REVIEW ARTICLE

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Calcium Signaling in Salivary Secretion

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Calcium has versatile roles in diverse physiological functions. Among these functions, intracellular Ca^{2+} plays a key role during the secretion of salivary glands. In this review, we introduce the diverse cellular components involved in the saliva secretion and related dynamic intracellular Ca^{2+} signals. Calcium acts as a critical second messenger for channel activation, protein translocation, and volume regulation, which are essential events for achieving the salivary secretion. In the secretory process, Ca^{2+} activates K^+ and Cl^- channels to transport water and electrolyte constituting whole saliva. We also focus on the Ca^{2+} signals from intracellular stores with discussion about detailed molecular mechanism underlying the generation of characteristic Ca^{2+} patterns. In particular, inositol triphosphate signal is a main trigger for inducing Ca^{2+} signals required for the salivary gland functions. The biphasic response of inositol triphosphate receptor and Ca^{2+} pumps generate a self-limiting pattern of Ca^{2+} efflux, resulting in Ca^{2+} oscillations. The regenerative Ca^{2+} oscillations have been detected in salivary gland cells, but the exact mechanism and function of the signals need to be elucidated. In future, we expect that further investigations will be performed toward better understanding of the spatiotemporal role of Ca^{2+} signals in regulating salivary secretion.

Key Words: Calcium-activated chloride channels; Calcium oscillations; Calcium signaling; Inositol 1,4,5-trisphosphate receptors; Salivary glands; Salivation

Introduction

Salivary glands are the representative exocrine system in oral and maxillofacial region, which play a crucial role in maintaining oral and general health. Impaired function of the salivary glands results in xerostomia that can trigger diverse dental diseases such as dental caries, burning mouth syndrome and oral candidiasis[1]. Therefore, to understand the accurate molecular mechanism underlying saliva secretion is an essential step for developing therapeutic approaches for the xerostomic conditions. Among myriad regulators, we focus on the role of calcium, a versatile second messenger in diverse physiological functions, in the salivation process. Moreover, we introduce calcium dynamics

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and related signaling pathways reported in salivary glands.

The Role of Calcium in Salivary Glands

Calcium plays a key role during the secretion in salivary glands[2]. It has been well known that many ion channels and membrane transporters are involved in this process. Among these, Cl^- and K^+ channels are putative ion channels in exocrine glands including salivary glands. In salivary glands, two types of K^+ channels has been reported; one is Ca^{2+}-dependent K^+ channels and the other is Ca^{2+}-independent K^+ channels. Ca^{2+}-dependent K^+ channels are found in acinar cells from rat lacrimal glands and salivary glands[3,4]. While, Ca^{2+}-independent K^+ channels were also found in submandibular gland acinar cells, which has an intermediate conductance[5]. The role of intermediate conductance K^+ channels is not clear, but it appears to play a role in maintaining resting membrane potentials. In salivary glands, Cl^- channels are also can be divided into two types based on calcium dependency; the one is Ca^{2+}-dependent[6] and the other is Ca^{2+}-independent[7,8]. Interestingly, Ca^{2+}-activated Cl^- channels also can be regulated by intracellular pH[9]. Pilocarpine, a partial muscarinic agonist and widely used in dental clinic as a scretagogue, was reported to generate the current of Ca^{2+}-activated Cl^- and K^+ channels, which further support the putative role of these channels and calcium in salivary secretion[10]. It has been known that calcium is also necessary for the translocation of some proteins involved in secretion. Aquaporin (AQP) water channel is water channels and plays an important role in water transport during salivary secretion. AQP also regulated by intracellular free calcium. Among the subtypes of AQP, AQP-5 dominantly expressed at the apical membrane. Previous work demonstrated that it is translocated from the cytosol at the resting state to the membrane surface by an increase of intracellular calcium[11].

Volume regulation is important for the survival of some mammal cells which is frequently exposed to osmotic changes. Therefore, volume regulation is important for salivary epithelial cells, since salivary secretion results in the perturbation of cell volume accompanied by water and electrolyte movement. There are many evidences that calcium is necessary for the volume regulation in salivary epithelial cells. Ca^{2+}-dependent BK^+ channels are activated by the hypotonic stress[3]. Beside Ca^{2+}-activated Cl^- channels, volume sensitive Cl^- channels and chloride channel-3 in acinar cells isolated from the rat lacrimal gland and submandibular salivary gland has also been reported[7,8]. In regarding to the importance of volume regulation, both types of Cl^- channels appear to be activated by hypotonic stress.

Then what's the source of intracellular free calcium? The previous results showed that Ca^{2+} can be released from the three kinds of intracellular calcium stores; inositol-1,4,5-trisphosphate ($InsP_3$) sensitive calcium store, ryanodine sensitive calcium store and mitochondria[12]. Among these, mitochondria appear to play as a Ca^{2+} barrier to block the global spread of calcium which can damage cells. The other two calcium storage systems, $InsP_3$ and ryanodine, evokes rapid Ca^{2+} efflux from endoplasmic reticulum (ER) to cytoplasmic space, inducing diverse cellular functions related to saliva secretion.

The Intracellular Calcium Stores Involved in the Secretory Process

ER is a major Ca^{2+} storage that governs intracellular Ca^{2+} dynamics. ER occupies largest area of cytoplasmic space of the cells, and diverse Ca^{2+} detecting molecules, channels, and buffers are included in this complex[13]. The counter part of ER is existed as a sarcoplasmic reticulum in muscle cells. In addition to intracellular Ca^{2+} regulation, ER involves in various cellular functions such as protein synthesis, phospholipid formation, and

molecular transport[13]. However, ER is known as the primary site of Ca^{2+} transport, resulting in dynamic changes in cytoplasm-ER lumen Ca^{2+} concentration. The major players of such regulation process are two well-known ligand-gated channel, an inositol-1,4,5-trisphosphate receptor ($InsP_3R$) and a ryanodine receptor (RyR). Just like its name, $InsP_3Rs$ induce Ca^{2+} mobilization in response to subtle changes of $InsP_3$ concentration, which is regulated by the metabolic processes of a number of membrane receptors[14]. RyR is typically opened by Ca^{2+} influx mediated by voltage-dependent Ca^{2+} channels, named by Ca^{2+}-induced Ca^{2+} release (CICR)[15]. This reaction is critical for amplifying the magnitude and/or duration of intracellular Ca^{2+} signals. To date, it have been reported that each receptor family comprises three isoforms ($InsP_3R1$-3 and RyR1-3), which show tissue-specific expression profile, especially in excitable cell types[16]. However, the accurate expression profile of these proteins in salivary glands is not clear yet. The opening of the receptor channels elicits rapid efflux of Ca^{2+} from ER stores, called Ca^{2+} puff (by $InsP_3R$) or Ca^{2+} spark (by RyR)[16]. This rapid perturbation of ionic gradient across the ER membrane can be immediately returned to basal state by replenishing Ca^{2+} ions by two routes from Ca^{2+} sources. Sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) pump is a major transport system for Ca^{2+} from cytoplasmic space to ER lumen. Moreover, recently introduced store-operated Ca^{2+} entry (SOCE) mediates direct Ca^{2+} uptake from extracellular space[17] (Fig. 1).

The mechanisms and functions of intracellular Ca^{2+} stores in nervous and muscular system are quite well understood. $InsP_3R$ response in pre/post synaptic neurons is involved in broad range of neuronal functions such as synaptic transmission and plasticity[18,19]. In muscle contraction, RyR-mediated CICR process is essential for actomyosin engagement[20]. Moreover, it has been reported that exocytotic secretion process is mainly regulated by ER Ca^{2+} release in several nonexcitable and excitable cells. Ryanodine sensitive Ca^{2+} stores in presynaptic neurons amplify spike-triggered Ca^{2+} signals in presynaptic terminals, and consequently enhance the transmitter release[18]. Gonadotropin-releasing hormone also induced exocytosis in pituitary gonadotrophs through $Ins(1,4,5)P_3$-mediated Ca^{2+} release[21]. In the exocrine pancreas, muscarinic acetylcholine receptors (mAChRs) mediated secretory process in pancreatic acinar cells through $Ins(1,4,5)P_3$ pathway[22].

The secretion process in salivary glands is also primarily mediated by mAChRs. Acetylcholine is a parasympathetic neurotransmitter that functions in neuromuscular junction, central nervous system, and also in salivary glands. Therapeutic use of muscarinic antagonists (*e.g.*, atropine) reported a frequent side effect including xerostomia and

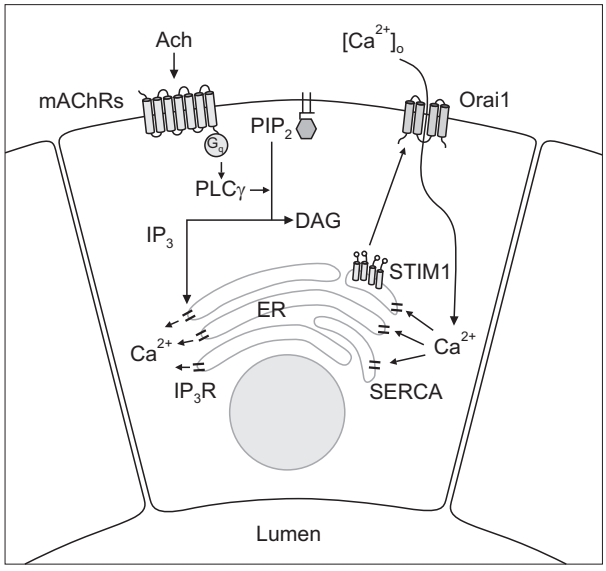

Fig. 1. Muscarinic acetylcholine receptor (mAChR) mediated Ca^{2+} signaling pathways in salivary glands. mAChR activation by acetylcholine mediates phospholipase C (PLC) pathway that increase $Ins(1,4,5)P_3$ (IP_3) production, resulting in Ca^{2+} mobilization from ER storage. Sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) pump is a major transport system for Ca^{2+} from cytoplasmic space to ER lumen. Moreover, store-operated Ca^{2+} entry (SOCE) induced by stromal interaction molecule 1 (STIM1)-Orai1 interaction mediates direct Ca^{2+} uptake from extracellular space. Ach: acetylcholine, PIP_2: phosphatidylinositol 4,5-bisphosphate, DAG: diacylglycerol, ER: endoplasmic reticulum.

chronic dry mouth[23], indicating that acetylcholine-mAChR plays a major role in saliva secretion. In knockout (KO) mouse study, both M1/M3 mAChRs single and double KO mice presented reduced saliva flow against muscarinic agonist pilocarpine treatment[24]. The expression profile of mAChRs subtypes is varied from the type of salivary glands: M1 and M3 mAChRs are expressed in the sublingual and submandibular glands, and M3 mAChRs is predominant in the parotid glands[25]. Our group previously reported the mAChR-related mechanism underlying reduced salivation in Sjögren syndrome (SS). Functional autoantibodies in serum of SS patients induced the internalization of M3 mAChR in salivary gland acinar cells, which could be important factor of hyposalivation[26].

Whole saliva secretion requires water transport to ductal space by osmotic pressure as well as transport of other salivary components. During salivation, the osmotic gradient is generated by ionic transport through Ca^{2+}-activated Cl^- channels (CACCs)[27]. The intracellular Ca^{2+} is a critical second messenger for the ion channel activation, and mAChR mediate this process by transmitting signaling pathways that induce intracellular Ca^{2+} mobilization. mAChR activation mediates phospholipase C pathway that increase Ins(1,4,5)P_3 production, resulting in Ca^{2+} mobilization from ER storage. InsP_3R-mediated Ca^{2+} efflux promotes the opening of CACCs, leading the efflux of chloride ions toward ductal space, and subsequent generation of an electrochemical gradient across the apical border of acinar cells. This spatially different ionic concentration triggers osmotic pressure that triggers water transport toward intercalated ductal space[28,29].

The functional expression of RyRs have been also reported in diverse salivary gland cells[30,31], but the exact role of the channel in saliva secretion is still poorly understood. We recently reported CICR response mediated by RyR in salivary gland acinar cells. In this study, we provide the expression profile of transient receptor potential (TRP) channel families in submandibular gland acinar cells, and demonstrated that Ca^{2+} influx via TRPM7 (melastatin) channel is amplified by RyR activation[32]. It was also reported that TRP channel activities are also related to CACC conductance[33]. These evidences suggest that TRP channel-mediated RyR response could be a functional component in saliva secretion through mobilizing internal Ca^{2+} stores.

The Pattern of Calcium Release Including Calcium Oscillation

In cytoplasmic area, Ca^{2+} signals are sophisticatedly regulated by diverse Ca^{2+} binding proteins, Ca^{2+} pumps, and intracellular orgarnelles with high spatiotemporal resolution. When the intracellular Ca^{2+} level locally increased with diverse extents, these regulators, so-called Ca^{2+} "buffers," spatiotemporally restrict the evoked diffusing calcium ions, resulting in the characteristic patterns of Ca^{2+} signals[16]. In this review, we will focus on the Ca^{2+} patterns arose from intracellular stores.

The spatial pattern of Ca^{2+} signals is initially determined by the type and number of involved channels. According to levels of stimulation, the number of InsP_3R and RyR can be varied from a single channel to single or multiple clusters of the channels (also called Ca^{2+} release unit [CRU])[34]. In high level of excitation degree, the clusters propagate the Ca^{2+} signals to adjacent units through CICR process[35]. There is distinct hierarchical terminology to refer the Ca^{2+} patterns induced by different Ca^{2+} channels. Ca^{2+} release from single InsP_3R channel is recorded as Ca^{2+} "blips." This single channel event can be expanded to locally-concentrated adjacent channels, inducing more broad and sustained, but localized Ca^{2+} signals (Ca^{2+} puffs). RyR has different terms for describing the extent of signals, Ca^{2+} quarks (embers) and sparks, which is released from a single channel and a single

CRU, respectively[36]. The autocatalytic process of CICR enables the amplification of the Ca^{2+} signals between CRUs, inducing the broad Ca^{2+} signal occupying whole cell area, called Ca^{2+} "waves." The Ca^{2+} waves can travel across the individual cells through intercellular proteins such as gap junction[37].

While a certain Ca^{2+} signal evoked, diverse intracellular mechanisms simultaneously operate to decrease the Ca^{2+} levels. Such balance between Ca^{2+} increase and decrease is essential for cellular homeostasis by preventing excessive Ca^{2+} increase. When a Ca^{2+} signal is induced by moderate stimulation within a physiological level, such reciprocal checks and balances can establish a characteristic regenerative Ca^{2+} efflux, called Ca^{2+} oscillation[38]. To understand the mechanism underlying the oscillative Ca^{2+} signals, a number of computational models and *in vitro* Ca^{2+} recordings have been tried in diverse biological contexts. Although there are remaining questions, these efforts have led to a general consensus that $InsP_3R$ is a dominant regulator of the Ca^{2+} oscillation. The regulatory mechanism of $InsP_3R$ in this event is mainly due to the biphasic property of the channel upon the cytoplasmic Ca^{2+} levels. Like $Ins(1,4,5)P_3$, moderate Ca^{2+} increase is known to activate $InsP_3R$, and the positive feedback of Ca^{2+} itself is generally accepted as a key mechanism in generating Ca^{2+} oscillations[39,40]. However, excessive increase of cytosolic Ca^{2+} (above 10^{-6} to 10^{-5} M) inhibits further Ca^{2+} release from $InsP_3R$ and RyR channels[41]. Based on these properties, it assumed that distinct allosteric binding sites of Ca^{2+} for activation and deactivation are existed in each subunit of $InsP_3R$, with different binding affinities[35]. In addition to this self-limiting process, the increased Ca^{2+} is additionally pumped out by SERCA and of plasma membrane Ca^{2+}-ATPase, which mobilize the cytoplasmic Ca^{2+} to ER and extracellular space, respectively. If the excitable signaling input was sustained, these biphasic processes eventually present the Ca^{2+} patterns of periodic discharges and entry[38].

The chemical information of oscillative Ca^{2+} signals is translated into versatile cellular functions through decoding process. The Ca^{2+} decoder (*e.g.*, calmodulin) make changes of the protein structures or amino acid residues upon Ca^{2+} binding on their binding sites, and then transmit the signals to downstream effectors[41]. To date, a number of biological functions induced by Ca^{2+} oscillation have been reported, such as fertilization, neurite outgrowth, and interleukin production[42-44]. In exocrine system, the effect of Ca^{2+} oscillation is well known to promote insulin secretion from pancreatic acinar cells[45,46]. The oscillative Ca^{2+} pattern was also reported in rat parotid acinar cells, which is generated by treatment with muscarinic agonist carbachol[47]. However, there is a lack of evidence for the relationship between Ca^{2+} oscillation and saliva secretion. Previous report that $InsP_3R2$ and 3 is essential for inducing pilocarpine-induced salivation[48] supports the hypothesis of the role of Ca^{2+} oscillation in saliva secretion.

Experimental Detection of Ca^{2+} Oscillation in Salivary Gland Cells and Future Perspectives

Based on the previous report[47], our group also demonstrated the oscillative patterns of Ca^{2+} in human submandibular gland (HSG) cells under a specific experimental condition.

As shown in Fig. 2, the cells stimulated by carbachol under extracellular calcium-free condition showed a robust Ca^{2+} oscillation than that under 1 mM Ca^{2+} bath solution. The result demonstrates that the continuous Ca^{2+} influx contribute to the sustained calcium plateau, but the mechanism of oscillation under Ca^{2+} free solution needs to be further investigated.

In Fig. 3, effects of 2-APB ($Ins(1,4,5)P_3$-sensitive calcium store blocker, dotted grey line) and 8-Br-

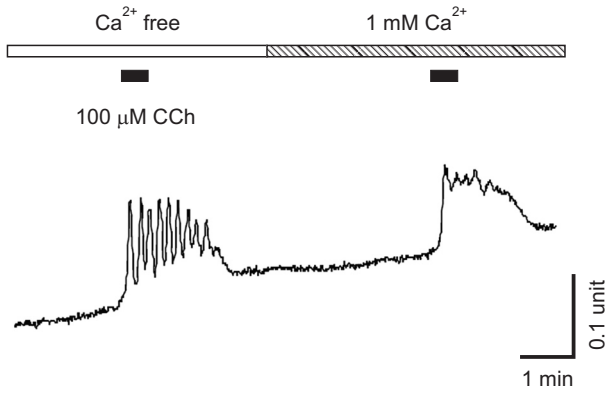

Fig. 2. Ca^{2+} oscillation evoked by carbachol in Ca^{2+}-free and Ca^{2+}-containing (1 mM) solution in human submandibular gland cell line. CCh: carbachol.

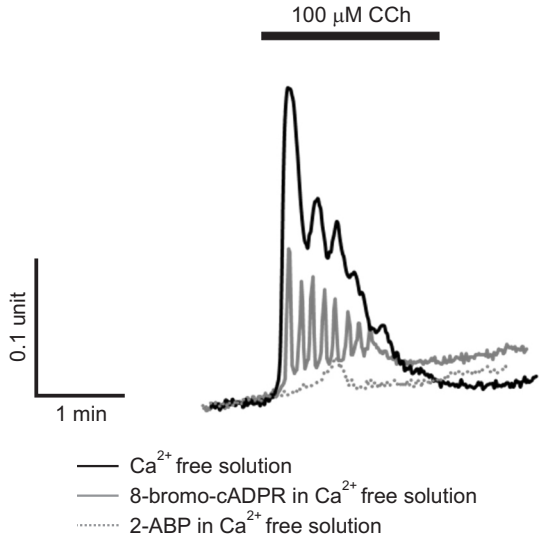

Fig. 3. Ca^{2+} oscillation evoked by carbachol in Ca^{2+}-free bath solution in presence of 2-APB ($Ins(1,4,5)P_3$-sensitive calcium store blocker, dotted grey line), 8-Br-cADPR (ryanodine-sensitive calcium store blocker, grey line), and control group (black). Human submandibular gland (HSG) cells were pretreated with either 2-APB (100 μM) or 8-Br-cADPR (10 μM) for 5 minutes, then carbachol was treated on both groups for 2 minutes. CCh: carbachol.

cADPR (ryanodine-sensitive calcium store blocker, grey line) on the Ca^{2+} release from HSG cells' intracellular Ca^{2+} store via carbachol stimulation of muscarinic receptor were observed. As shown in the results 8-Br-cADPR suppressed Ca^{2+} response only by 35%±8.3% (n=29) but 2-APB suppressed it by 72.2%±8.6% (n=26). It is of note that pattern of Ca^{2+} oscillation via carbachol stimulation under Ca^{2+}-free solution was much more augmented when treated with 8-Br-cADPR, while Ca^{2+} oscillation hardly observed when treated with 2-APB (Fig. 3). Therefore the result suggests that intracellular Ca^{2+} release and Ca^{2+} oscillation triggered by muscarinic receptor stimulation mainly affected by $Ins(1,4,5)P_3$-sensitive calcium store rather than RyR.

As discussed in this review, intracellular Ca^{2+} has versatile roles in salivary secretion. Ca^{2+} acts as a critical second messenger for channel activation, protein translocation, and volume regulation, which are essential events for achieving the secretory process. The future researches will focus on the spatiotemporal role of intra- and extracellular Ca^{2+} in regulating salivary secretion by using state-of-the-art experimental techniques. In particular, further investigations are required to understand the generating mechanism and physiological role of Ca^{2+} oscillations in salivary glands.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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