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The imprint of salivary secretion in autoimmune disorders and related pathological conditions

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ABSTRACT

Xerostomia is a state of oral dryness associated with salivary gland dysfunction and is induced by stress, radiation and chemical therapy, various systemic and autoimmune diseases, and specific medications. Fluid secretion is interrupted by the stimulation of neurotransmitter-induced increase in cytosolic calcium ($[Ca^{2+}]_i$) in salivary gland acinar cells, prompting the mobilization of ion channels and their transporters. Salivary fluid and protein secretion are principally dependent on parasympathetic and sympathetic nerves. Various inflammatory cytokines allied with lymphocytic infiltration cause glandular damage and Sjogren's syndrome, an autoimmune exocrinopathy associated with hyposalivation. A defect in IP_3Rs, a major calcium release channel, prompts inadequate agonist-induced $[Ca^{2+}]_i$ in acinar cells and deters salivary flow. The store-operated calcium entry-mediated Ca^{2+} movement into the acini activates K^+ and Cl^- channels, which further opens a water channel protein, aquaporin-5, and triggers the release of fluid secretion from the salivary glands. The cellular mechanism of salivary gland dysfunction and hyposalivation has not yet been elucidated. In this review, we focused mainly on the proteins responsible for deficient saliva, the correlation between inflammation and salivation, autoimmune disorders and other ailments or complications associated with hyposalivation.

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Abbreviations: cAMP, cyclic adenosine monophosphate; GPCRs, G protein–coupled receptors; GLP-1, glucagon-like peptide 1; ATP, adenosine triphosphate; cGMP, cyclic guanosine monophosphate; Na^+/K^+/ATPase, sodium-potassium adenosine triphosphatase; TRPC, transient receptor potential canonical; IL, interleukin; TNF-α, tumor necrosis factor-alpha; NF-kB, nuclear factor-kappa B; TGF-β, transforming growth factor beta; IFN-γ, interferon-gamma; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinases; CD4, cluster of differentiation 4; PKC δ, protein kinase C *delta*; anti-Ro/SSA, anti-Ro/Sjogren's syndrome-related antigen A; anti-La/SSB, anti-La/Sjogren's syndrome-related antigen B; *NMDAR*, *N*-methyl-D-aspartate receptor; Gy, gray.

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1. Introduction

Salivation is the discharge of watery fluid containing electrolytes and complex protein blends from salivary glands. Saliva is an exocrine secretion comprised of different enzymes and antimicrobial proteins, immunoglobulins, growth factors, mucosal glycoproteins, and regulatory peptides [1,2]. Salivation has numerous functional properties including digestion aid, lubrication and maintenance of the oral cavity, buffering capacity, wound healing, and safeguarding from mechanical and chemical traumas. The final composition of saliva relies on the type of salivary gland and depends on either parasympathetic or sympathetic stimulations; the parasympathetic system stimulates an expansive number of fluid secretions, while the sympathetic system secretes various proteins [2]. Several membrane transport proteins and the association of cytosolic calcium ($[Ca^{2+}]_i$) signaling in salivary acinar cells determine the composition of salivary secretion [3]. In addition to cholinergic parasympathetic and adrenergic sympathetic incitement, ion and water channels have a cardinal role in saliva production of proteins and electrolyte emission through muscarinic M_3 and adrenoreceptors on salivary acinar cells [4,5]. Salivary gland acinar cells create primary saliva, an isotonic fluid comprised mainly of Na^+ and Cl^-. The ionic composition is modified in the duct framework and renders hypotonic saliva [4,6].

Calcium ions assume a crucial role in early functions of the secretory pathway and are used to regulate degradation in the endoplasmic reticulum (ER) [7]. The reduction in $[Ca^{2+}]_{ER}$ results in secretory dysfunction, which prompts improper posttranslational handling of ER proteins, including the folding and exit of proteins that cause ER stress and activate the unfolded protein response (UPR). However, the duration and severity of the stress determine whether the cells will experience either normal ER function or cell death. Loss of lumenal Ca^{2+} can diminish salivary protein and amylase activity, which can prompt result in dry mouth (xerostomia) [8]. Xerostomia is of concern because hyposalivation can lead to sialosis, gingivitis, loss of taste sensation, and other disorders of the oral cavity [8,9]. Metabolic illnesses like diabetes mellitus (especially, type 1) can cause xerostomia, and the diminished saliva production can cause enamel hypo-mineralization and dental caries [10]. Thus, the long-term effects of nerves and hormonal imbalance, autoimmune diseases, aging, and certain pharmaceuticals on salivary gland hypofunction have been discussed and contemplated [11].

Especially in autoimmune diseases including Sjogren's syndrome (SS), rheumatoid arthritis (RA), type I diabetes, systemic lupus erythematosus, progressive systemic sclerosis, and scleroderma, salivary secretion disturbance has not been successfully addressed under the highly developed medication treatment for immune systems. Therefore, we need to better understand the physiology, pathology, associated medications, and clinical limitations of saliva secretion problems.

This review summarizes and highlights the current understanding of the mechanism of salivary fluid secretion and the diseases or conditions that can play a vital role in the pathophysiology of hyposalivation-induced xerostomia.

2. Control of salivary secretion

The secretion of saliva and salivary proteins is under the control of the autonomic nervous system. Saliva is secreted mainly from three noteworthy salivary glands (parotid, submandibular, and sublingual glands) but also from innumerable minor salivary glands found in the oral mucosa [12,13]. Control of neuronal, endocrine, and paracrine signaling significantly contributes to salivary gland function and secretion [5].

2.1. Neuronal regulation

2.1.1. Role of parasympathetic and sympathetic nervous systems

The fundamental neural control of salivary secretion is by the parasympathetic (PNS) and sympathetic nervous systems (SNS). The PNS is imperative for secretion of the salivary fluid containing water and electrolytes and occurs after the release of acetylcholine. The acetylcholine released from the PNS activates M3 (to a lesser degree) and M1 muscarinic receptors in acinar and duct cells to increase $[Ca^{2+}]_i$ [5,12,13]. Calcium acts as an important signaling molecule in cells, and the balance of Ca^{2+} between cells and the outside milieu should be regulated very precisely [9]. The SNS increases cAMP by activating β-adrenergic receptors in acinar and duct cells. The SNS contributes to the secretion of proteins joined by exocytosis in acinar cells [13,14] and has a role in enzyme secretion through β-adrenergic stimulation [5]. The most abundant salivary enzyme is salivary amylase and is secreted by the activation of β-adrenoreceptors and a high level of intracellular cAMP [13]. Stimulation from sympathetic nerves releases noradrenaline, which invokes the release of stored proteins from both acinar and ductal cells [12].

2.1.2. Role of neuropeptides

The occurrence and release of neuropeptides play an important role in the function of salivary glands [15]. The co-expression of neuropeptides and neurotransmitters in each neuron encodes a specific signal to the target cells, contributing to a functionally diverse class of nerves. Neuropeptides such as neuropeptide Y (NPY), vasoactive intestinal

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