REVIEW ARTICLE

Proteins Regulating Salivary and Lacrimal Flow in Xerostomia and Dry Eye Syndrome

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Oral and ocular homeostasis is dependent upon saliva, lacrimal fluid and their protein components. The function of major protein families regulating salivary and lacrimal fluid secretion is well established. The aim of this review is to summarize the role of different proteins that regulate salivary and lacrimal fluid secretion and to discuss mysregulations in diseased conditions especially xerostomia and dry eye syndrome. This review paper provides a detailed description of the abnormal localization and function of proteins, which could be responsible for loss of saliva and lacrimal fluid secretion in xerostomia and dry eye syndrome patients.

KEY WORDS: Proteins, Salivary flow, Lacrimal flow, Xerostomia, Dry eye syndrome.
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INTRODUCTION

Saliva is a complex fluid, secreted by salivary glands, plays an important role in health and maintenance of oral cavity through its vast array of functions including, lubrication, protection, buffering action, antimicrobial function, facilitates swallowing and taste, helps in digestion and tissue repair.[1] Saliva has important diagnostic implications as it contains various biomarkers that can be helpful in detection and monitoring of various oral and systemic diseases.[2]

The lacrimal fluid, secreted by lacrimal glands, is essential for the maintenance of healthy eyes. It performs important functions such as protection of the eye by producing IgA and various antibacterial and fungicidal substances and molecules, the aqueous component keeps the ocular surface moist and helps in maintaining normal visual acuity. It is also important for the normal growth and maintenance of ocular tissue by producing various growth factors, for example, Epidermal growth factor, Fibroblast growth factor, Transforming growth factor-beta.[3]

Proper secretion of saliva and lacrimal fluid is dependent upon different proteins for example aquaporins, tight junction proteins and ion channel proteins. Defective structure and function of these proteins leads to mys-regularities in saliva and lacrimal fluid secretion, resulting in xerostomia and dry eye syndrome.

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Xerostomia in Common Clinical Conditions

Salivary gland hypofunction leads to a clinical condition known as xerostomia. Xerostomia is defined as a subjective complaint of dry mouth due to insufficient secretion of saliva.[4] The absence of saliva in the oral cavity can cause difficulty in swallowing, tasting and chewing, oesophagal dysfunction (chronic esophagitis), nutritional compromises, loss of oral buffering capacity, increased susceptibility to dental caries, inability to wear dental prostheses, increased susceptibility to mucosal injury, increased incidence of glossitis, candidiasis, halitosis, angular cheilitis, bacterial sialadenitis and Burning Mouth Syndrome.[5]

The local and systemic causes of xerostomia are given in table 1.

Xerostomia and hyposalivation have been reported as common oral manifestations of diabetes mellitus (DM). Xerostomia in DM patients can be due to a number of reasons, such as damage to the salivary gland parenchyma, alteration in the microcirculation of gland, dehydration and disturbed glycemic control, but the exact cause is still unknown.[6] The salivary glands of head and neck are highly sensitive to radiation, and radiotherapy can cause temporary or permanent damage to the glands. Xerostomia is the most common presentation of glandular dysfunction in the head and neck region .[7] Sjogren's syndrome is an autoimmune disease of salivary and lacrimal glands, resulting in dry mouth and dry eyes.[8] Xerostomia is common in the geriatric population. The main causes for xerostomia are attributed to different medications, long-term systemic diseases and head and neck radiotherapy.[9] Ectodermal dysplasia is a

Table 1: Causes of Xerostomia

Causes	Examples	References
1. Medications	Antihypertensive drugs (calcium channel blockers, diuretics, beta blockers) Analgesics Muscle relaxants Anti-Parkinson drugs Anti-emetics Anxiolytics	Wolff et al.,2017
2. Systemic Disorders	Diabetes mellitus Granulamatous diseases(tuberculosis, sarcoidosis) End-stage renal disease	López-Pintor et al., 2016 Babazade et al., 2012 Postorino et al., 2003
3. Autoimmune Disorders	Sjogren's syndrome Mikulicz syndrome Rheumatoid arthritis Autoimmune thyroid disease Systemic lupus erythmatosis	Brito-Zerón et al., 2016 Rao et al., 2017 Zalewska et al., 2013 Hammoudeh et al., 2018
4. Genetic Disorders	Ectodermal dysplasia LADD syndrome ALSG syndrome Cystic fibrosis Down syndrome	Lexner et al., 2007 Pathivada et al.,2016 Brandon et al., 2009 Noël et al., 2008 Chaushu et al., 2002
5. Others	Head and neck radiotherapy Dehydration Old age Bacterial and viral infections	Berk et al., 2005 Postorino et al.,2003 Ouanounou et al., 2016 Nokta et al., 2008

heterogeneous group of inherited disorders, which affects the development of tissues, derive from embryonic ectoderm. Decreased salivary flow has been reported in affected males and females with Ectodermal dysplasia due to defects in salivary glands development.[10]

Dry eyes in Common Clinical Conditions

Dry eye syndrome (DES) or keratoconjunctivitis sicca is a multifactorial disease, it is a common sequel of inadequate lacrimal fluid production, resulting in blurred vision, foreign body sensation, stinging sensation, photophobia or pain.[11] There are many causes of keratoconjunctivitis sicca (Table 2).

Table 2: Causes of Keratoconjunctivitis Sicca (Dry eye syndrome)

Causes	Examples	References
1. Inflammatory/ 2. Autoimmune conditions	Sjogren's syndrome Diabetes Thyroid disease Graft versus host disease Sarcoidosis	Brito-Zerón et al., 2016 Zhang et al., 2016 Kan et al.,2014 Pasadhika et al., 2015
3. Infections	HIV Hepatitis- C CMV	Alves et al., 2013
4. Genetic Dsorders	LADD syndrome ALSG syndrome Cystic fibrosis	Pathivada et al., 2016 Brandon et al., 2009 Mrugacz et al., 2004
5. Others	Aging Radiation therapy Dehydration	De Paiva et al., 2017 Turaka et al., 2016

Defective function of the lacrimal gland can occur due to various causes, including ageing, inflammation and infection and results in insufficient tear production that leads to various ocular complications.[12]

Dry eyes are also a distinctive feature of Sjogren's syndrome. It is characterized by chronic inflammation of salivary and lacrimal glands resulting in dry mouth and dry eyes.[13] Dry eye syndrome is one of the common complications of diabetes mellitus.[14] Hyperglycemia has an adverse effect on the lacrimal functional unit, leading to decrease tear production, or excessive tear loss, resulting in dry eye syndrome.[15] Dry eye syndrome is common in elderly patients; the exact cause is still unknown. However, it is suggested that DES is related to biochemical, molecular and immune system disturbances.[16] Dry eyes are an unfortunate side effect of radiotherapy. Radiotheraphy causes damage to the cells that leads to necrosis and apoptosis, resulting in the release of inflammatory mediators that are responsible for dry eye syndrome.[17]

Proteins Regulating Salivary and Lacrimal Flow
Proteins Involved in Salivary Secretion

The major component of saliva is water which is approximately 99%, and remaining 1% consist of electrolytes and salivary proteins.[18] Major proteins families that are involved in salivary secretion are mentioned in table 3.

Table 3: Proteins Involved in Saliva Secretion

Major Protein Families	Examples	References
1. Aquaporins	Aquaporin-1 Aquaporin-3 Aquaporin-5 Aquaporin-6 Aquaporin-7	Delporte et al., 2016
2. Tight Junction Proteins	Claudin Occludin Junctional adhesion molecule	Baker et al., 2016
3. Linker Protein	Ezrin Radixin Moesin	Pérez et al., 2010
4. Ion Channel Proteins/ Receptors	Chloride channels (CFTR) Calcium activated potassium channels TRPC IP3R	Roussa et al., 2007

Aquaporins:

Aquaporins (AQPs) is a family of transmembrane proteins, which serve an important role in transfer of water and some other solutes across the cell membranes. Until now, 13 types of AQP's have been identified (AQP 0- AQP 12) .[19]

Aquaporin-1 protein expression has been found on the capillary epithelium and myoepithelial cells of salivary gland, aquaporin-3 localize to basolateral membranes of acinar cells and aquaporin-5 has been found to be localized

on canalicular and luminal membranes of acinar cells.[20]

The salivary secretion has been reported to be increased by upregulating the expression of aquaporin-1 in xerostomia patients.[21] Decreased expression of aquaporin-1 on myoepithlial cells of primary Sjogren's syndrome patients has been reported.[22]

In humans, AQP-5 mRNA has been detected in submandibular gland by RT-PCR. Functionally, it is believed that AQP-5 is the aquaporin which seems to play an important role in saliva secretion. It helps in primary saliva production.[23] Abnormal localization of AQP-5 has been reported in Sjogren's syndrome (SS) patients as compared to non-Sjogren's syndrome patients with xerostomia. AQP-5 was found to be present at both apical and basolateral membrane in SS patients as compared to non- SS patients in which the AQP-5 was restricted to the apical membrane of acinar cells.[24] The defect in the AQP-5 trafficking in parotid glands has been reported in streptozocin-induced diabetic rats.[25]

Tight Junction Proteins

Tight junctions also known as occluding junctions are a multiprotein junctional complex,whose primary function is to prevent leakage of transported solute and water, thus they seal the paracellular pathway. The main tight junction proteins are occludin, claudin and junctional adhesion molecule.[26] Occludin has been found on the ductal and acinar cells of human major salivary glands and endothelial cells.[27] The occludin level has been reported to be downregulated in patients with Sjogren's syndrome.[28] Claudin is the most important protein of tight junctions; it controls paracellular as well as the intercellular flow of molecules.[29] Claudin[1] has been found on striated and intercalated duct epithelium of human salivary glands. Caludin -2 has been detected on acinar cells of human salivary glands.[30] Claudin-3 has been detected on mucus and serous acinar cells of human salivary glands and Claudin-4 has been detected both on ductal and acinar cells of human salivary glands.[31] Claudin play important role in saliva secretion by maintianing cell polarity and tansepithalial gradient necessary for unidirectional flow of saliva.[32]

Linker Protein (Ezrin)

Ezrin is a cytoplasmic peripheral membrane protein that serves as a bridge between the plasma membrane and the actin cytoskeleton, it plays an important role in cell adhesion, organization and migration. Ezrin was reported to be colocalized with actin at apical membrane and plays an important role in microvilli organization.[33] Abnormal localization of ezrin has been reported in acinar cells of Sjogren's syndrome patients.[34]

Ion Channel Proteins

Ion channel proteins are found in cell membranes, through which ions and electrolytes can move in and out of the cell .[35] The acinar cells of salivary glands express different types of ion channel proteins, that are present mostly on apical or basolateral membranes, to facilitate fluid secretion .[36] Cystic fibrosis transmembrane regulator (CFTR) is a protein and chloride channel that controls the fluid and electrolyte transport in epithelial cells. In human salivary gland, CFTR has been found on the luminal surfaces of striated ducts.[37] Mutations or any abnormality in CFTR has been reported to be associated with altered salivary function in cystic fibrosis patients.[38]

Proteins Involved in Lacrimal Fluid Secretion

The lacrimal fluid comprises mainly of water, electrolytes, proteins & metabolites in smaller quantities. Major proteins that are involved in lacrimal fluid secretion are given in table 4.

Table 4: Proteins Involve in Lacrimal Fluid Secretion

Major Protein Families	Examples	Reference
Aquaporins	AQP-1 AQP-3 AQP-4 AQP-5	Verkman et al., 2008
Gap Junction Proteins	Cx 32 Cx 26	Walcott., 2002
Hormones (serotinin)	Serotinin	Imada et al., 2017
Ion Channel Proteins	CFTR	Berczeli et al., 2018
Extracellular and Cytoplasmic Proteins	PRR4 S100A8 DMBT1 PROL1	Perumal et al., 2016

Auqaporins

In eyes, the aqueous component of tear film/lacrimal fluid is regulated by aquaporins.[39] The main aquaporins that have been found on the acinar and ductal cells of lacrimal glands are; AQP-1, AQP-3, AQP-4and AQP-5.[40] The expression of AQP-5 has been found on the acinar and ductal cells of rat and mice.[41] Aquaporin- 5 expression have also been found on the apical surface of acinar cells in human lacrimal glands. A defect in aquaporin- 5 trafficking and lacrimal fluid secretion have also been reported in Sjogren's syndrome patients.[42] The expression of aquaporin-4 and -5 was altered in pregnant rabbits with induced autoimmune dacryoadenitis.[43]

Gap Junction Proteins

Gap junctions are organized clusters of protein channels present in cell membranes that permit transfer of small molecules and ions between neighbouring cells. These

channels are made up of connexon proteins . The acinar cells of lacrimal glands are attached to each other by gap junctions. The main gap junction proteins present in lacrimal glands are Cx 32 and Cx 26.[44] Decreased lacrimal flow has been reported in Cx 32 null mice, which suggests that gap junctions play an important role in lacrimal fluid secretion.[45]

Serotonin Protein

Serotonin derived from amino acid tryptan, performs a multiple array of functions. In brain it functions as a neurotransmitter, while in peripheral organs it acts as a hormone or a signalling molecule.[46] Recently, it has been reported that decrease level of serotinin in blood is related to lacrimal gland atrophy and autophagy leading to loss of tear production in a mice model.[47]

Ion Channel Proteins

CFTR is a chloride channel that plays an important role in fluid transport across epithelial cells.[48] It has been reported that CFTR is present on acinar and ductal cells of rat and rabbit model. Recently, decrease in the production of lacrimal fluid has been reported in knockout mice.[49]

Extracellular and Cytoplasmic Proteins

In addition to above mentioned proteins, there are various extracellular and cytoplasmic proteins that are involved in the formation of tear film such as PRR4, S100A8, DMBT1 and PROL1. It has been reported that some of these proteins were differntially expressed in dry eye syndrome patients as compared to controls and the pathology of DES can be associated with decrease expression of these proteins.[13]

CONCLUSION

Xerostomia and dry eye syndrome occurring due to defects in salivary and lacrimal fluid secretion can result in a multifacet degradation of patients' quality of life. Xerostomia is caused by disturbances in regulation of protiens such as aquaporins (APQ-1 & -5), tight junction proteins (occludin, claudin), linker protein (ezrin) and ion channel proteins (CFTR). Similiarly, dry eye syndrome is caused by defective funstioning of aquaporins (APQ-4 & -5), gap junction proteins (Cx 32 and Cx 26), ion channel proteins and extracellular and cytoplasmic proteins.

Further research can explore possibilities of these molecules as relevant biomarker for abnormal conditions associated with salivary and lacrimal fluid flow.

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CONFLICT OF INTREST

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