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Role of calcium signaling in epithelial bicarbonate secretion

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ABSTRACT

Transepithelial bicarbonate secretion plays a key role in the maintenance of fluid and protein secretion from epithelial cells and the protection of the epithelial cell surface from various pathogens. Epithelial bicarbonate secretion is mainly under the control of cAMP and calcium signaling. While the physiological roles and molecular mechanisms of cAMP-induced bicarbonate secretion are relatively well defined, those induced by calcium signaling remain poorly understood in most epithelia. The present review summarizes the current status of knowledge on the role of calcium signaling in epithelial bicarbonate secretion. Specifically, this review introduces how cytosolic calcium signaling can increase bicarbonate secretion by regulating membrane transport proteins and how it synergizes with cAMP-induced mechanisms in epithelial cells. In addition, tissue-specific variations in the pancreas, salivary glands, intestines, bile ducts, and airways are discussed. We hope that the present report will stimulate further research into this important topic. These studies will provide the basis for future medicines for a wide spectrum of epithelial disorders including cystic fibrosis, Sjögren's syndrome, and chronic pancreatitis.

1. Introduction

Bicarbonate (HCO_3^-) secretion plays a key role in the formation and proper function of bodily fluids in the central organs. These include pancreatic juice in the exocrine pancreas, airway surface fluids in the lungs, the aqueous humor in the eyes, and the cerebrospinal fluids in the brain. HCO_3^- controls the pH of the fluids and facilitates the hydration and expansion of dissolved macromolecules, such as digestive enzymes and mucins [1,2]. Cumulative evidence suggests that aberrant HCO_3^- secretion in these fluids leads to a wide spectrum of diseases. For example, reduced HCO_3^- secretion in the surface epithelium of hollow viscera is associated with the pathogenesis of cystic fibrosis (CF), chronic pancreatitis, respiratory infectious disease, dental caries, and infertility [3–7].

Epithelial HCO_3^- secretion is under the control of multiple cellular signaling pathways, most prominently by cytosolic cyclic adenosine monophosphate (cAMP) and Ca^{2+} signaling. Cellular mechanisms of cAMP signaling-induced HCO_3^- secretion, that regulate and coordinate ion transporters in the apical and basolateral membranes of epithelial cells, are fairly well characterized, especially those involved in the regulation of the cystic fibrosis transmembrane conductance regulator (CFTR). In secretory epithelia, many neurohumoral signals that are induced by diverse secretagogues are transduced into secretory signals through changes in $[Ca^{2+}]_i$. Increasing evidence suggests that these Ca^{2+} agonists play a significant physiological role in HCO_3^- secretion at least in certain epithelia, such as duodenum and biliary tracts. In addition, Ca^{2+} agonists potentiate the cAMP-induced HCO_3^- and fluid secretion in many epithelia. However, molecular mechanisms of Ca^{2+} signaling-induced HCO_3^- secretion remain largely elusive.

The Ca^{2+} signal is highly polarized in most epithelial cells, thus the apical and basolateral poles can have different functions [8,9]. In addition, membrane transporters in epithelial cells, including those that are involved in HCO_3^- secretion, are expressed in a polarized pattern at the apical or basolateral membrane. This spatial separation of transporters is essential for the vectorial transport of electrolytes and fluids [10]. In the present review, we attempt to systemically review the current status of knowledge on the role of Ca^{2+} signaling in transepithelial HCO_3^- secretion, especially in the gastrointestinal and respiratory organs. Furthermore, loci of cross-talk between Ca^{2+} and cAMP signaling in these epithelia are highlighted and discussed.

2. Molecular mechanism of Ca^{2+}-induced bicarbonate secretion

2.1. Ca^{2+} signaling in secretory epithelia

Most HCO_3^--secreting epithelia receive multiple inputs from hormones, neurotransmitters, and autacoids that evoke cytosolic

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Ca^{2+} signaling. For example, in pancreatic ducts, acetylcholine secreted by vagal parasympathetic nerves binds to cholinergic muscarinic receptors in the basolateral membrane and increases $[Ca^{2+}]_i$ [11,12]. The intestinal hormone, cholecystokinin (CCK), increases $[Ca^{2+}]_i$ via the activation of CCK type A receptors in the basolateral membrane of pancreatic duct cells [13]. Luminal ATP secreted from the duct or acinar cells and basolateral ATP released from nerve endings can induce Ca^{2+} signaling via purinoceptors in each membrane of duct cells [14].

The binding of the agonists to these receptors induces the activation of the G protein G_q or G_i to generate $G_{\alpha q}$·GTP or release $G_{\beta\gamma}$, respectively, from the hetero-trimeric G protein complex. $G_{\alpha q}$·GTP or released $G_{\beta\gamma}$ activates phospholipase C to generate inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) by hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) [15]. Increases in the concentration of cytosolic IP_3 stimulate the IP_3 receptor (IP_3R) in the endoplasmic reticulum (ER) and rapidly release free Ca^{2+} from the ER Ca^{2+} store to the cytosol. Among the three IP_3R paralogs (IP_3R1–IP_3R3), IP_3R2 and IP_3R3 are the major isoforms in secretory epithelial cells [16]. ER Ca^{2+} release is frequently followed by activation of the store-operated channels (SOCs) in the plasma membrane, such as the Orai [17–19] and transient receptor potential cation (TRPC) channels [20–22]. In response to the depletion of Ca^{2+} stores, the ER Ca^{2+} sensor, stromal interaction molecule 1 (STIM1), clusters with these SOCs to activate them [23,24]. In some epithelia, such as the duodenal mucosa, Ca^{2+} entry via the reverse mode of the Na^+/Ca^{2+} exchanger (NCX) can play a role in the sustained increase in $[Ca^{2+}]_i$ [25]. Finally, the increase in $[Ca^{2+}]_i$ activates the sarco/endoplasmic Ca^{2+} ATPase (SERCA) and the plasma membrane Ca^{2+} ATPase (PMCA) pumps to restore $[Ca^{2+}]_i$ to basal levels [10].

Ca^{2+} signals in the epithelial cells are highly polarized. The polarized expression of secretagogue receptors and Ca^{2+} signaling proteins generates polarized Ca^{2+} signals. The polarized expression of Ca^{2+}-signaling proteins, such as IP_3Rs [26–28], the SERCA and PMCA pumps [29,30], TRPC channels [31], Orai channels, and STIM1 [32,33], has been demonstrated in epithelial cells. Interestingly, IP_3Rs and many secretagogue receptors, even receptors in the basolateral membrane, are gathered at, or near, tight junctions that are close to the apical pole [34,35]. This localization frequently generates cytosolic Ca^{2+} signals that initiate at the apical pole and propagate to the basal pole in the form of Ca^{2+} waves, as typically shown in pancreatic and parotid acinar cells [8,10]. The Ca^{2+} signals, evoked by physiological agonist concentrations, are in the form of Ca^{2+} oscillations, where the Ca^{2+} signal is periodically repeated. The frequency and amplitude of the oscillation is determined by the intensity of receptor stimulation [11,36].

Ca^{2+} signals can modulate the activity of membrane transporting proteins via multiple mechanisms. The direct binding of cytosolic free Ca^{2+} to the target transporter can modulate its function, as has been shown in the case of the Ca^{2+}-activated Cl^- channel (CaCC) [37]. In addition, increases in $[Ca^{2+}]_i$ can modulate the function of the target protein by way of a Ca^{2+} signal-transducing protein, such as calmodulin and Ca^{2+}/calmodulin-dependent protein kinases (CamKs). Finally, Ca^{2+} agonists that evoke receptor-mediated Ca^{2+} signaling can regulate membrane transporters by producing byproducts, such as DAG and IP_3. The DAG-mediated activation of protein kinase C (PKC) or the IP_3-induced release of the IP_3 binding protein released with IP_3 (IRBIT) from IP_3Rs has been shown to regulate a number of epithelial transporters [38,39].

2.2. Bicarbonate transporting proteins that are regulated by cytosolic Ca^{2+} signaling

The transporters that are involved in calcium-activated HCO_3^- secretion in epithelial cells are depicted in Fig. 1. As mentioned above, these transporters also have a polarized expression pattern that is critical for the directional transport of HCO_3^- and fluids. Among these transporters, the HCO_3^- permeable or transporting proteins in the apical membrane, such as CFTR, CaCCs, and the solute-linked carrier 26A (SLC26A) Cl^-/HCO_3^- exchangers, are directly responsible for HCO_3^- efflux to the lumen. On the contrary, transporting proteins in the basolateral membranes, such as Na^+-HCO_3^- cotransporter (NBC), Na^+/K^+ ATPase, and K^+ channels, accumulate HCO_3^- in the cytoplasm or provide the driving force for apical HCO_3^- efflux.

2.2.1. CFTR

CFTR is a cAMP-activated anion channel that is mutated in CF [40]. Since the discovery of defective HCO_3^- secretion in the pancreatic juice of patients with CF [41], it is now evident that CFTR expression is essential for HCO_3^- secretion in most gastrointestinal and airway epithelia [42]. In these epithelia, a significant proportion of transepithelial HCO_3^- transport is mediated by electrodiffusive pathways, suggesting that anion channels are involved in this process [43–45]. According to the Nernst Equation, having a HCO_3^- selective channel at the apical membrane makes it theoretically possible to secrete up to 200 mM HCO_3^-, when cells maintain a membrane potential of −60 mV and $[HCO_3^-]_i$ of 20 mM [37]. Notably, the CFTR anion channel can be highly permeable to HCO_3^- under conditions of the low $[Cl^-]_i$-induced activation of with-no-lysine kinase 1 (WNK1) [37]. Although CFTR is principally activated by cAMP signaling, Ca^{2+} agonists can partially activate or potentiate the cAMP-mediated activation of CFTR by PKC-mediated phosphorylation or by releasing IRBIT from IP_3Rs [38,39]. Currently, whether the PKC-mediated phosphorylation of CFTR can increase epithelial HCO_3^- secretion is unknown. However, the role of IRBIT in epithelial HCO_3^- secretion is relatively well defined [39,46].

2.2.2. CaCCs

CaCCs can also mediate electrodiffusive HCO_3^- transport in the apical membrane of epithelia. Recently, members of the anoctamin (ANO; also known as TMEM16) family, in particular ANO1/TMEM16A and ANO2/TMEM16B, were shown to function as CaCCs in the gut, trachea, salivary glands, and olfactory organs [47–51]. The Ca^{2+}-induced activation of CaCC has been suggested to contribute to HCO_3^- secretion in some epithelia. For example, cholinergic stimulation, which evokes an increase in $[Ca^{2+}]_i$, induces HCO_3^- secretion via CaCCs in rat and human salivary gland cells [52,53]. Interestingly, the HCO_3^- permeability (P_{HCO3}/P_{Cl}) of ANO1 can be dynamically regulated by Ca^{2+}/calmodulin, and the ANO1 CaCC becomes highly permeable to HCO_3^- when $[Ca^{2+}]_i$ is above ~1 μM [54]. In the apical microdomain of secretory epithelial cells where IP_3Rs and CaCCs are clustered [27,48], $[Ca^{2+}]_i$ is estimated to be increased to levels as high as 50 μM by physiological stimuli [55,56]. Therefore, an increase in ANO1 P_{HCO3}/P_{Cl} would be a major mechanism of epithelial HCO_3^- secretion in response to cytosolic Ca^{2+} signals, at least in salivary gland acinar cells. Whether the ANO1-mediated secretion of HCO_3^- can play a significant physiological role in other epithelia needs to be determined in future studies.

2.2.3. Cl^-/HCO_3^- exchangers

In many epithelia including pancreatic ducts, salivary gland ducts, and duodenum, apical HCO_3^- secretion is frequently associated with Cl^- absorption, which is mediated by Cl^-/HCO_3^- exchangers [10,42]. Notably, the activity of Cl^-/HCO_3^- exchangers at the apical membrane is highly dependent on the expression of CFTR in epithelial cells [57–59]. In humans and other mammals, gene products of SLC4 and SLC26 families are known to have Cl^-/HCO_3^- exchange activities. Recent evidence suggests that transporters in the SLC26 family can mediate Cl^-/HCO_3^- exchange