Cell Calcium 55 (2014) 337–345

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Calcium signaling in pancreatic ductal epithelial cells: An old friend and a nasty enemy

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ARTICLE INFO

Article history:
Received 20 January 2014
Received in revised form 4 February 2014
Accepted 5 February 2014
Available online 15 February 2014

Keywords:
Pancreatic ductal secretion
Epithelial Ca^{2+} signaling
Exocrine pancreas

ABSTRACT

Ductal epithelial cells of the exocrine pancreas secrete HCO_3^- rich, alkaline pancreatic juice, which maintains the intraluminal pH and washes the digestive enzymes out from the ductal system. Importantly, damage of this secretory process can lead to pancreatic diseases such as acute and chronic pancreatitis. Intracellular Ca^{2+} signaling plays a central role in the physiological regulation of HCO_3^- secretion, however uncontrolled Ca^{2+} release can lead to intracellular Ca^{2+} overload and toxicity, including mitochondrial damage and impaired ATP production. Recent findings suggest that the most common pathogenic factors leading to acute pancreatitis, such as bile acids, or ethanol and ethanol metabolites can evoke different types of intracellular Ca^{2+} signals, which can stimulate or inhibit ductal HCO_3^- secretion. Therefore, understanding the intracellular Ca^{2+} pathways and the mechanisms which can switch a good signal to a bad signal in pancreatic ductal epithelial cells are crucially important. This review summarizes the variety of Ca^{2+} signals both in physiological and pathophysiological aspects and highlight molecular targets which may strengthen our old friend or release our nasty enemy.

1. Introduction

The acinar-ductal functional unit of the exocrine pancreas secretes 1–2 L alkaline, digestive enzymes-rich juice daily [1,2]. The acinar cells produce an acidic, Cl^- and protein-rich, high viscosity fluid [3], whereas the ductal epithelial cells (PDEC) secretes high quantity of HCO_3^--rich low viscosity fluid [4]. The final HCO_3^- concentration of the pancreatic juice varies among species; importantly human PDEC can produce a maximal intraluminal HCO_3^- concentration of 140 mM. The alkaline pancreatic fluid secretion, in response to meal, washes the digestive enzymes out of the pancreatic ductal tree and neutralizes the acidic chyme entering the duodenum. The function of the pancreatic ductal fluid and HCO_3^- secretion used to be underestimated, however recent findings suggest that it plays a central role in the physiology and pathophysiology of the pancreas. Importantly, HCO_3^- neutralizes protons secreted by the acinar cells and keeps trypsinogen and most probably other proteases in an inactive form [5]. Pallagi et al. have recently demonstrated that the autoactivation of trypsinogen is a pH dependent process, with increased activity in acidic environment, which means that HCO_3^- secretion prevents the premature trypsinogen activation [5]. We also have to highlight that the most common pathogenic factors for acute pancreatitis (bile acids, ethanol and ethanol metabolites) impair ductal HCO_3^- secretion which likely contributes in a major manner to the pancreatic damage [6–8].

The pancreatic ductal HCO_3^- secretion is regulated by complex signaling systems, in which both cAMP and intracellular Ca^{2+} play crucial roles. Agonists (such as secretin or acetylcholine) binding to G protein coupled metabotropic receptors activate adenylyl cyclases and/or release Ca^{2+} from the intracellular stores in PDEC. On the other hand, some of the molecules do not need membrane receptors to induce an intracellular Ca^{2+} elevation. Low concentrations of unconjugated bile acids and ethanol also evoke oscillatory intracellular Ca^{2+} signals and stimulate HCO_3^- secretion in PDEC. However, these molecules in high concentrations induce sustained Ca^{2+} elevations, which inhibit the secretory processes and lead to cell necrosis. These pathogenic steps, which result in the development of toxic, sustained Ca^{2+} signals, might offer potential therapeutic targets in pancreatic diseases. In this review we summarize the recent advances in pancreatic ductal physiology and

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http://dx.doi.org/10.1016/j.ceca.2014.02.004
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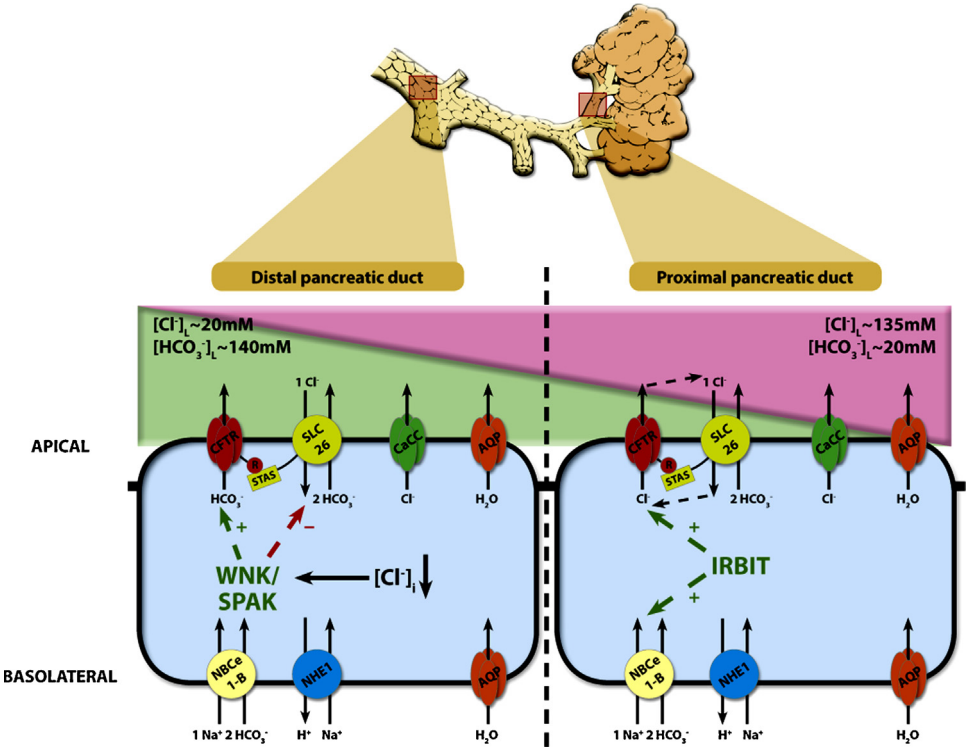

Fig. 1. Mechanism of pancreatic ductal HCO_3^- secretion. Pancreatic ductal cells accumulate HCO_3^- across the basolateral membrane via the electrogenic Na^+/HCO_3^- cotransporter NBCe1-B. On the luminal membrane PDEC express electrogenic Cl^-/HCO_3^- exchangers (SLC26A6 and possibly A3) and cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel. The operation of these transporters allows the pancreatic ductal cells to create 140 mM maximal HCO_3^- concentration during stimulated secretion. The R domain of CFTR interact with the STAS domain of the SLC26 Cl^-/HCO_3^- exchanger, which increases overall open probability of CFTR. In the proximal ducts, where the intraluminal Cl^- concentration ($[Cl^-]_L$)is high, HCO_3^- is secreted via the electrogenic Cl^-/HCO_3^- exchange, driven by the high $[Cl^-]_L$. Under these conditions CFTR functions as a Cl^- channel. In the distal ducts, where the $[Cl^-]_L$ is low, the low intracellular Cl^- concentration ($[Cl^-]_i$) activates the WNK/SPAK kinases, which phosphorylate CFTR, switching the ion selectivity to HCO_3^-. The SLC26 mediated HCO_3^- transport is inhibited under these conditions.

pathophysiology, highlighting the dual effects of Ca^{2+} signaling in PDEC.

2. Bicarbonate secretion in pancreatic ductal cells

Pancreatic ductal HCO_3^- secretion can be divided to two separate steps, first the accumulation of the HCO_3^- ions in the cells via the basolateral membrane and second the secretion into the ductal lumen across the apical membrane (Fig. 1). The basolateral accumulation is carried out by a Na^+/HCO_3^- cotransporter (NBCe1-B), which transports 1 Na^+ and 2 HCO_3^- into the cells, driven by the high intracellular Na^+ gradient [9]. Another possible mechanism for the HCO_3^- accumulation is the passive diffusion of CO_2 trough the cell membrane, followed by the carbonic anydrase mediated conversion of CO_2 to HCO_3^- [10]. The electroneutral Na^+/H^+ exchanger might also contribute to the HCO_3^- accumulation, although its role differs among species [11,12], it is essential for intracellular pH (pH_i) homeostasis. On the luminal membrane PDEC express electrogenic Cl^-/HCO_3^- exchangers (SLC26A6, which operates with a 1 Cl^-: 2 HCO_3^- stoichiometry and possibly SLC26A3, which transports 2 Cl^-: 1 HCO_3^-) [13] and the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel [14]. The electrogenic Cl^-/HCO_3^- exchange allows the pancreatic ductal cells to transport HCO_3^- into the ductal lumen and establish the very high (140 mM) maximal intraluminal HCO_3^- concentration during stimulated secretion, resulting in an intraluminal HCO_3^- level which is ~5–6 fold higher compared to the cell interior [1,2]. It is important to note that CFTR mutations, which are associated with exocrine pancreatic insufficiency, also establish a major deficiency in the apical CFTR-dependent Cl^-/HCO_3^- exchange activity [15]. Recent improvements in the field help to understand the puzzling role of CFTR in HCO_3^- secretion. In the proximal pancreatic ducts, where the luminal Cl^- concentration ($[Cl^-]_L$) is high, CFTR functions as a Cl^- channel, providing the necessary substrate (luminal Cl^-) for the Cl^-/HCO_3^- exchange of the SLC26A6 and A3 transporters. In the distal pancreatic ducts however, where the $[Cl^-]_L$ and intracellular Cl^- concentration ($[Cl^-]_i$) is low, HCO_3^- secretion through CFTR can play an important role. Under these conditions the CFTR Cl^- permeability is switched by the With-No-Lysine (WNK)/STE20/SPS1-related proline/alanine-rich kinase (SPAK) kinase pathway (which is regulated by $[Cl^-]_i$), changing CFTR into a HCO_3^- permeable channel [16]. Another recently described regulatory protein, named IRBIT, seems to play a crucial role in the regulation of HCO_3^- secretion as well. Under resting conditions WNK/SPAK constitutively inhibit the activity of CFTR and NBCe1-B, which is antagonized by IRBIT upon stimulation. Moreover IRBIT promotes the insertion of CFTR into the apical membrane [17]. In addition, IRBIT seems to mediate synergism between Ca^{2+} and cAMP signaling pathways [18]. The detailed regulation of HCO_3^- secretion by IRBIT and by the WNK/SPAK pathway has been reviewed elsewhere and is beyond the scope of this manuscript[1,2,19,20]. PDEC also express Ca^{2+} activated Cl^- channels on the luminal membrane [21], however the molecular identity and contribution to the pancreatic HCO_3^- and fluid secretion is unknown at the time. Recently, ANO1 (TMEM16A) was identified on the luminal membrane of the pancreatic acinar cells as the Ca^{2+} activated Cl^- channel, which plays an important role in acinar Cl^- secretion [22]. Besides the transporters and channels, which participate in the HCO_3^- secretion, PDEC also express aquaporin (AQP) water channels. AQP1 is expressed on both the basolateral and luminal membrane and AQP5 only on the luminal membrane [23]. Moreover, AQP5 was shown to strongly colocalise with CFTR in the