Chapter 2
Salivary Gland Anatomy and Physiology

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Abstract In mammals, saliva is a mildly acidic secretion made mostly of water (99.5–99.8%). In a healthy state, humans produce between 500 mL and 1.5 L of saliva per day. Saliva has numerous functions including lubrication, digestion, and immunity. Salivary glands are classified as exocrine, and as such, they produce secretions (i.e., saliva) onto an epithelial surface via a system of ducts. Saliva secretion and production are mediated by the autonomic nervous system (ANS) and thus; salivary glands have both parasympathetic and sympathetic innervation.

Within the oral cavity, there are three major salivary glands; parotid, submandibular, and sublingual, as well as hundreds of minor glands. These glands produce serous, mucous, or seromucous secretions that contain proteins and compounds, which are significant to salivary bioscience studies. Saliva composition depends upon health status and overall physiologic need.

This chapter will delve further into the macro- and microanatomy of the normal salivary gland and will detail the physiologic and neural regulation of saliva production, composition, and secretion.

Keywords Oral cavity · Duct · Submandibular · Parotid · Sublingual

2.1 Basic Anatomy of the Oral Cavity

As the entrance to the digestive system, the oral cavity senses, mechanically processes, lubricates, and initiates the digestion of food (Martini, Timmons, & Tallitsch, 2009). The mouth is lined with epithelial cells and is structurally supported by fat (buccal fat pads) and muscle (buccinator muscles) in the cheeks. The teeth are

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anchored to the maxilla (upper jaw) and mandible (lower jaw) and surrounded by gum tissue. The space where a tooth meets the gum tissue is known as the gingival sulcus where gingival crevicular fluid (GCF) is found. The tongue muscle provides mechanical processing and manipulation of food for chewing and swallowing. It also plays a role in sensory analysis (i.e., temperature and taste) and produces secretions for digestion (i.e., mucins and lipase).

2.2 Salivary Gland Anatomy

Salivary glands are classified as exocrine glands just like sweat, mammary, and sebaceous glands. By definition, they produce and secrete substances via a duct onto an epithelial surface (e.g., the skin or oral cavity). All exocrine glands are categorized into three types, based on the type of secretions that they deliver; (1) Serous glands produce a watery liquid, which usually contains enzymes; (2) Mucous glands yield mucins, which combine with water to form mucus; and (3) Seromucous (mixed) exocrine glands yield both serous and mucous secretions. Additionally, salivary glands are considered merocrine glands as they secrete their products via exocytosis.

Anchored deep to epithelial lining of the mouth, salivary glands are histologically classified according to their structure and secretion, but the basic components are the acinar/alveolar cells, a duct system, and myoepithelial cells. Acinar cells form clusters called acini, which act as the secretory unit of the gland. The epithelium-derived duct system delivers products (Anatomy & Physiology, 2018) to the oral cavity. The length and diameter of the duct system depends upon the type of gland and secretion that is produced (Pedersen, Sørensen, Proctor, Carpenter, & Ekström, 2018). Saliva is first secreted by the acini and thus, the type of acinar cell of the gland dictates the type of secretion to be produced (e.g., serous, mucus, or mixed secretion). Even if a salivary gland has a combination of acinar cells, the individual gland will still predominantly produce serous or mucous secretions.

The fluid that initially constitutes saliva is isotonic, but as it reaches the duct system, it eventually becomes hypotonic (a liquid with more water and less solute than that of blood serum). The tonicity of saliva can be indicative of a basal (unstimulated, more hypotonic) or stimulated state (less hypotonic). The duct system is composed of various cell types; intercalated, striated, and excretory duct cells. Intercalated cells make up the first segment of a duct. The second and third duct portions are made up of striated and excretory cells, respectively. The composition of saliva is altered in these last duct sections where striated cells regulate electrolytes by resorbing sodium. This sodium resorption continues in the excretory duct cells, which also secrete potassium. Finally, the saliva reaches the oral cavity with the help of myoepithelial cells. Located at the base of the acini, and sometimes the intercalated duct cells, myoepithelial cells contract to facilitate salivary secretion. The contraction/relaxation of myoepithelial cells is regulated by the sympathetic or parasympathetic nervous systems, which act upon brain salivary centers (Garrett,

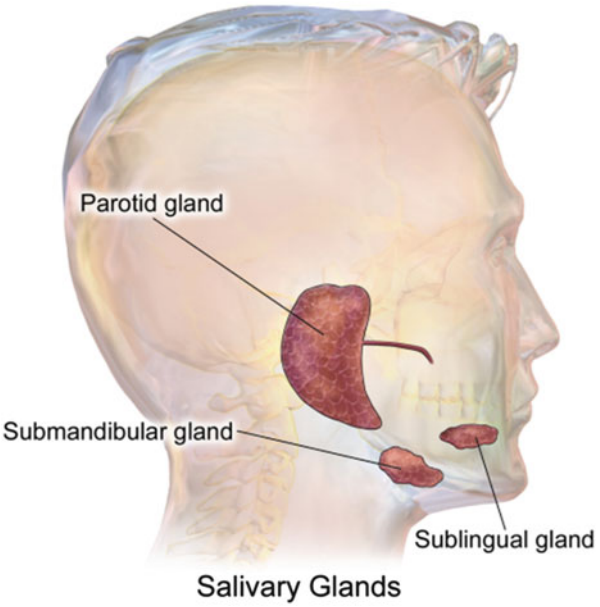

Fig. 2.1 The three major human salivary glands. From https://en.wikipedia.org/wiki/Salivary_gland

1987). Although they are contractile in nature, the myoepithelial cells are not necessary for saliva secretion (Pedersen et al., 2018).

There are three major pairs of salivary glands; the submandibular, parotid, and sublingual glands (Fig. 2.1; Blausen.com staff, 2014). These are classified as major glands based on their anatomical size, and they all have long, branched duct systems as describe above. However, the ducts of the sublingual glands lack striated cells, which means that they resorb sodium to a lesser extent than the other glands. While the major glands produce greater quantities of saliva, they do not necessarily add more to the overall quality of saliva. In fact, major salivary glands contribute the most to volume and electrolyte content, but little to other significant proteins of interest. The submandibular glands produce about 60% of total unstimulated saliva. Inferred by their name, they are located on the floor of the mouth, medial to the lower jaw (mandible). As a mixed gland, it produces a viscous fluid, rich in enzymes and mucins. Mucins combine with water to form mucus, which protects the epithelial lining of the oral cavity by coating food as it makes its way to the esophagus. The parotid glands are the largest glands, but they produce only about 20–25% of total unstimulated saliva. These glands are located just inferior to the cheekbones (zygomatic arches) and are anterior to the ears. Saliva from these glands is serous and abundant in enzymes (e.g., amylase). The sublingual glands are located under the tongue (Fig. 2.1; Blausen.com staff, 2014) and primarily produce viscous saliva that is rich with mucins. In combination with a multitude of other minor salivary glands, they contribute to the remaining 5–10% of total unstimulated saliva. The percent contribution of each gland toward saliva production changes when saliva flow rate is highly stimulated. For instance, the parotid glands increase their yield to account for

50% of total stimulated saliva volume versus 25% under resting conditions (Edgar, 1990).

As previously mentioned, minor salivary glands are only classified as such because of their smaller size, not because of their lesser significance. Minor glands can be found in the lips, cheeks, palate, behind the molars, and on the tongue (Roth & Calmes, 1981). It is estimated that there are 600–1000 minor glands and some are the primary producers of protective components like antibacterial and antimicrobial agents. Like sublingual glands, they lack striated duct cells and they supply a majority of the blood group substances (Edgar, O'Mullane, & Dawes, 2004) found in saliva, such as C-reactive protein (CRP) and some immunoglobulins. Most minor glands produce mucin-rich secretions except for the lingual glands, which generate watery saliva with ample amounts of lipase (Pedersen et al., 2018). Altogether, minor glands produce about 8% of total unstimulated saliva.

2.3 Saliva Composition

Whole saliva, also known as mixed saliva, is a combination of unstimulated and stimulated saliva, microorganisms, gingival crevicular fluid, food debris, and medication metabolites, if any (Fig. 2.2). Habits (e.g., oral hygiene), behavior (e.g., physical activity), and nutritional intake drive the relative contributions of these

Fig. 2.2 Major components of whole saliva

components. Thus, the composition of whole saliva is dynamic and influenced by an exact combination of stimuli. The electrolyte and protein concentration of whole saliva are regulated by circadian rhythms and salivary protein values generally peak in the late afternoon (Rudney, 1995). Electrolyte concentration is largely dependent upon saliva flow rate, which is influenced by health status (e.g., hydration) and overall physiologic needs. In the long-term, whole saliva composition is stable, however; short-term changes in proteins can occur due to daily emotions (Jemmott et al., 1983), respiratory infections (Cockle & Harkness, 1983), inflammation (Henskens, Veerman, Mantel, Van der Velden, & Nieuw Amerongen, 1994), and reproductive status (Cockle & Harkness, 1983; Tenovuo, Laine, Söderling, & Irjala, 1981; Widerström & Bratthall, 1984). These temporary changes may be limited by genetic factors (Rudney, 1995). Systemic disease such as metabolic or immunologic disease also impact saliva protein composition over time. It is therefore important to record an individual's initial health status and then any significant changes thereafter.

Unstimulated and stimulated saliva are the two basic components of whole saliva. Unstimulated saliva is the basal level of saliva production as opposed to stimulated saliva, which is produced in response to chewing (mastication). The submandibular glands are the primary generators of unstimulated saliva. During sleep, this basal production is almost absent. Most stimulated saliva comes from the parotid glands. The sublingual and minor glands contribute equally to both unstimulated and stimulated saliva production. Unstimulated saliva is very hypotonic and has a pH that is neutral or slightly acidic. Stimulated saliva is less hypotonic and has an alkaline pH.

The protein concentration of saliva is inversely proportional to the flow; if there is a high rate of flow, there is less time for the acinar and duct cells to modify saliva and protein concentration is lower. At highest flow rates, saliva is the most isotonic to plasma. Conversely, if flow is at a low rate, protein concentration is increased and saliva is more hypotonic than plasma. The protein content of saliva is highly specific to each person as it is influenced by the individual's genetics, environment, and habits (Rudney, 1995). Most salivary proteins originate solely from the salivary glandular cells and not the blood. Salivary proteins represent only about 10% of the 2500 proteins found in the whole saliva. The remaining 90% is from microorganisms and epithelial cells that are shed from the lining of the mouth (Ekström, Khosravani, Castagnola, & Messana, 2011).

Another innate component of whole saliva is gingival crevicular fluid (GCF), which is found in the gingival sulcus (the space between a tooth and gum tissue). It has a varied composition that is similar to whole saliva, but is produced only in small amounts. It is thought that the main role of GCF is to help to clear food debris and impart antimicrobial/immune protection. Alternatively, GCF has been linked to inflammatory processes, which cause an increase in vessel permeability. Cytokines such as IL-1β, TNF-α, and immunoglobulins G and M, can be found in GCF (Gupta, 2012). Similar to unstimulated saliva, GCF production is regulated by a circadian rhythm with an increase during the typical waking hours and a decline in the late evening. Although it is quite stable during waking hours (Suppipat, Johanasen, &

Gjermo, 1977), GCF production is higher after periodontal interventions, while eating (chewing), if a person smokes, and during hormonal fluctuations in females (e.g., menstruation, oral contraceptives, and pregnancy).

2.4 Functions of Saliva

The constituents of saliva (Fig. 2.3) help to maintain oral health and also facilitate systemic health. Saliva contains electrolytes, immunoglobulins, proteins, enzymes, mucins, and nitrogen products. These entities are multifunctional and work in concert to perform the primary functions of saliva, which are: (1) immunity and antibacterial activity, (2) buffering action, (3) lubrication and tissue protection, (4) taste and predigestion, and (5) tooth integrity. As a primary gateway to the external environment, the oral cavity bears a strong capacity for protection and immune function. Secretory immunoglobulin A (sIgA), the largest immunologic component of saliva, is produced in connective tissue and translocated through the duct cells of major and minor salivary glands (Humphrey & Williamson, 2001). Antibacterial activities are provided by immunoglobulins, proteins, and enzymes. Glycoproteins (proteins attached to oligosaccharide chains) and mucins help to rid the mouth of microorganisms and reduce dental plaque. The pH of saliva in a healthy state ranges from 6.6 to 7.6 (Choi, Lyons, Kieser, & Waddell, 2017) and its buffering capacity is imparted by bicarbonates, phosphates, and urea. Saliva pH is influenced by consumption of sugary or acidic foods (e.g., cherries) and drinks (e.g., soft

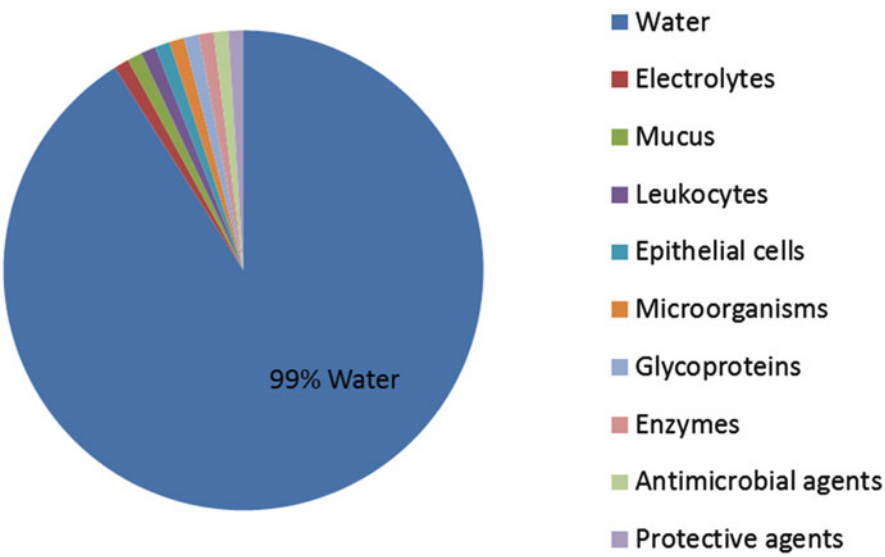

Fig. 2.3 Minor components of whole saliva

drinks), which can temporarily reduce the pH to about 5.5. Mucins help to form mucus, which provides a physical barrier to protect tissues, to soften food for chewing and swallowing, and to facilitate speech. Another major saliva substance is epidermal growth factor, which promotes healing by stimulating DNA synthesis and cell growth/differentiation. Enzymes, such as salivary alpha amylase and lingual lipase, initiate the breakdown of carbohydrates and fats, respectively. Finally, one of the most important functions of saliva is to support tooth integrity. It has been written that "Saliva is to tooth enamel what blood is to the cells of the body." (Moss, 1995). Together, calcium, phosphate, and other proteins combine to form an "antisolubility factor," which modulates the formation of tooth enamel (Humphrey & Williamson, 2001).

2.5 Salivary Flow

Unstimulated saliva production is mediated by the parasympathetic nervous system, which is colloquially known as the "rest and digest" portion of the autonomic nervous system (ANS). Saliva production or volume can also be influenced by environmental and pharmacologic factors, however; the average amount of saliva produced by a healthy adult is estimated to be about 1–1.5 liters/day. Salivary flow is unique to an individual and their responses to internal and/ or external stimuli, but the general range for unstimulated flow rate is about 0.3–0.4 mL/min. Stimulated saliva is the major contributor to changes in waking saliva production. For example, the flow rate in response to food can increase up to a maximum of 7 mL/min (Humphrey & Williamson, 2001). As previously mentioned, unstimulated salivary flow is almost completely absent during sleep. Salivary flow is an important consideration in both clinical and research contexts. Since saliva affords a great deal of immune function and protection, low flow, or hypofunction, can be detrimental. It is important to identify low saliva production, or hyposalivation, under stimulated circumstances, which is defined as a rate <0.1 mL/min. Gland hypofunction can result in an increase in cavities, soft tissue ulcerations, infections, and altered taste (dysguesia) as well as reduced healing from aesthetic dental surgeries and the loss of prosthetic dental restorations (Moss, 1995). Overall, salivary gland function has been reported to be quite robust to the aging process (Pedersen et al., 2018). But, illness, disease, prescription medications (Humphrey & Williamson, 2001; Rudney, 1995), chemotherapy, and radiation (to the head and neck), can cause hypofunction. The anticholinergic side effects of antihistamines or antidepressants may reduce saliva flow and cause xerostomia (dry mouth). Any medications that act upon the beta-adrenergic receptors (e.g., asthma or heart medications) may affect acinar cell protein production. Some antipsychotics, blood pressure, and Parkinson's disease medications may also act on these receptors, resulting in lower flow. Furthermore, hydration status will affect saliva secretion and it has been demonstrated that flow is reduced following restriction of liquid and food (Pedersen et al., 2018). With respect to research, recording hydration status, stress level, presence of respiratory infection, signs of inflammation, and hormone changes (e.g., ovulation and pregnancy) is

prudent since it has been shown that these factors can profoundly affect short-term saliva composition (Rudney, 1995).

Salivary flow is not uniform throughout the oral cavity and there are specific intraoral areas known as the "salivary highways and byways" (Moss, 1995) where flow is either larger or smaller. For example, areas of the lower mouth produce a high volume of saliva while the upper front of the mouth produces very little. Intraoral flow influences the composition of whole saliva as well as composition within different areas of the mouth. This is especially important when instructing a patient or study participant on saliva collection. The analyte(s) being detected will dictate the ideal intraoral area to be sampled (e.g., under the tongue, in the cheek pocket, etc.). Finally, salivary flow is known to change predictably throughout the day (day versus night) and also between seasons (e.g., summer versus winter). Clock genes, which are implicated in circadian rhythm function, have been identified within the salivary glands of mice (Zheng, Seon, McHugh, Papagerakis, & Papagerakis, 2012) and this suggests that flow is regulated by circadian rhythms. To date, the protein expression and characterization of the periodicity of clock genes in human salivary glands have not been reported.

2.6 Neural Regulation of Salivary Glands

Salivary glands are primarily controlled by salivatory nuclei, which are called the "salivary centers." This cluster of nuclei is located in the brainstem (medulla); specifically, in the dorsal pons. Salivary glands also receive input from other brain centers and are influenced by gastrointestinal hormones (Pedersen et al., 2018). The superior salivatory nucleus innervates the submandibular and the sublingual glands. The inferior salivatory nucleus innervates the parotid gland. Both nuclei are components of the main cranial nerves; the superior salivatory nucleus is part of the facial nerve (cranial nerve VII) and the inferior salivatory nucleus belongs to the glossopharyngeal nerve (cranial nerve IX). These nuclei confer parasympathetic input to the glands to produce vasodilation and saliva secretion. In a normal state, there are different types of sensory stimuli for secretion: (1) mechanical, (2) gustatory, and (3) olfactory (Humphrey & Williamson, 2001). In altered states, secretion can be stimulated by pain and pharmacological agents. Other conditions such as depression, fatigue, and fear, can reduce saliva flow (Feher, 2017). In these instances, the common misconception is that salivary flow is reduced by sympathetic inhibitory fibers. In fact, flow is decreased due to "supranuclear control," the influence of higher brain regions like the hypothalamus. Nevertheless, knowledge about the neural regulation of salivary glands is mostly derived from animal studies and the precise connections between the salivary centers and higher brain centers remain unidentified in humans (Ekström et al., 2011).

Under control of the ANS, salivary glands are innervated predominantly by parasympathetic fibers, but they also receive sympathetic input. Binding of autonomic neurotransmitters with their respective receptors in salivary glands produces a myriad of outcomes and effects. When cholinergic parasympathetic nerves release

acetylcholine (ACh), which binds to muscarinic receptors, saliva is secreted from the acini. Adrenergic (adrenaline and noradrenaline) and cholinergic neurotransmitters are the first messengers of a sympathetic secretory response (Garrett, Ekström, & Anderson, 1999). Sympathetic nerves release noradrenaline to activate adrenergic receptors, which induce smaller volumes of saliva, but with larger amounts of protein, to be expressed from the acini and duct cells (Proctor & Carpenter, 2007). Other neuropeptides released from autonomic nerves can also increase saliva production and alter membrane permeability.

Neural actions on salivary glands include water mobilization, protein secretion, stimulation of cell synthesis, and maintenance of cell function and size. Activation of the parasympathetic and sympathetic systems results in saliva secretions, which interact synergistically to secrete fluid and proteins (Ekström et al., 2011) to meet physiologic demand. Additionally, capillary vessels, which are adjacent to the salivary ducts, indirectly influence saliva secretion. As mentioned earlier, the cranial nerves confer parasympathetic innervation, which causes vasodilation of these vessels. This type of parasympathetic stimulation favors abundant volumes of serous or watery secretions. Conversely, sympathetic innervation is conferred directly by the spinal nerves (i.e., thoracic and cervical), and indirectly by the capillary plexus, which supplies the glands (Garrett, 1987). Indirect input by the capillary plexus is exerted more so by vascular control and not by reflexive sympathetic pathway (Garrett, 1987).

This described model of neuronal control becomes more complicated when considering input from second messenger systems, like cyclic adenosine monophosphate, nitric oxide, and calcium or, neuropeptides such as vasoactive intestinal peptide. Intracellular signaling and co-transmitter receptor activation allow for enhanced coupling between the ANS and the current salivary protein content to create a "real-time" response that ensures the maintenance of optimal saliva composition. Irrespective of the source of stimulation (either parasympathetic or sympathetic), if saliva production is increased, there is a concomitant rise in other salivary ingredients like water, electrolytes, proteins, and other organic molecules (Proctor & Carpenter, 2007).

2.7 Summary

An understanding of the salivary gland anatomy and the regulation of saliva production in a normal state is the first step toward maximizing the power of salivary bioscience. Precise knowledge of gland location can optimize the sampling of analytes. Familiarity with the nuances of saliva production can help to identify sampling confounds (i.e., controlling for flow rates and circadian rhythm) and can also enhance data interpretation. Altogether, this foundational information supports pristine research results and may significantly augment patient-centered care in a clinical setting.

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