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Chapter 1

Secretions of Human Salivary Gland

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Additional information is available at the end of the chapter

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Abstract

The salivary glands play an important role in our body by the virtue of its ability to secrete saliva. Saliva has a role to play in maintaining the health of the oral cavity and for carrying out physiological functions like mastication, taste perception, speech etc. It also acts as a mirror to the systemic status of an individual owing to its ability to act as a diagnostic fluid for detecting a number of conditions and diseases. Saliva is a potential non-invasive diagnostic fluid for detection of a number of biomarkers of disease and health. Advancement in diagnostic methods has helped in identifying biomarkers of disease in saliva. In order to understand and diagnose pathological changes, a thorough understanding of the salivary gland anatomy, physiology and regulation of its secretion is warranted. This chapter aims to provide the basic understanding of the secretions of saliva.

Keywords: saliva, secretion, salivary gland, diagnostic fluid

1. Introduction

Salivary glands are organs which synthesize and secrete their secretions over an epithelial surface via a hollow channel. These glands are present in and around the oral cavity and its secretions play an important role in the physiological processes of the oral cavity [1].

2. Overview of salivary glands

The salivary glands can be classified as major and minor salivary glands. The major salivary glands, located outside the oral cavity include the parotid salivary gland, submandibular/submaxillary salivary gland and sublingual salivary gland. The minor salivary glands are

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classified based on their location in the oral cavity as labial/buccal glands, glossopalatine glands, palatine glands, lingual glands which are further classified as anterior lingual (glands of Blandin and Nuhn) and posterior lingual glands (Von Ebner's) [1, 2]. The following diagram (**Figure 1**) shows the anatomical location of major and minor salivary glands. The salivary glands consists of a secretory part and ducts (**Table 1**).

2.1. Parenchymal elements of salivary gland

The salivary glands are made of secretory units called acini, which are made up of acinar cells which could be serous or mucous. The serous cells are pyramidal or triangular in shape while the mucous cells are columnar in shape. The serous cells are occasionally seen capped by structures called demilunes. The acini cells are surrounded by contractile cells called as myoepithelial cells/basket cells, which are responsible for the flow of secretions of saliva by contraction of the cell. The acini of salivary glands are connected to hollow tubular structures which are called salivary ducts. The lining of the duct changes with the type of duct and its location within the salivary gland [1–3]. A description of the ducts observed is given in **Table 2** and the parenchymal elements are shown in **Figure 2**.

2.2. Development of salivary gland

Salivary glands arise from the ectoderm of oral cavity. The minor salivary gland arise from the oral and nasopharyngeal ectoderm. The chronology of the development of salivary gland is mentioned in **Table 3**. Each gland develops at a specific location in the oral cavity by the inward growth of an epithelial bud into the underlying mesenchyme. These epithelial buds then grow and later branch into a system of cords of cells. These get canalized and develop

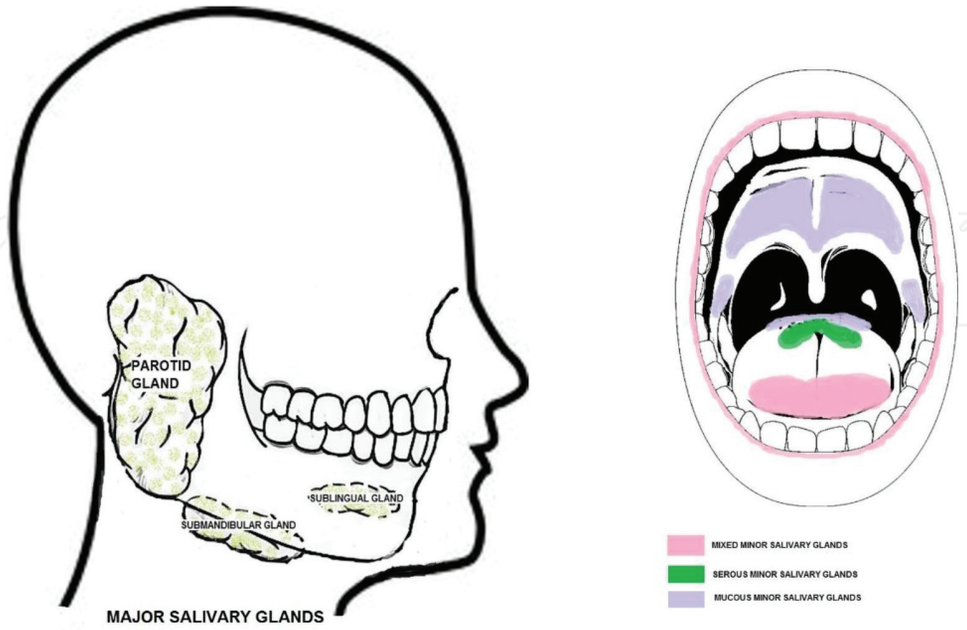


Figure 1. Anatomical locations of major and minor salivary glands.

S. no	Salivary gland	Salivary gland duct	Location of salivary duct orifice
1.	Parotid	Stensen's duct	Opens at papilla in buccal mucosa opposite maxillary second molar
2.	Submandibular	Wharton's duct	Opens at sublingual papillae
3.	Sublingual	Bartholin's duct	Opens with or near submandibular duct
		Duct of Rivinus	Opens independently along sublingual fold
4.	Minor salivary glands	Short ducts	Open directly via short ducts into mouth

Table 1. Location and names of salivary gland ducts.

S. no	Duct	Description	Epithelium
1.	Intercalated duct	Connect the terminal secretory unit with the next system of ducts	Single layer of low cuboidal cells
2.	Striated duct	Intercalated ducts drain into striated duct	Tall columnar epithelial cells with centrally placed nucleus. Cells are partitioned by deep sheet like foldings of membrane, which appear as striations under light microscope
3.	Interlobular duct/ excretory duct	Formed by joining of striated ducts	Pseudo-stratified columnar epithelial cells with outer connective tissue adventitia

Table 2. Description of salivary ducts.

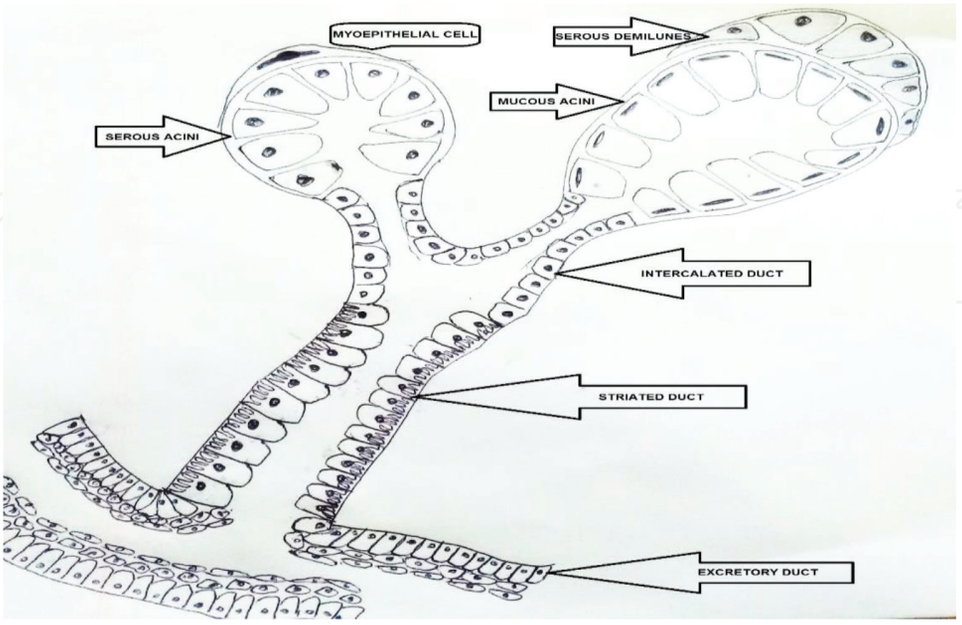


Figure 2. Architecture of salivary ducts and acini.

S. no	Time	Event
1.	Sixth week	Development of the primordia of parotid and submandibular salivary gland
2.	Seventh to eighth week	Development of sublingual salivary gland
3.	Third month	Development of minor salivary gland

Table 3. Chronology of salivary gland development.

a lumen by the action of microfilaments at apical areas of cell to become ducts. The secretory part develops later by repeated branching and budding of finer cell cords, to form pregland cells which give rise to acini [1].

3. Secretions of salivary gland

The salivary glands are primarily involved in secretion of saliva. There are other substances also which are secreted by the salivary glands which are found in saliva. They can secrete proteins in large amounts apically or basolaterally to the saliva [1–4].

3.1. Saliva

Saliva is a complex physiological fluid of the oral cavity which coats the teeth and oral mucosa. It contains a myriad of components like enzymes, mucinous substances, antibacterial components etc. Saliva functions to maintain the oral cavity in the physiological state owing to its lubricating, buffering, antibacterial and immune properties by acting as a physiological barrier to infections. The saliva is a mixed fluid, as it is composed of saliva secreted by both major and minor salivary glands which are both serous and mucous in nature [2–4].

3.1.1. Composition of saliva

Saliva is composed of 99% water and 1% of components such as inorganic ions like sodium, potassium, chloride, bicarbonate, calcium, magnesium, fluoride, thiocyanate, hydrogen phosphate etc. It contains proline-rich proteins, histatins, cystatin, defensins. Kallikrein, cathelicidin-LL37, lactoferrin and enzymes such as amylase (ptyalin), peroxidase, lysozyme, etc. Immunoglobulins A, G and M, glucose, amino acids, urea, uric acid, lipid molecules and blood group antigens, epidermal growth factors, factor VII, factor VIII and factor IX are also present. Saliva in the mouth also consists of desquamated epithelial cells, microorganisms and their products, few inflammatory cells etc. [2–4].

3.1.2. Formation of saliva

According to Tencate [2], the formation of saliva occurs in two stages. The first stage involves the formation of saliva by the acinar cells. The acinar cells whether serous or mucous cells produce salivary secretion by ribosomal protein synthesis in the rough endoplasmic reticulum

which is followed by the packaging of the proteins by the golgi complex. The secretions are stored as granules and later released into the lumen by the process of exocytosis or by vesicular mechanism. Exocytosis involves fusion of the secretory granules with the membrane allowing release of the contents into the lumen. Vesicular mechanism involves transport of vesicles filled with secretions from golgi complex to plasma membrane. Transcytosis involves passage of substances like immunoglobulin A through the acini. Water is taken up by the cells from the bloodstream and the resulting saliva secreted is isotonic. The serous cells produce serous saliva which is thin, watery and is composed of zymogen granules and contains more proteins, while mucous cells produce thick, viscous saliva containing mucopolysaccharides and mucin. Parotid gland and von Ebner's gland is purely serous gland, while sublingual, glossopalatine and palatine glands have more of mucous secretions. Submandibular gland and other minor salivary gland have both serous and mucous acini, resulting in mixed saliva [2–6].

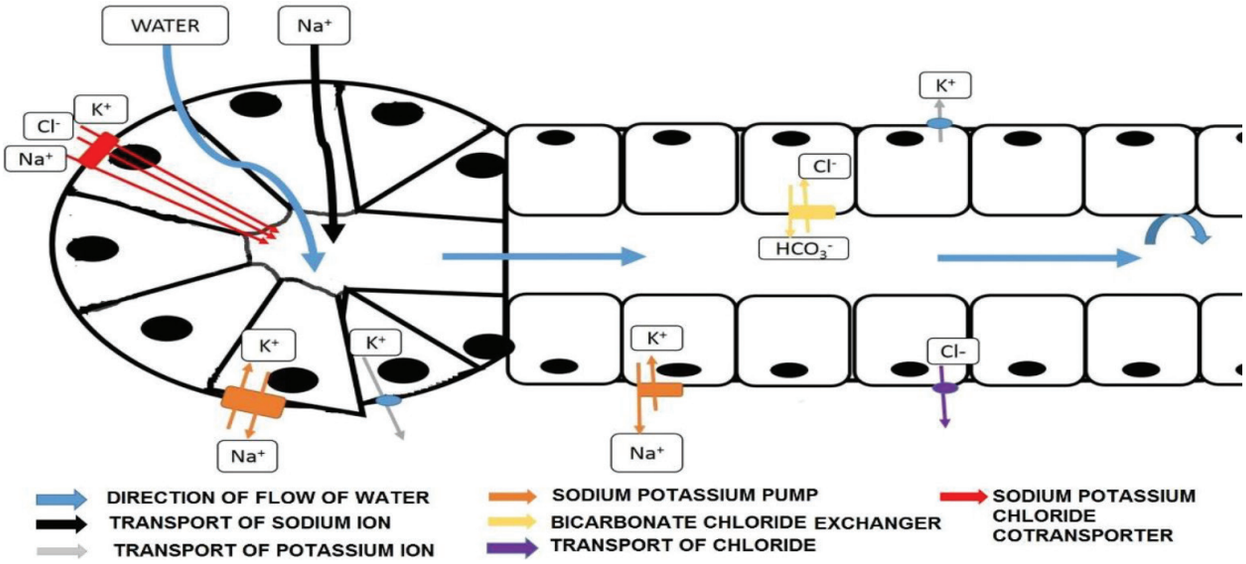


Figure 3. Modification of saliva.

In the second stage the saliva undergoes changes as it passes through the salivary ductal system into the oral cavity. Saliva secreted from the acini is isotonic or slightly hypertonic when it reaches the intercalated ducts. The intercalated duct cells also release lysozymes and lactoferrin. Striated and excretory ducts are impermeable to water. In the striated duct, reabsorption of sodium and chloride occurs more as compared to the secretion of potassium and bicarbonate ions, which makes saliva hypotonic (**Figure 3**). Striated duct cells also secrete kallikrein and epidermal growth factor. Thus, saliva secreted into the oral cavity is hypotonic as compared to serum [1–6].

3.1.3. Saliva secretion in health and disease

The myoepithelial cells are responsible for the contraction of the acini cells, aiding in the flow and secretion of saliva. In health, the total volume of saliva produced is 750–1000 ml

daily which is contributed by major and minor salivary glands. The resting flow of saliva is 0.2–0.4 ml/min. Salivary flow at rest refers to as unstimulated saliva, whereas salivary flow in response to a stimulus refers to stimulated saliva having a flow rate of 2–5 ml/min. The normal pH of saliva is 6.4–7.4 [1, 2].

A number of factors control the quality and quantity of saliva secreted. The control of salivary gland secretion is mediated by the autonomic nervous system (ANS). All the salivary gland cells receive ANS supply. Control of secretion is also dependent on the perception of taste and smell. The gustatory stimulus is more important than the masticatory stimulus in controlling the salivary secretion. The secretion of saliva occurs by the process of stimulus secretion coupling. This refers to the events involving release of neurotransmitter from vesicles in nerve terminals adjacent to parenchymal cells which stimulate them to discharge secretory granules, water and electrolytes as well as contraction of myoepithelial cells. Norepinephrine activates both alpha and beta adrenergic receptors, while parasympathetic transmitter like acetylcholine activate cholinergic receptors. Alpha adrenergic receptor stimulation results in protein secretion while beta adrenergic or cholinergic stimulation results in low protein secretion and secretion of water and electrolytes. Substance P stimulates alpha adrenergic and cholinergic secretion of saliva. The following flow chart (**Figure 4**) shows the events associated with stimulus secretion coupling which involves the basic process of receptor stimulation which results in increase in the concentration of a secondary messenger, which will further trigger additional events leading to a cellular response [3–6].

Copious watery saliva is secreted in response to parasympathetic stimulation and thicker saliva in response to sympathetic stimulation. Other factors affecting saliva composition are flow rate, circadian rhythm, duration of stimulus, nature of stimulus and diet. During sleep very little saliva is secreted by major salivary glands and majority of the saliva secreted is by the minor salivary glands. Concentration of saliva depends on rate of flow and not on nature of stimulus [2–6].

Historically, it was suggested that parotid salivary gland secretes a hormone called parotin which was considered to have a protein-anabolic function and deficiency resulted in diseases such as chondrodystrophia fetalis, Kaschin-Beck disease, etc. [7].

An increase in the flow of saliva is referred to as sialorrhea (ptyalism), while a decrease in the salivary flow is referred to as xerostomia (dry mouth). Ptyalism is observed after insertion of new orthodontic appliance, in pregnancy, epilepsy, cerebral palsy and Parkinson's disease. Xerostomia is observed in menopause, patients treated by radiation therapy, old age, prolonged use of tranquilizers, amphetamines, antihypertensive and anticonvulsant drugs. A number of systemic conditions affect the functioning of the secretion of salivary glands. Hyperthyroidism, pernicious anemia, vitamin D deficiency, multiple sclerosis and poorly controlled diabetes mellitus affect the salivary glands. Autoimmune diseases like Sjogren's syndrome, Mikulicz's disease affect the salivary gland secretion as the parenchymal elements are affected. Inflammatory, infective and neoplastic diseases also disrupt the activity of salivary gland secretion. Salivary secretion is influenced by hormones. For example antidiuretic hormone facilitates water reabsorption by striated duct, aldosterone causes increased sodium reabsorption by striated duct, testosterone and thyroxine increase salivary secretion [2, 8, 9].

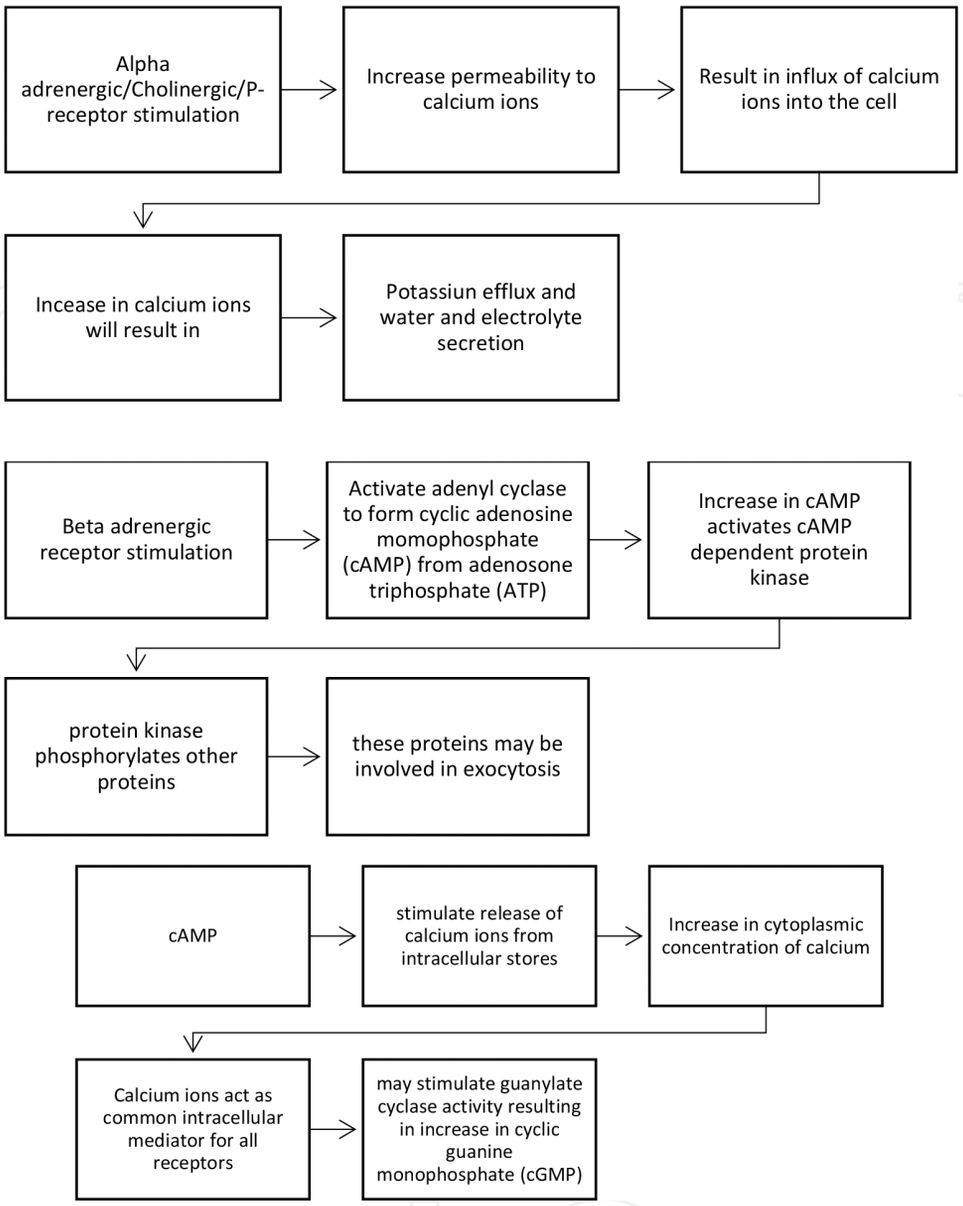


Figure 4. Flowchart depicting sequence of events following neural stimulation.

4. Significance of salivary secretion

The saliva has a number of important functions as mentioned below.

Protection: the saliva contains mucin and glycoproteins which provides it with lubricating properties and moistening the oral cavity, thus preventing friction between the oral structures during physiological functions like mastication. The constant flow of saliva provides clearance of accumulated food debris and microorganisms. Mucins also provide thermal and chemical insulation. Proteins, glycoproteins and mucins form a coating called pellicle formation. Saliva acts as a source of calcium, phosphate, fluoride, statherin and proline rich protein which maintain the integrity of enamel and repair.

Digestion: water and mucin content of saliva aids in bolus formation during the process of mastication. Saliva contains salivary amylase (ptyalin) which helps in digestion of starch and lingual lipase secreted by von Ebner's gland breaks down triglycerides.

Antimicrobial activity: mucins aid in providing a physical barrier to infections by preventing attachment of microorganisms to tooth and tissue surface. Presence of secretory immunoglobulin A provides immune defense. Peroxidase, lysozyme, lactoferrin, histatin, mucins, agglutinin, defensins and cathelicidin also help in providing antimicrobial activity.

Buffering: bicarbonate, phosphate, basic proteins, urea and ammonia help maintain the pH and neutralization of acids.

Tissue repair: salivary glands release growth factors, trefoil proteins into saliva which aid is tissue repair and regeneration.

Taste: saliva acts as a solvent in which molecules from food items can dissolve and reach the taste buds, epidermal growth factor and carbonic anhydrase VI maintains taste buds.

Role of saliva in periodontal pathology: saliva exerts a major influence on plaque initiation, maturation and metabolism. The first step in plaque formation is formation of pellicle followed by plaque formation and maturation [1–6, 8, 9].

Salivary proteins may play a role in plaque mineralization. It is indicated that esterase, pyrophosphatase, acid phosphatase and lysozyme may be involved. Persons with heavy calculus, have higher levels of salivary glycoproteins than non-calculus formers [1–6, 8, 9].

Polymorphonuclear neutrophils (PMNs) reach the oral cavity by migrating through the lining of gingival sulcus. Skougaard and Bay, 1994 believe that orogranulocytic migratory rate correlates with severity of gingival inflammation and is therefore reliable index for assessing gingivitis [8–11].

The saliva acts as an important diagnostic oral fluid owing to its ease and non-invasive mode of collection. A number of components secreted in saliva can be assessed and used to assess diseased states.

A few of the components used as specific biomarkers for detection of periodontal disease include immunoglobulins (Ig) such as IgA, IgM, IgG which interfere in adherence and bacterial metabolism and are present in increased concentration in saliva of chronic and aggressive periodontal patients. Nonspecific markers for aggressive periodontitis include mucins which interfere with the colonization of Aggregatibacter actinomycetemcomitans (A. a), lactoferrin which inhibits microbial growth/increased correlation with A. a. Markers for chronic periodontitis include lysozyme which regulates biofilm accumulation and peroxidase which interferes with biofilm accumulation. Nonspecific markers for both chronic and aggressive periodontitis include histatin which neutralizes lipopolysaccharide and enzymes known to affect periodontium and C-reactive proteins which are present in increased concentrations in saliva and serum of patients with periodontitis [8].

Other areas where saliva can be used for diagnosis of diseases and conditions include cystic fibrosis, which is a genetically transmitted disease of children and young adults characterized

by generalized exocrinopathy. In this condition, saliva contains increased calcium levels, elevated levels of sodium and a decrease in flow rate [8, 9].

Sjogren's Syndrome is associated with reduction in lacrimal and salivary secretions. It is characterized by the presence of a lymphocytic infiltrate (predominantly CD4+ T-cells) in the salivary gland parenchyma. A low resting flow rate and abnormally low stimulated flow rate of whole saliva. An antibody p53 can also be detected in the saliva of patients diagnosed with oral squamous cell carcinoma (SCC). Viral diseases like measles, mumps, and rubella can be detected, polymerase chain reaction (PCR)-based identification of virus in saliva is a useful method for the early detection of HSV-1 reactivation in patients with Bell's palsy. Acute hepatitis A (HAV) and hepatitis B (HBV) can be diagnosed based on the presence of Immunoglobulin M antibodies in saliva [8, 9].

Saliva can be used for monitoring of anti-epileptic drugs as a positive correlation between salivary and serum carbamazepine levels has been observed. In another study, salivary levels of phenobarbital and phenytoin demonstrated excellent correlations with serum levels of these medications. Other drugs that can be identified in saliva are amphetamines, barbiturates, benzodiazepines, cocaine, phencyclidine (PCP), and opioids [8–10].

Steroid hormones can be detected in saliva. Salivary cortisol levels were found to be useful in identifying patients with Cushing's syndrome and Addison's disease [12].

Recent focus on the potential role of periodontal disease as a risk factor for cardiovascular and cerebrovascular diseases [13, 14] and the occurrence of pre-term low-birth-weight babies [15] bring new importance to this aspect of salivary analysis [8–15].

Salivary markers as potential diagnostic tests for periodontal disease include proteins of host origin (i.e., enzymes, immunoglobulins), phenotypic markers, host cells, hormones (cortisol), bacteria and bacterial products, ions and volatile compounds [8, 9, 11].

Salivary levels of MMP-8 and IL-1β appear to serve as biomarkers of alveolar bone loss and hence periodontitis [8, 9, 11].

National Institute of Dental and Craniofacial Research, has highlighted the use of saliva for translational and clinical application by use of salivary proteome and the salivary transcriptome for early detection, disease progression and therapeutic monitoring [8, 9].

Gene therapy has been developed to deliver growth hormone in deficiency states by salivary gland expression of growth hormone [16].

5. Conclusion

The secretions of salivary gland form an integral part of maintaining the physiology of the oral cavity. Saliva is the most important and essential secretion of the salivary glands. Saliva itself has varied functions in the oral cavity and provides additional insight and details of the systemic status of the individual as well. With the advancement in the field of proteomics,

transcriptomics and genomics, better and easier methods of detecting diseases by analyzing saliva are being discovered. For this reason the study of salivary glands and its secretion becomes needful.

Conflict of interest

There is no conflict of interest.

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