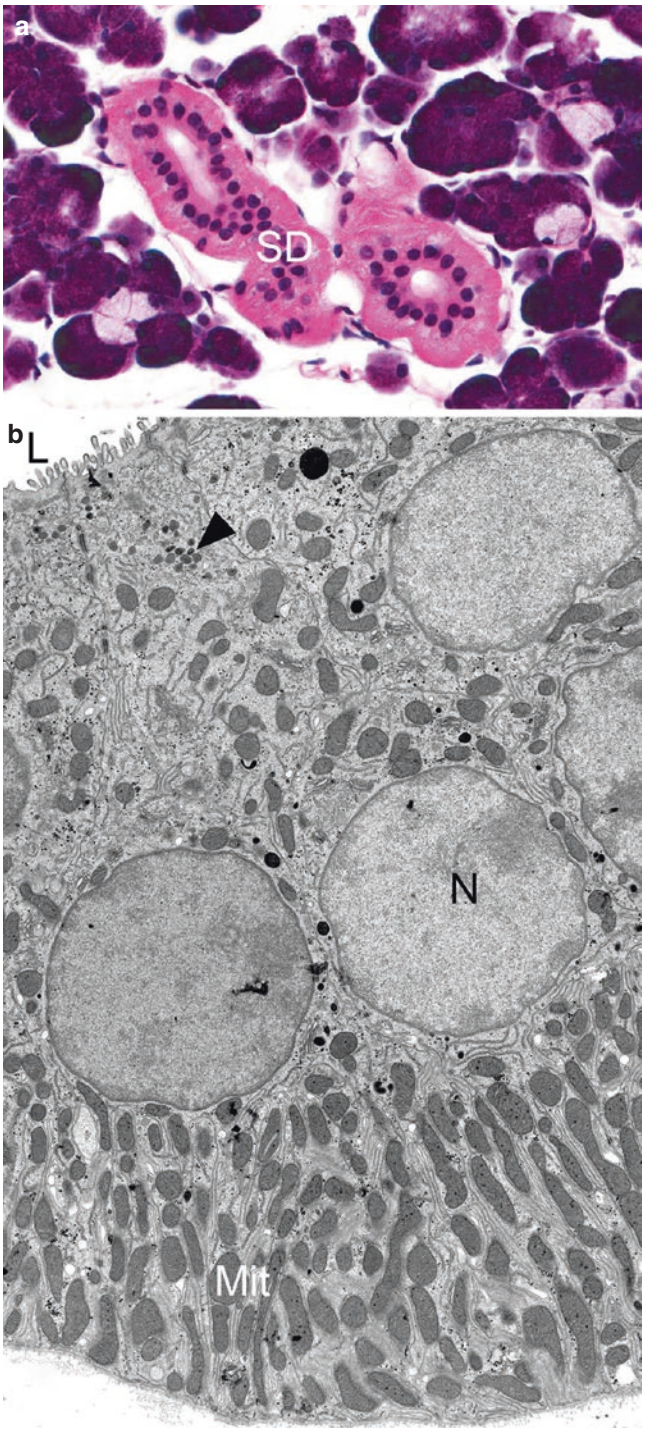

Fig. 6.8 Striated ducts. (**a**) Striated ducts (SD) are lined by a simple columnar epithelium. (**b**) Electron micrograph of striated duct cells. Numerous mitochondria (Mit) are located between infoldings of the basal cell membranes. A few small secretory granules (arrowhead) are present in the apical cytoplasm. *L* lumen, *N* nucleus. (Panel **b**, modified from [2]; reprinted with permission from the American Society for Biochemistry and Molecular Biology)

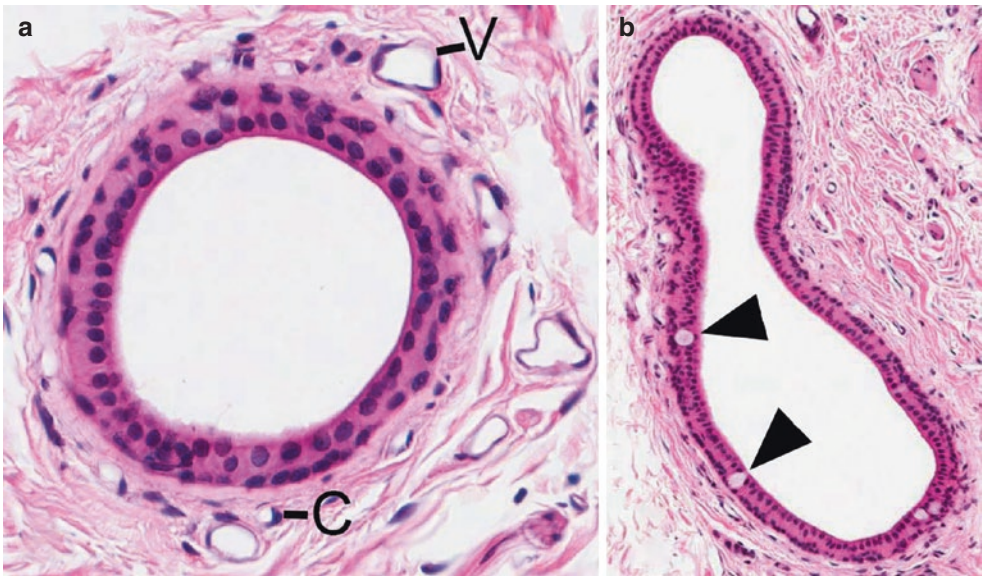

Fig. 6.9 Excretory ducts. (**a**) Medium, and (**b**) large excretory ducts with pseudostratified epithelium. A few goblet cells (arrowheads) are present in the epithelium of the large duct. Numerous small venules (V) and capillaries (C) are present in the connective tissue around the ducts

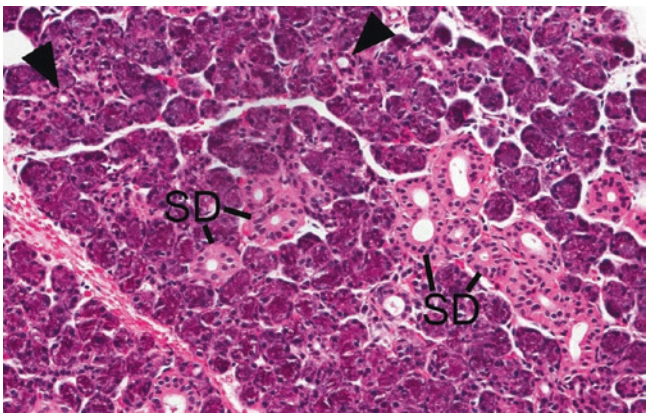

Fig. 6.10 Parotid gland: The parotid consists entirely of serous endpieces. Striated ducts (SD) are numerous and a few intercalated ducts (arrowheads) are visible

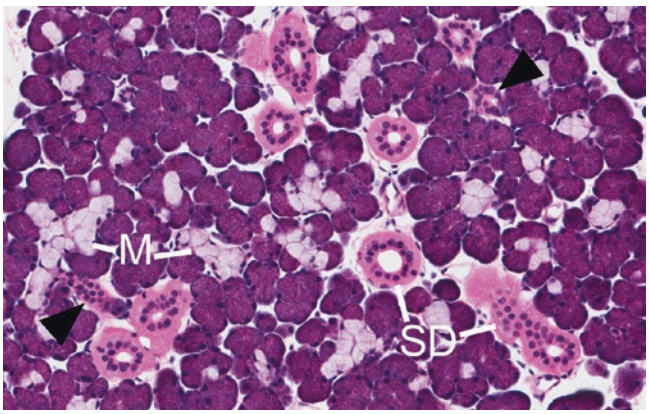

Fig. 6.11 Submandibular gland: The submandibular gland consists mainly of serous endpieces with some mucous endpieces (M). Striated ducts (SD) are prominent and a few intercalated ducts (arrowheads) are visible

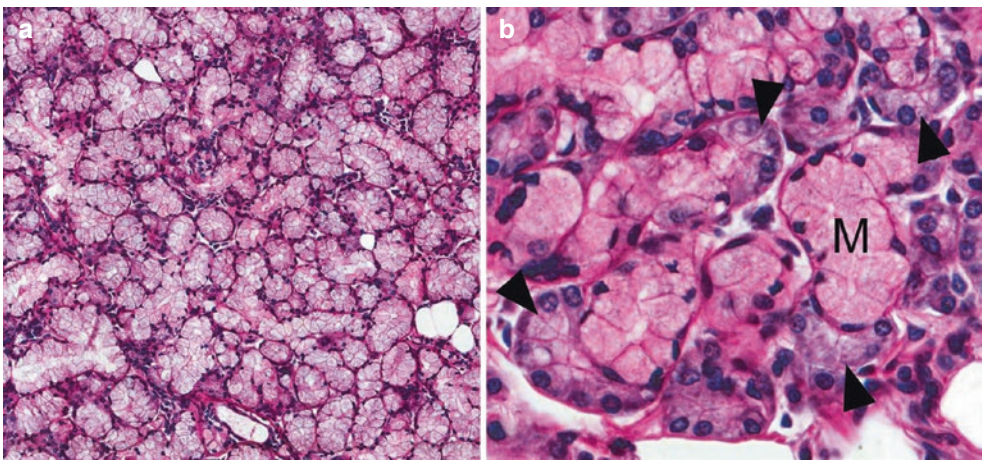

Fig. 6.12 Sublingual gland. (**a**) The sublingual gland consists predominantly of mucous endpieces and has fewer striated ducts than the parotid and submandibular glands; none are seen in this micrograph. (**b**) Higher magnification showing serous demilunes (arrowheads). *M* mucous endpiece

Table 6.1 Major salivary glands

Component	Parotid	Submandibular	Sublingual
Acini	All serous	Mostly serous; some mucous with serous demilunes	Mainly mucous with serous demilunes; a few serous acini may be present
Ducts			
Intercalated	Long, branching	Moderate length	Short, relatively few
Striated	Numerous, well developed	Numerous, well developed	Short, poorly developed
Main excretory	Stensen's; opens at parotid papilla on cheek opposite maxillary second molar	Wharton's; opens at sublingual caruncle at ventral tongue	Bartholin's; opens with submandibular duct at sublingual caruncle; ducts of Rivinus open along sublingual fold
Connective tissue capsule	Well defined	Well defined	Poorly developed
Blood supply	Branches of external carotid artery	Lingual artery	Sublingual artery
Nerve supply			
Parasympathetic	Cranial nerve IX via lesser petrosal nerve, otic ganglion, and auriculotemporal nerve	Cranial nerve VII via chorda tympani nerve, lingual nerve, and submandibular ganglion	Cranial nerve VII via chorda tympani nerve, lingual nerve, and submandibular ganglion
Sympathetic	Superior cervical ganglion with blood supply	Superior cervical ganglion with blood supply	Superior cervical ganglion with blood supply
Development begins	4th–6th fetal week	6th–8th fetal week	8th–12th fetal week

Modified from [1]

Table 6.2 Minor salivary glands

Gland	Location	Histological structure
Labial	Submucosa of lips	Mucous acini, serous demilunes
Buccal	Submucosa of cheeks	Mucous acini, serous demilunes
Palatine		
Hard palate	Posterior lateral submucosa	Mucous acini, serous demilunes
Soft palate	Submucosa of soft palate and uvula	Mucous acini, serous demilunes
Glossopalatine	Isthmus of palatoglossal fold	Mucous acini
Lingual		
Anterior	Ventral submucosa of tongue	Mucous acini, serous demilunes
Posterior	Lamina propria and between muscle fibers posterior to circumvallate papillae	Mucous acini, serous demilunes
Lingual serous	Lamina propria and between muscle fibers of posterior and lateral regions; ducts open into troughs of circumvallate and foliate papillae	Serous acini
Minor sublingual	Submucosa of floor of mouth	Mucous acini, serous demilunes

Modified from [1]

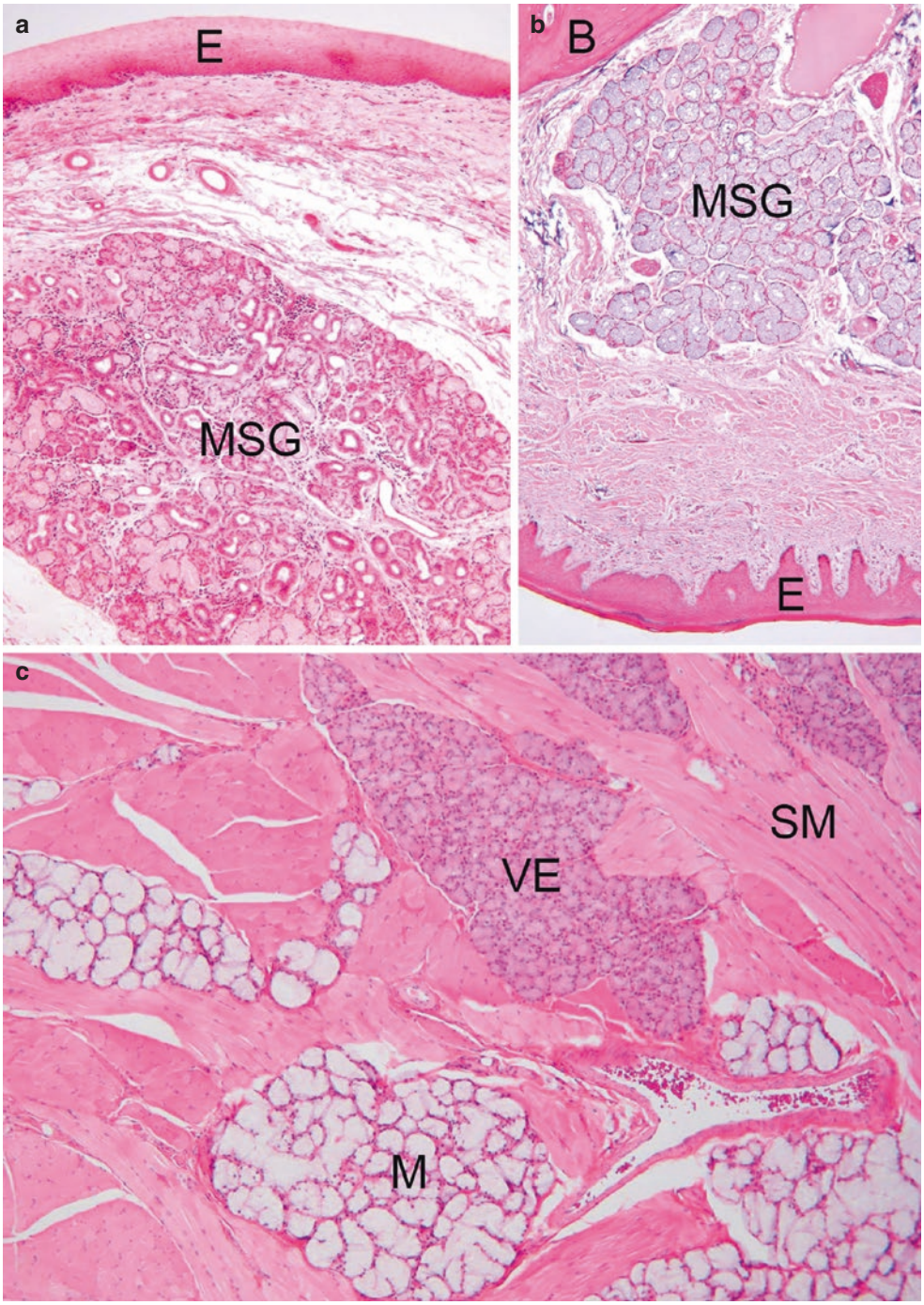

Fig. 6.13 Minor salivary glands. (**a**) Minor salivary gland (MSG) in the submucosa of the lip. (**b**) Minor salivary gland in the submucosa of the hard palate. (**c**) Lingual serous (von Ebner's, VE) glands and mucous (M) glands located between skeletal muscle fibers (SM) of the tongue. *B* bone, *E* oral epithelium. (Panel **c** modified from [1]; reprinted with permission from Wiley-Blackwell)

Development

The salivary glands begin their development as a proliferating bud of epithelial cells of the primitive oral mucosa at the sites where the main ducts will eventually open on the mucosal surface (Fig. 6.14a) [5–7]. The parotid gland arises from ectoderm; the submandibular and sublingual glands originate from the floor of the mouth at the transition between ectoderm and endoderm. A solid cord of cells formed by continued proliferation grows into the mesenchyme underlying the mucosa. Under the paracrine influence of several growth factors produced by the mesenchymal and epithelial cells, and the activity of specific transcription factors, the initial cell cord begins the process of *branching morphogenesis*, with repeated dichotomous branches, that eventually results in a bush- or tree-like structure (Fig. 6.14b). The inner cells of the terminal end buds and connecting cell cords then undergo apoptosis to create lumina, leaving a two-cell-thick

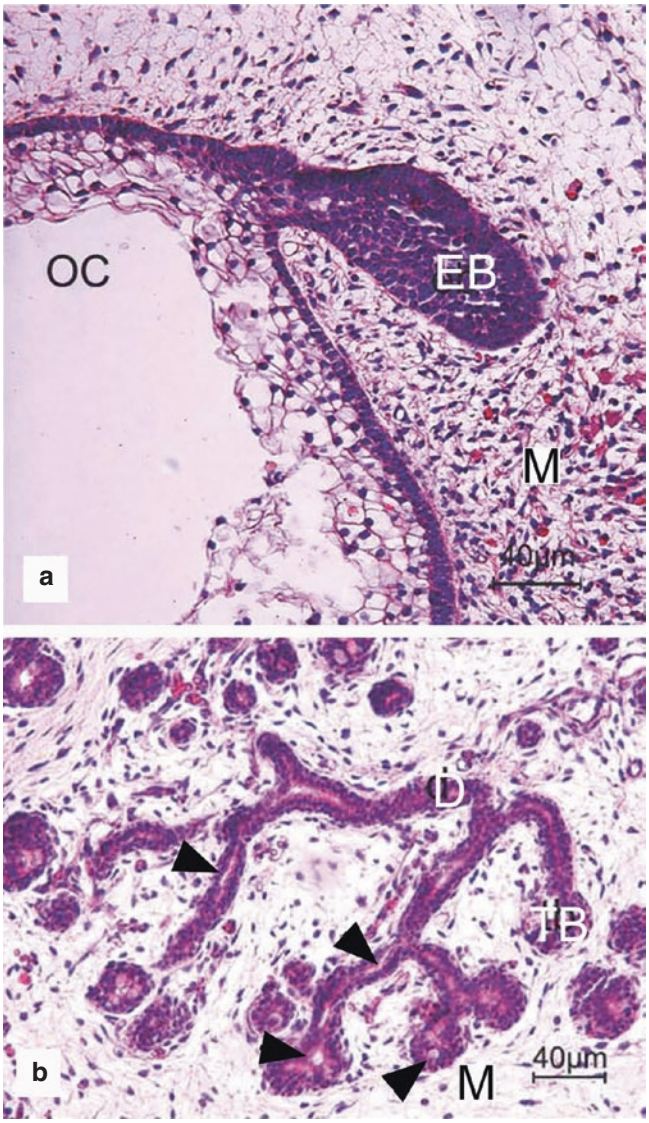

Fig. 6.14 Developing parotid gland. (**a**) An epithelial bud (EB) of proliferating cells from the oral epithelium grows into the underlying mesenchyme (M). Oral cavity (OC). (**b**) Repeated branching of terminal buds (TB) results in a bush-like structure with secretory endpieces and ducts (D) derived from the connecting cell cords. Lumina are forming in the ducts and some terminal buds (arrowheads). (Modified from [4]; reprinted with permission from Wiley-Liss, Inc.)

layer of epithelium. Cytodifferentiation of the cells of the inner layer produces the secretory cells of the endpieces and eventually the cells of the intercalated and striated ducts, whereas the cells of the outer layer differentiate into myoepithelial cells. The secretory cells develop the intracellular organelles of the secretory system and accumulate secretory granules. With the development of the autonomic innervation and functional neurotransmitter receptors on the secretory cells, the ability to secrete saliva is attained.

The development of the parotid gland begins at 4–6 weeks of embryonic life, the submandibular gland at 6–8 weeks, and the sublingual and minor glands at 8–12 weeks. Maturation of the secretory and duct cells is completed in the final 2 months of gestation, and the glands continue to increase in size postnatally.

Salivary Secretion

Secretion of saliva from the three major glands occurs at a low rate in awake individuals in the absence of an external stimulus [1, 8–11]. This *"unstimulated"* or *"resting"* secretion is due to input to the salivary nuclei in the brainstem from higher centers. In healthy adults the resting saliva flow rate ranges from 0.2 to 0.4 mL/min. The submandibular and sublingual glands contribute about two-thirds of the resting saliva, somewhat less than one-third comes from the parotid glands, and only a few percent from the minor glands. Saliva secretion is subject to a circadian rhythm, with peak flow in mid-afternoon and low flow in the early morning. During sleep and anesthesia, there is little to no secretion from the major glands, although the minor glands continue to secrete at a low rate.

Stimulation of taste receptors by taste substances in food and drink provides the most potent stimulus for salivary secretion. Mechanoreceptors in the periodontal ligament and oral mucosa, activated by chewing and movement, also provoke secretion, as do olfactory stimuli. *Stimulated* saliva flow rates may be five- to tenfold greater than resting rates, with the parotid gland making a greater contribution than the submandibular and sublingual glands. The total daily secretion of saliva typically is in the range of 0.6–1.0 L, most of which is swallowed.

The glands receive and respond to both sympathetic and parasympathetic innervation. The unmyelinated autonomic nerve fibers travel in the connective tissue in bundles supported by Schwann cells. In the parotid and submandibular gland, the acinar cells receive a dual sympathetic and parasympathetic innervation, whereas the mucous cells of the sublingual and minor glands are innervated predominantly by parasympathetic fibers.

The secretion of protein by serous cells occurs predominantly by exocytosis at the luminal cell surface of stored secretory granules, mainly in response to sympathetic nerve stimulation. Noradrenaline released by nerve terminals binds to β-adrenergic receptors on the serous cells. These G-protein-coupled receptors activate adenylyl cyclase, which generates cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The subsequent activation of protein kinase A (PKA) initiates an intracellular signaling cascade involving other proteins and intracellular Ca^{2+} that results in docking of the granules and fusion of their membranes with the luminal cell membrane and discharge of their contents (Fig. 6.15). Parasympathetic nerve stimulation also results in

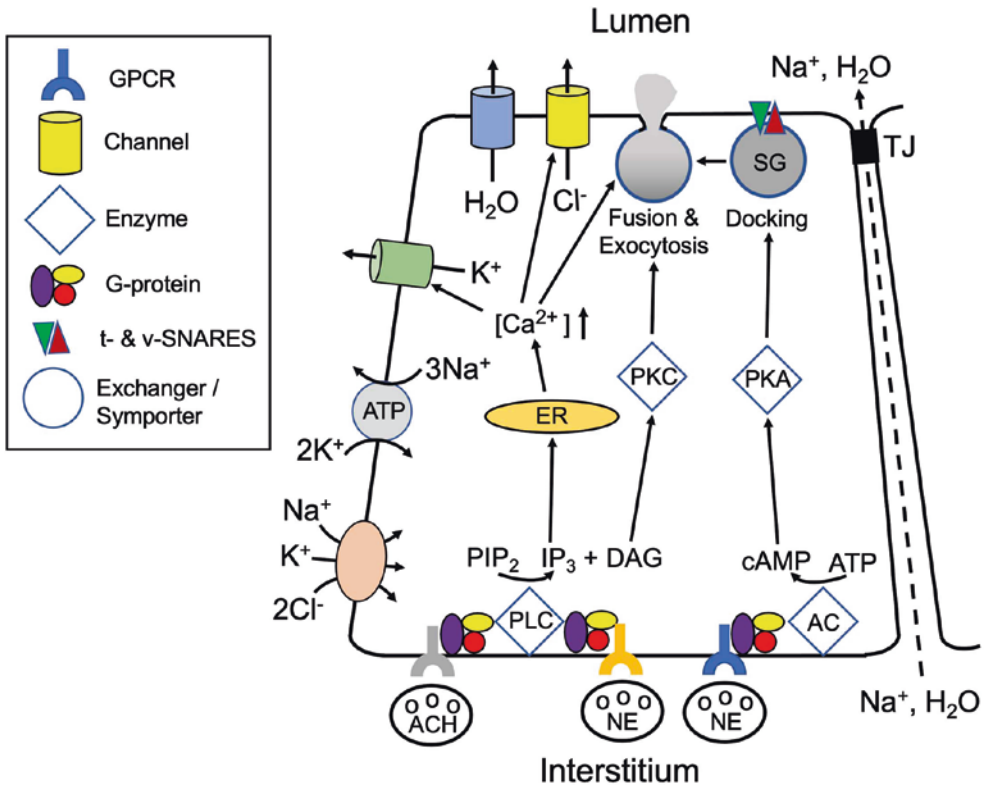

Fig. 6.15 The main pathways regulating fluid and protein secretion in salivary gland acinar cells. Fluid secretion is stimulated primarily by binding of acetylcholine (ACH) released from parasympathetic nerve endings to muscarinic M_3 G-protein coupled receptors (GPCRs) in the basolateral cell membranes. Norepinephrine (NE) released from sympathetic nerve endings elicits a smaller amount of fluid secretion by binding to α_1-adrenergic GPCRs. The $G_{q/11}$ G-protein activates phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG). IP_3 binds to receptors on the endoplasmic reticulum (ER), resulting in release of stored Ca^{2+}. The elevated level of intracellular Ca^{2+} opens Cl^- channels in the luminal cell membrane and K^+ channels in the basolateral membrane. Cl^- efflux creates an electrochemical gradient that pulls extracellular Na^+ into the lumen via the paracellular pathway through tight junctions (TJ). The resulting osmotic gradient causes water to enter the lumen through tight junctions and via aquaporin 5 channels in the luminal membrane. During strong stimulation leading to high salivary flow rates, HCO_3^- efflux via luminal Cl^- channels can contribute to the luminal electrochemical gradient. The Na^+/K^+-ATPase and $Na^+/K^+/Cl^-$ co-transporter in the basolateral membrane, along with other channels and transporters, maintain the cell's pH and ionic equilibria. Protein secretion is stimulated mainly by NE binding to β_1-adrenergic GPCRs. The G_s G-protein activates adenylyl cyclase (AC), which forms cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP activates protein kinase A (PKA), which phosphorylates other proteins leading to docking of secretory granules (SG) at the luminal cell membrane through interactions of vesicle-associated Soluble *N*-ethylmaleimide-Sensitive Factor Receptor (v-SNARE) and target-associated t-SNARE proteins. Increased Ca^{2+} levels cause fusion of the granule and cell membranes and formation of a pore, resulting in release of the granule content by exocytosis. ACH binding to M_3 receptors, activation of protein kinase C (PKC) by DAG, and increased intracellular Ca^{2+} also result in exocytosis, but at a lower level than β_1-adrenergic receptor stimulation

some protein secretion, at much lower levels than sympathetic stimulation, through protein kinase C (PKC) activation and Ca^{2+} release. Secretion of mucus from mucous cells occurs mainly in response to parasympathetic stimulation.

Fluid and electrolyte secretion by the acinar cells is stimulated predominantly by the parasympathetic nervous system. Acetylcholine released from nerve terminals binds to G-protein-coupled muscarinic M_3 receptors, leading to activation of phospholipase C and the hydrolysis of phosphatidylinositol bisphosphate into diacylglycerol and inositol trisphosphate (IP_3). Binding of IP_3 to its receptor on the endoplasmic reticulum releases Ca^{2+} to the cytoplasm. The increased intracellular [Ca^{2+}] opens Cl^- channels on the luminal membrane, leading to an increase in luminal [Cl^-], which draws extracellular Na^+ into the lumen via the paracellular pathway. The resulting increase in luminal osmotic pressure draws water into the lumen via the paracellular route and also through aquaporin 5 (AQP5) water channels in the luminal membrane (Fig. 6.15). Noradrenaline, binding to G-protein-coupled α-adrenergic receptors, also stimulates some fluid and electrolyte secretion. Sympathetic and parasympathetic stimulation also results in contraction of myoepithelial cells, propelling the saliva into and through the duct system.

This *primary saliva*, which contains the organic products of the acinar cells as well as some substances present in

blood plasma and the extracellular fluid that are transported or diffuse across the epithelium, is essentially isotonic with respect to Na^+ and Cl^- concentrations. As the primary saliva moves through the duct system, it is modified by reabsorption of Na^+ and Cl^- and secretion of K^+ and HCO_3^- by the striated duct cells. Important for this process are the Na^+/K^+/ATPase in the infolded basolateral cell membranes and the abundant mitochondria between the infoldings, along with co-transporters, ion exchangers, and channels in the basolateral and luminal cell membranes, including the cystic fibrosis transmembrane regulator (CFTR). Because the striated ducts are relatively impermeable to water, the resulting saliva that enters the mouth is hypotonic. Na^+ and Cl^- reabsorption also occurs in the excretory ducts, but to a lesser extent than in the striated ducts.

In addition to modifying the electrolyte content of saliva, striated ducts also modify the protein content. The small apical granules present in cells in the first part of the ducts contain *kallikrein*, a serine protease, which is released into saliva. Experimental animal studies have shown that the duct cells are capable of endocytosing salivary and exogenous proteins from the lumen; whether this occurs in human glands is unknown.

Saliva Composition and Function

Saliva consists of about 99% water; the remaining 1% consists of proteins, glycoproteins, mucins, small molecules, and electrolytes (Table 6.3) [1, 8, 11–14]. Its composition varies depending upon the source of the saliva (*glandular saliva*, collected from the main duct of a major gland, or *whole* or *mixed saliva*, the fluid present in the mouth), the specific stimulus evoking secretion, and the physiological condition of the subject. In addition to the components present in glandular saliva as noted above, whole saliva contains oral microorganisms, desquamated oral epithelial cells, and food remnants, as well as molecular components, white blood cells, and fluid derived from the gingival crevice that surrounds each tooth.

Table 6.3 Composition of whole saliva

Parameter	Characteristics
Volume	600–1000 mL/day
Flow rate: resting/stimulated	0.2–0.5 mL per min/2 ≥ 6 mL per min
pH	6.7–7.4
Osmolality	~50–75 mOsm/kg
Electrolytes	Na^+, K^+, Cl^-, HCO_3^-, Ca^{2+}, Mg^{2+}, HPO_4^{2-}, SCN^-, F^-, I^-
Protein concentration	0.5–1.5 mg/mL
Major proteins	Amylase, PRPs, cystatins, mucins, S-IgA, statherin, carbonic anhydrase VI, histatins, lysozyme
Small molecules	Glucose, amino acids, urea, uric acid, lipids
Other components	Growth factors, cytokines, insulin, cyclic AMP-binding proteins, serum albumin

Modified from [1]

The flow of saliva around the oral cavity and swallowing result in the dilution and clearance of food, cellular debris, non-adherent microorganisms, and the metabolic substrates and products of adherent microorganisms. In individuals with reduced salivary function, the prolonged presence of these substances increases the risk of disease. The volume of saliva present in the mouth before a swallow averages 1.1 mL. This volume is spread over the entire surfaces of the teeth and oral mucosa, resulting in a thin film that varies in thickness (0.07–0.1 mm) and rate of movement in different regions of the oral cavity. On the lingual side of the mandibular incisors and the facial side of the maxillary molars, movement of saliva is rapid due to the openings of the ducts of the major salivary glands. In contrast, the presence of only minor glands in the lips results in slow movement of saliva along the facial surfaces of the maxillary incisors.

Saliva also moistens and lubricates the soft and hard tissues of the oral cavity and the pharyngeal and esophageal mucosae. Individuals with reduced salivary function typically complain of a dry mouth and difficulty with chewing, swallowing, and speech. Salivary mucins (mainly the large gel-forming *MUC5B* mucin and the small soluble *MUC7* mucin) bind water and coat the teeth and mucosa, making them slippery. Other salivary constituents contributing to tissue lubrication include *glycosylated proline-rich proteins* (PRPs) and *statherin*, along with the *salivary pellicle* (described below).

The pH of whole saliva ranges from 6.7 to 7.4. Bicarbonate (HCO_3^-), secreted by the major salivary glands, is the main buffering system in saliva; HCO_3^- serves to neutralize acid ingested in food and drinks and produced by oral microorganisms. *Carbonic anhydrase VI*, secreted by serous cells of the salivary glands, catalyzes the reaction:

$$H^+ + HCO_3^- \rightleftarrows H_2CO_3 \rightleftarrows H_2O + CO_2 \uparrow$$

Phosphate (HPO_4^{2-}) makes a small contribution to saliva buffering, as do some cationic salivary proteins. Ammonia, derived from salivary urea by the action of urease secreted by some oral bacteria, also serves to neutralize acid.

Salivary proteins, glycoproteins, mucins, and lipids adsorb onto the teeth and mucosa, and, along with cellular and serum proteins, create a thin film (up to 1 μm thick) of organic material called the salivary pellicle. While numerous salivary proteins are found in the pellicle, the major ones include statherin, *histatins*, *cystatins*, *acidic PRPs*, *carbonic anhydrases*, *amylase*, and mucins. The pellicle formed on tooth surfaces, also called the *acquired enamel pellicle*, has been most studied. It begins to form within seconds after the tooth surface is cleaned. Although thin, it may serve in a

small capacity as a diffusion barrier, slowing the penetration of acid into the enamel and the loss of mineral from the enamel. As saliva is supersaturated with respect to Ca^{2+} and PO_4^{3-}, the pellicle also prevents mineral deposition on the enamel surface. However, during the initial formation of dental caries, the presence of calcium-binding proteins in the pellicle, such as statherin, histatin 3, and acidic PRPs, provides a reservoir of Ca^{2+} and PO_4^{3-} at the tooth surface, which can remineralize early subsurface lesions. In the presence of F^-, the remineralizing enamel crystals form as fluoroapatite, which is less soluble than carbonate substituted hydroxyapatite. The tooth and mucosal pellicles also help protect the teeth from abrasion by acting as a surface lubricant. Finally, several pellicle components serve to bind oral microorganisms, initiating the formation of a *bacterial plaque* on the tooth surfaces.

Many salivary proteins and peptides have antimicrobial activity. These antimicrobial factors, along with good oral hygiene, contribute to the maintenance of oral health even in the presence of the hundreds of species of microorganisms in the normal oral flora. Histatins, a family of small cationic proteins, inhibit the growth of *Candida albicans*, and also have antibacterial activity. *β-Defensins*, small peptides that can insert into bacterial membranes and cause lysis, are secreted by epithelial cells and neutrophils that enter the mouth via the gingival crevice. *Lysozyme* hydrolyzes the peptidoglycan of bacterial cell walls causing lysis, and *lactoferrin* binds iron, inhibiting the metabolic activity of several microorganisms. In the presence of hydrogen peroxide (H_2O_2), *salivary peroxidase* secreted by salivary acinar cells and *myeloperoxidase* released by white blood cells convert thiocyanate (SCN^-) to hypothiocyanite ($OSCN^-$), which can enter and kill bacterial cells; myeloperoxidase also produces the more potent hypochlorite ion (OCl^-). Cystatins and *secretory leukocyte protease inhibitor* (SLPI) can inhibit bacterial proteases, preventing metabolism of salivary proteins to amino acids. Several salivary proteins bind and agglutinate microorganisms, preventing their attachment to the teeth and mucosa and facilitating their removal by swallowing. MUC7, PRPs, *salivary agglutinin* (also known as *GP340* and *DMBT1*), synthesized and secreted by salivary gland epithelial cells, and dimeric *secretory immunoglobulin A* (S-IgA), produced by salivary gland plasma cells and transferred across the gland epithelium into saliva, act in this manner. While a small amount of pentameric *immunoglobulin M* (IgM) is transferred into saliva by this route, both IgM and *immunoglobulin G* (IgG) enter saliva via the gingival crevice. Finally, a number of salivary proteins have antiviral activity; these include defensins, cystatins, PRPs, MUC7, S-IgA, lactoferrin, peroxidases, SLPI, *thrombospondin 1*, and *cathelicidin LL37*. Some of these proteins have been shown in vitro to inhibit the infectivity of the human immunodeficiency virus-1 (HIV-1), and recent studies have demonstrated that the early post-symptom immune response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection results in neutralizing S-IgA antibodies in saliva and at other mucosal surfaces.

It is well known that injuries to the oral mucosa heal more rapidly and with less scar formation than skin injuries [8, 15]. Several factors in saliva have been shown to enhance wound healing. Mucins keep the mucosa moist, tissue factor accelerates blood clotting, and salivary antimicrobial components help to prevent infection. Growth factors in saliva that may contribute to oral wound healing include *epidermal growth factor* (EGF), *transforming growth factor alpha* (TGFα), and *vascular endothelial growth factor* (VEGF). *Trefoil factor 3* (TFF3), a small peptide secreted by mucous cells, promotes mucosal healing, and histatin 1 stimulates epithelial cell and fibroblast migration.

Saliva makes a modest contribution to the digestion of food. Saliva, and particularly mucins, helps to form a food bolus and facilitate swallowing. *α-Amylase*, secreted by serous cells, is the main digestive enzyme in saliva. It hydrolyzes starch into maltose and other small oligosaccharides. Its activity is largely confined to the oral cavity and esophagus, as it is inactivated by gastric acid. *Lingual lipase*, produced in small amounts by the lingual serous glands and pharyngeal glands, makes a minor contribution to lipid digestion. *Ribonuclease* and *deoxyribonuclease* are present in saliva, but their contribution to nucleic acid digestion is unknown. Kallikrein is secreted by striated duct cells, although a specific role in digestion has not been described.

Certain salivary proteins have been shown to bind toxic substances in food, and in response to these substances, the synthesis of the proteins is increased. Tannins inhibit growth and have toxic effects and are found in many plant-derived foods. Basic PRPs and histatins bind tannins and inhibit their uptake by intestinal epithelial cells; experimental studies in rodents have shown a marked increase in PRP synthesis in animals fed food containing tannins. Cystatins, cysteine peptidase inhibitors, may help protect against plant-derived papain-like enzymes. The synthesis of other salivary proteins may be modified by other food constituents or drugs. The sugar substitute xylitol increases salivary peroxidase activity, and treatment of rodents with β-adrenergic agonists increases PRP synthesis.

Saliva is essential for taste. It solubilizes taste substances in food and distributes them to the taste buds located on fungiform, circumvallate, and foliate papillae of the tongue, as well as the soft palate and epiglottis. Saliva in the mouth is hypotonic, with low Na^+ and Cl^- concentrations, which allows tasting of dilute salty solutions. Bicarbonate in saliva neutralizes acid thus decreasing sour taste. The concentrations of other substances present in saliva that potentially could stimulate taste receptors, such as glucose, glutamate, and urea, are below their taste thresholds.

Salivary Diagnostics

It has long been appreciated that certain substances present in saliva can offer information about the physiological status and health of the individual [8, 16–18]. Steroid hormones (cortisol, testosterone, estrogen) are readily detectable in saliva; cortisol in particular has been used as an indicator of stress. The concentration of α-amylase in saliva, released by sympathetic nerve stimulation and adrenal activity, also has been correlated to stressful situations. Changes in salivary concentrations of cortisol and/or α-amylase frequently are used in psychological studies of stressful situations. Numerous drugs, including drugs of abuse (e.g., cocaine, marijuana, barbiturates, amphetamines), are transferred into saliva. Their presence in saliva is determined by their lipid solubility, size, dissociation constant, and plasma-protein-binding characteristics. The use of saliva for drug testing often is more convenient, and less prone to sample substitution, than urine. Commercial devices and kits are available for the detection of several drugs in saliva.

Saliva is a convenient fluid for diagnosis of several viral infections as well as certain bacterial and parasitic infections [19, 20]. A number of viruses have been detected in saliva using molecular methods (e.g., polymerase chain reaction [PCR]) or antigen-based immunodetection. Although the majority of oral viruses are bacteriophages, several pathogenic viruses can be detected using these methods (Table 6.4). For some pathogens, antibodies present in saliva are used for diagnosis. Specialized collection devices as well as detection kits for some of these organisms are commercially available.

During the last two decades an emphasis has been placed on enumerating all of the proteins present in saliva, i.e., the *salivary proteome* [21]. The rationale is that if changes in the presence or quantity of specific salivary proteins can be detected, saliva could be used as an alternative or supplement to blood plasma/serum analyses for diagnosis of disease or monitoring physiological conditions [8, 16, 22]. More recently the presence of DNA, RNA, and microRNAs in saliva, as well as the ability to collect and analyze salivary *exosomes* (small cell-derived membrane-bound vesicles), has broadened the diagnostic possibilities. Current research is focused on identification of biomarkers for specific disease conditions. These include oral conditions such as periodontal disease and oral cancer, and systemic diseases such as pancreatic cancer, Parkinson's disease, and Alzheimer's disease. The ease and non-invasive nature of saliva collection make its use as a diagnostic fluid an attractive option.

Saliva also has important uses in forensic medicine [18]. The oligosaccharide groups present on salivary mucins are identical to ABO and Lewis blood group substances in about 80% of the population, making it possible to determine the blood type of an individual from a sample of saliva. Genetic polymorphisms in the PRPs, α-amylase, and several other salivary enzymes have been used for personal identification and paternity tests. The PRPs, including acidic, basic, and glycosylated forms, constitute a family of over 100 members derived by alternative splicing of 6 genes; PRPs account for greater than 50% of the protein secreted by the parotid gland. DNA derived from desquamated mucosal epithelial cells is frequently used to determine genotype and to positively identify an individual.

Table 6.4 Pathogenic organisms detectable using saliva

By PCR or immunodetection	By salivary antibodies
HIV-1	HIV-1, -2
Zika	West Nile
SARS-CoV-1, -2	Rotavirus
Influenza	Norovirus
Rabies	*Helicobacter pylori*
Epstein-Barr	*Campylobacter jejuni*
Human herpesviruses	*Entamoeba histolytica*
Human papilloma virus	*Toxoplasma gondii*
Herpes simplex 1	*Ascaris lumbricoides*
Hepatitis A, B, C	*Trichinella spiralis*
Measles	*Taenia solium*
Mumps	
Cytomegalovirus	
Dengue	
Ebola	
Chikungunya	
Nipah	

From [19]

Clinical Correlations

Altered salivary gland function, especially dry mouth, is a relatively common patient complaint. The feeling (subjective sensation) of a dry mouth is *xerostomia* [8]. The objective measurement of a reduced amount of saliva is termed *salivary hypofunction*; usually this is defined as <0.1 mL/min whole saliva. Much less common is the subjective feeling or objective measurement of too much saliva, termed *salivary hyperfunction* or *sialorrhea*. *Salivary gland dysfunction* is the general term applied to such alterations of gland function.

There are several potential causes for salivary hypofunction including drugs with central or peripheral effects on the autonomic nervous system, autoimmune diseases, and damage to gland tissue from therapeutic radiation for head and neck cancer. In addition to reduced salivary flow, the electrolyte and/or protein composition of saliva may be altered in many of these conditions. The consequences of salivary hypofunction include dental caries; mucosal infections and ulcerations; difficulties in swallowing, chewing, and speaking; and an overall reduced quality of life.

The most common cause of dry mouth is prescribed medications, over-the-counter drugs, and illegal drugs [23–25]. Categories of drugs causing salivary hypofunction or xerostomia are given in Table 6.5. Strong to moderate clinical evidence has identified as many as 100 drugs that are associated with salivary hypofunction. Weaker evidence implicates nearly 50 additional drugs as causing salivary hypofunction. Fewer drugs cause objective (clozapine, olanzapine, venlafaxine, clobazam) or subjective (quetiapine, risperidone, enalapril, haloperidol, methyldopa) sialorrhea. Animal studies have shown that clozapine may cause both sialorrhea and reduced salivation by stimulation of muscarinic M1 receptors and by inhibition of muscarinic M3 and α_1-adrenergic receptors, respectively. Dry mouth has been reported as a side effect of some chemotherapeutic agents, e.g., 5-fluorouracil, cisplatin, or bevacizumab. Prescribing an alternative medication or, if feasible, reducing the dosage may help to alleviate the symptoms.

Autoimmune diseases may damage the salivary glands and result in salivary hypofunction. *Sjögren's syndrome* (SS) is the most common autoimmune disease affecting the salivary glands, with a preponderance of cases in females [8, 26–28]. Lymphocytic invasion of the glands occurs with destruction especially of the secretory cells. The loss of fluid secretory capacity and the protection offered by salivary proteins and buffering cause dry mouth; difficulty in speaking, chewing, and swallowing food; and the risk of dental caries, mucosal infections, and ulcers. In *primary SS*, or *sicca syndrome*, lacrimal glands also are affected, resulting in dry eyes. *Secondary SS* includes the presence of other autoimmune diseases, such as rheumatoid arthritis, lupus erythematosus, or systemic sclerosis. Although a few antigens have been linked to the onset of SS, and several viral infections are thought to be predisposing factors, a specific cause has not been unequivocally identified. Recent studies indicate that the activation of toll-like receptors (TLRs) on salivary gland epithelial cells and immune cells plays a significant role in the pathogenesis of SS. TLRs recognize exogenous (microbial) as well as endogenous ligands, including nucleic acids. Diagnosis of SS often can be confirmed by measurement of whole saliva flow rates, biopsy of a labial minor salivary gland with microscopic examination, and the presence of serum anti-Ro/SSA and anti-La/SSB antibodies in 70% and 45% of patients, respectively.

Table 6.5 Categories of drugs causing salivary gland hypofunction

By pharmacologic classification	By system
Anticholinergics	Alimentary tract and metabolism
Sympathomimetics	Cardiovascular system
Skeletal muscle relaxants	Genitourinary system and sex hormones
Antimigraine agents	Musculoskeletal system
Benzodiazepines, hypnotics, opioids, drugs of abuse	Anti-neoplastic and immunomodulating agents
H2 antagonists, proton pump inhibitors	Nervous system
Cytotoxic agents	Respiratory system
Retinoids	Sensory organs
Anti-HIV agents	
Cytokines	

From [23, 25]

IgG4-related disease (IgG4-RD) is an autoimmune condition most often occurring in middle-aged to elderly males that affects many organs, including the salivary glands [27, 29]. It is characterized by elevated serum IgG4 levels (≥135 mg/dL), gland swelling, storiform tissue fibrosis, obliterative phlebitis, a lymphoplasmacytic infiltrate with abundant IgG4-positive plasma cells, and tissue eosinophilia. Salivary secretion may or may not be reduced, with xerostomia occurring in about 30% of patients. IgG4-RD usually responds well to immunosuppressants such as glucocorticoids.

Hematopoietic stem cell transplantation resulting in graft-vs.-host disease also can affect salivary gland function. Early effects include salivary gland inflammation, salivary flow reduction, and decreases in some antimicrobial components in saliva, including S-IgA. At later times after transplantation, other antimicrobial proteins showed an increase, particularly SLPI, lactoferrin, and β_2-miroglobulin.

Salivary glands are particularly sensitive to damage from radiation therapy for head and neck cancer [27, 30]. Loss of acinar secretory cells and damage to vascular tissues result in reduced secretion of fluid and protective salivary proteins. Dental caries, mucosal infections, and ulcers are common. Radioactive iodine treatment for thyroid cancer also can damage salivary glands [31]. The striated duct cells express the Na^+/I^- symporter and are most commonly affected, resulting in damage to the ducts and surrounding tissue with subsequent inflammation and fibrosis. Serous cells also concentrate I^-; thus the parotid gland is more affected by radioactive iodine therapy than the submandibular and sublingual glands. Radioactive iodine therapy also poses an increased risk of developing a secondary primary malignancy in the salivary glands. Patients should have any necessary dental treatment done prior to the radiotherapy, and post-treatment follow-up with particular attention to oral hygiene, regular dental checkups, and fluoride treatments.

Treatment of salivary hypofunction is generally palliative, e.g., sipping water, use of artificial saliva. If functional gland tissue remains, chewing sugar-free gum, use of a saliva substitute containing a topical stimulus such as malic acid, or prescribing oral parasympathomimetic drugs (low-dose pilocarpine, cevimeline, bethanechol) may increase salivary flow. Considerable research into the use of gene therapy to improve salivary function, as well as a phase 1 clinical trial, has been conducted, although currently it is not in general

use [32]. The procedure involves retrograde ductal infusion of an adenovirus or adeno-associated virus containing the gene for human aquaporin-1 to increase fluid secretion. Also being studied are means to prevent radiation damage with radioprotective compounds (e.g., tempol), biologicals (growth factors, cytokines), and apoptosis inhibitors (dasatinib). In appropriate patients, surgical transfer of one submandibular gland to a region not included in the field of radiation (e.g., submental space, parotid region) has been shown effective in reducing post-radiation hypofunction. Finally, therapeutic uses of stem cells derived from salivary glands or other tissues (e.g., mesenchyme, adipose tissue, dental follicle, dental pulp) to regenerate the glands, as well as tissue engineering approaches, are being studied [33].

True sialorrhea is a rare condition. Drooling, due to poor oral motor control and swallowing impairment, frequently is associated with neurological disorders, such as Parkinson's disease, amyotrophic lateral sclerosis, stroke, and cystic fibrosis [34]. Besides embarrassment and reduced quality of life, the inability to swallow saliva can result in skin infection, choking, and aspiration. Behavioral therapy for mild drooling may be successful. Pharmacologic approaches to control drooling include anticholinergic drugs, e.g., scopolamine, benztropine, glycopyrrolate, tropicamide, or injection of botulinum toxin into the parotid or submandibular gland. Surgery to remove the submandibular glands, ligate or re-route the ducts, or ligation or re-routing of the parotid ducts, may be appropriate for children.

Other factors also may affect salivary flow and/or composition [8, 27, 35]. Obstruction of the main duct of a gland due to a stricture, mucous plug, or calcified stone (*sialolith*) will reduce salivary flow and cause gland swelling and pain, especially during eating. Stones most commonly occur in the submandibular duct due to the higher content of calcium and phosphate salts in submandibular saliva. Duct obstruction also may occur after an injury to the duct. A common occurrence is an accidental lip bite, which may sever the duct of a minor salivary gland. The pooling of mucus in the connective tissue results in a swelling called a *mucocele*. Trauma to one of the minor ducts (Rivinus) of the sublingual gland results in submucosal mucus accumulation called a *ranula*. Dehydration causes reduced salivary flow rates and increased saliva osmolality and can lead to retrograde bacterial infection from the oral cavity. Elderly patients often complain of a dry mouth, which may or may not be a side effect of medications. While many studies have shown a decline in salivary function with aging, some well-conducted studies suggest that stimulated salivary secretion in healthy non-medicated elderly individuals is comparable to that of younger people. Aplasia or hypoplasia of the salivary glands, associated with some genetic syndromes (e.g., lacrimo-auriculo-dento-digital syndrome [LADD], trisomy 21) or mutation of the fibroblast growth factor-10 (FGF-10) gene or its receptor, FGFR2b, can result in a dry mouth. Parotid gland aplasia (~1:5000 live births) occurs much more frequently than submandibular gland aplasia.

Inflammation of the salivary glands, *sialadenitis*, can occur with bacterial or viral infections [8, 19, 27, 35]. Bacterial infections, most common in the parotid gland (*acute parotitis*), typically are caused by *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus* species, or anaerobic Gram-negative bacilli and result in swelling, pain, and suppuration. Prior to vaccine (MMR: measles-mumps-rubella) introduction, the most common viral infection of salivary glands was mumps. Patients with mumps experience a prodromal period with flu-like symptoms and subsequent unilateral or most frequently bilateral gland swelling and pain, especially the parotid. Although cases of mumps are now rare, occasional outbreaks have occurred even in vaccinated populations. Swelling, reduced salivary flow, benign lymphoepithelial cysts, diffuse infiltrative lymphocytosis syndrome, and salivary gland lymphomas may occur in HIV-infected patients, even those on antiretroviral therapy, and in immunocompromised individuals. HIV-associated salivary gland disease is linked to infection with the BK polyoma virus. Epstein-Barr (EB) virus replicates in the salivary glands and is present in 90% of the population. Although primary infections are usually asymptomatic, EB causes infectious mononucleosis, is associated with nasopharyngeal carcinoma, oral hairy leukoplakia, and Burkitt's lymphoma, and is considered a predisposing factor for SS. Cytomegalovirus (CMV) infections are present in as many as 70% of adults; the virus infects and replicates in the salivary glands. After the initial infection CMV patients may exhibit mononucleosis and few or no other symptoms, and the virus remains latent. In immunocompromised patients the virus may reactivate, and cause liver failure, inflammation in several organs, atherosclerosis, and possibly some cancers.

Sialadenosis (*sialosis*) is a bilateral, non-neoplastic, asymptomatic, painless swelling of the salivary glands, most frequently the parotid glands [27, 35]. It can occur in diabetic patients, alcoholics, in bulimia nervosa, and as a consequence of chronic malnutrition. The gland enlargement is due to acinar cell hypertrophy, with accumulation of secretory granules, possibly related to an underlying neuropathy.

Although relatively rare, several different neoplastic lesions may occur in the salivary glands [27, 35–37]. They possess a wide range of histological characteristics and clinical behavior, and generally present as slow-growing painless masses. Most tumors occur in the parotid gland, and most of these are benign. While only 5–8% of tumors occur in minor salivary glands, the majority occur in the palate and most of them are malignant. The most common benign parotid tumors are *pleomorphic adenoma*, *papillary cystadenoma lymphomatosum* (*Warthin tumor*), and *oncocytoma*. The most common malignant parotid tumor is *mucoepidermoid carcinoma*, and the most common malignant submandibular

and minor gland tumor is *adenoid cystic carcinoma*. Metastatic tumors also occur in the salivary glands, the most common being *squamous cell carcinoma*.

Summary

The three major salivary glands, parotid, submandibular, and sublingual, along with minor glands in the oral mucosa, produce and secrete saliva that creates and regulates the oral environment. Saliva secretion occurs in response to taste and olfactory stimulation, as well as mechanical stimulation of the periodontium and oral mucosa, conveyed via both sympathetic and parasympathetic fibers of the autonomic nervous system. The products of the serous and mucous secretory cells of the glands serve to moisten and lubricate the oral tissues, solubilize food, initiate digestion, facilitate mastication, taste, and swallowing, and protect the oral tissues through the actions of antibacterial and antiviral components, calcium-binding proteins, and the bicarbonate buffering system. In addition to substances secreted by the glands, whole saliva in the mouth contains substances transferred from blood plasma, gingival crevicular fluid, oral microorganisms and their products, and food debris.

Saliva frequently is used in forensic medicine, and increasingly being used as a diagnostic fluid to determine health and physiological conditions. Several hormones and drugs of abuse can be detected in saliva, and a variety of viral and bacterial pathogens can be detected using immunological and molecular methods. Protein, DNA, RNA, and microRNA biomarkers present in saliva are being studied for the diagnosis of several oral and systemic diseases.

Salivary dysfunction leading to dry mouth is a common clinical complaint. Side effects of prescribed medications can reduce saliva secretion, and autoimmune diseases and radiation therapy for head and neck cancer can destroy the secretory cells of the glands. Infection or inflammation of the glands, blockage of a duct, or, rarely, glandular aplasia, also may lead to a dry mouth. The consequences of salivary dysfunction include dental caries, mucosal infection and ulceration, difficulty swallowing and speaking, and a reduced quality of life. Although not common, benign and malignant tumors may occur in the major and minor salivary glands and must be differentiated from gland enlargement caused by infection, inflammation, or non-inflammatory processes.

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