



Acid-base transport in pancreas—new challenges

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Along the gastrointestinal tract a number of epithelia contribute with acid or basic secretions in order to aid digestive processes. The stomach and pancreas are the most extreme examples of acid (H^+) and base (HCO_3^-) transporters, respectively. Nevertheless, they share the same challenges of transporting acid and bases across epithelia and effectively regulating their intracellular pH. In this review, we will make use of comparative physiology to enlighten the cellular mechanisms of pancreatic HCO_3^- and fluid secretion, which is still challenging physiologists. Some of the novel transporters to consider in pancreas are the proton pumps (H^+ - K^+ -ATPases), as well as the calcium-activated K^+ and Cl^- channels, such as $K_{Ca}3.1$ and TMEM16A/ANO1. Local regulators, such as purinergic signaling, fine-tune, and coordinate pancreatic secretion. Lastly, we speculate whether dys-regulation of acid-base transport contributes to pancreatic diseases including cystic fibrosis, pancreatitis, and cancer.

Keywords: bicarbonate transport, proton transport, H^+ - K^+ -ATPase, $K_{Ca}3.1$, IK, TMEM16A, ANO1, pancreatic duct

INTRODUCTION: ACID-BASE FLUXES ALONG THE GASTROINTESTINAL TRACT

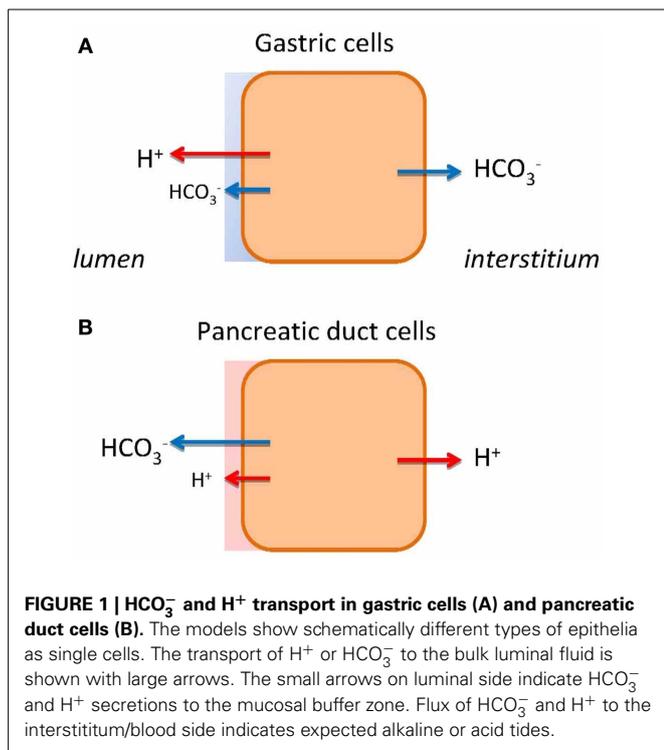
In multicellular organisms the digestive system exhibits marked acid/base segmentation and gradients across the epithelia. The most extreme examples of the acid/base transporters are the stomach and the pancreas, which conduct a vectorial transport of acid/base to one side and base/acid to the other side of the epithelium (Figure 1). In the stomach, the parietal cells of the pyloric glands secrete H^+ toward lumen (HCl), leaving HCO_3^- to be transported into the interstitium and blood. Thus, the phenomenon of the alkaline tide, i.e., higher blood pH in connection with digestion, is well known as part of the post-prandial gastric phase secretion, which in humans is relatively small compared to animals that ingest large amounts of food at one time

Abbreviations: BK, big conductance K^+ channel, also named $K_{Ca}1.1$ and maxi- K^+ , coded by *KCNMA1*; CaCC, Ca^{2+} -activated Cl^- channel, e.g., TMEM16A also known as ANO1; CA, carbonic anhydrase; CCK, cholecystokinin, CF, cystic fibrosis; $[Ca^{2+}]_i$, intracellular Ca^{2+} activity; CFTR, the cystic fibrosis transmembrane conductance regulator; EBIO, 1-ethyl-2-benzimidazolinone; G_K , conductance for K^+ ; H^+ - K^+ -ATPases or pumps, colonic type (coded by *ATP12A*) and gastric types (coded by *ATP4A* and *ATP4B*); IK, intermediate conductance K^+ channel, also named $K_{Ca}3.1$; IRBIT, inositol 1,4,5-triphosphate (InsP3) receptor-binding protein released with InsP3; NBCe1 or pNBC, electrogenic Na^+ - HCO_3^- transporter; NBCn1, electroneutral Na^+ - HCO_3^- transporter; NHE, Na^+ / H^+ exchanger; NKCC1, Na^+ - K^+ - $2Cl^-$ cotransporter; PKA, protein kinase A; PKC, protein kinase C; SLC26A6, electrogenic Cl^- - $2HCO_3^-$ exchanger; VNUT, vesicular nucleotide transporter, SLC17A9; V- H^+ -pump, vacuolar type H^+ -ATPase; ZG, zymogen granules.

(Rune and Lassen, 1968; Wang et al., 2001; Niv and Fraser, 2002). In the intestinal phase of digestion, pancreatic ducts secrete HCO_3^- -rich fluid that contributes to alkalization of acid chyme in duodenum. The acid generated is then transported toward the interstitium, and one would expect an acid tide, depending on ingested food and passage through the stomach (Rune and Lassen, 1968; Ashley et al., 1994).

From these simple considerations several questions arise. Do the stomach and pancreas epithelia have some transport mechanisms in common, or do they solve the task of acid-base transport in different ways?

The molecular mechanism and regulation of stomach acid secretion is well established. In short, it involves gastric H^+ - K^+ -ATPases comprising of $\alpha 1$ and β subunits coded by *ATP4A* and *ATP4B* genes. These pumps are present in tubulovesicles of parietal cells and delivered to the luminal membranes in conjunction with specific K^+ (*KCNQ1*, *KCNJ15*, *KCNJ10*) and Cl^- channels (*CFTR*, *CLIC-6*, *SCL26A9*), and thereby resulting in HCl secretion (Sachs et al., 2007; Forte and Zhu, 2010; Chu and Schubert, 2012). Gastric acid secretion is regulated by neural, hormonal, paracrine and chemical stimuli, e.g., acetylcholine, gastrin, ghrelin, histamine. As a protection against strong acid and pepsins, the surface epithelium secretes HCO_3^- , mucus and other factors, forming gastric diffusion barrier (Figure 1A). The validity of the model is confirmed by well-used drugs, including proton pump inhibitors and H_2 -histamine receptor blockers, to curb the



peptic and duodenal ulcers and reflux diseases (Sachs et al., 2010). In contrast, we do not understand the mechanism behind pancreatic alkaline (HCO_3^-) secretion fully. Therefore, therapeutic intervention is not possible, e.g., for cystic fibrosis patients.

PANCREATIC SECRETION—CONTRIBUTION FROM ACINI AND DUCTS

Pancreas is composed of two main types of epithelia—secretory acini and excretory ducts. Acini have relatively uniform morphology. They secrete digestive enzymes, NaCl-rich fluid and various factors that contribute to signaling in down-stream ducts. Studies on normal human and rodent pancreas, stimulated by predominantly acinar agonists, e.g., cholecystokinin (CCK), result in neutral or weakly alkaline pancreatic juice (Sewell and Young, 1975; You et al., 1983; Case and Argent, 1993). However, a recent study using acinar preparation and bioimaging techniques shows that acinar secretion is acidic due to acidic zymogen granules (ZG) (Behrendorff et al., 2010), although acidity of mature ZG has been discussed (Haanes and Novak, 2010; Chu and Schubert, 2012). Nevertheless, a potential acid load from acini challenging proximal ducts has been considered (Hegyí et al., 2011a). One possible defense mechanism could be activation of ducts by acinar agonist; generally this seems not to be the case. Alternatively, paracrine agonists such as ATP released by acini could stimulate ducts by purinergic signaling (Sørensen and Novak, 2001; Novak, 2008). Lastly, pancreatic ducts might have ability to sense and react to acid/base locally. There are a number of acid/base sensors at the single cell and whole organ level (Tresguerres et al., 2010; Brown and Wagner, 2012; DeCoursey, 2013). These include acid sensitive ASIC and TRP channels, HCO_3^- sensitive adenylate cyclase, pH-sensitive K^+ channels, and P2X receptors. Except for

the latter two, which are expressed in pancreas (see below), other candidates remain to be explored.

Pancreatic ducts comprise 5–20% of the tissue mass, depending on the species; morphologically they are different - progressing from flat centroacinar cells, cuboidal cells in intercalated, and small intralobular ducts to columnar heterogenous cells lining larger distal ducts (Kodama, 1983; Ashizawa et al., 1997; Bouwens and Pipeleers, 1998). At large, it is accepted that pancreatic ducts secrete isotonic $NaHCO_3$ rich fluid. However, the concentration of HCO_3^- is not constant; it decreases with secretory rates—a pattern that is mirrored by Cl^- . The HCO_3^- excretory patterns are remarkably similar between various species, providing that secretory rates are corrected for the duct mass (Figure 2A). In early studies (Bro-Rasmussen et al., 1956), it was proposed that pancreatic secretion and ionic composition is a two stage process—primary secretion and ductal modification, the so called admixture hypothesis. Another, the exchange theory, also named the salvage mechanism, states that at lower secretory rates ductal transporters are presumably not saturated and therefore, are capable of exchanging luminal HCO_3^- for interstitial Cl^- . This exchange phenomenon was first demonstrated on the main cat duct (Case et al., 1969). The third explanation, regarding varying HCO_3^- concentrations, pertains H^+ secretion from acini (see above) or ducts (see below).

NOVEL ION CHANNELS AND PUMPS CONTRIBUTING TO ACID-BASE TRANSPORT IN PANCREATIC DUCTS

The ion transport models for pancreatic ducts have been described in several recent reviews (Steward et al., 2005; Steward and Ishiguro, 2009; Lee et al., 2012; Wilschanski and Novak, 2013). The outline of the model is given in Figure 2B. The following sections will focus on novel additions to the model.

PROTON PUMPS

Ion channels and transporters proposed in the classical model for HCO_3^- secretion rely on gradients created by the Na^+/K^+ -ATPase (Figure 2B). However, we cannot explain formation of high HCO_3^- concentrations and the fact that inhibitors of NHE1, NBC (and NKCC1), and CA are relatively ineffective in blocking secretion (Grotmol et al., 1986; Fernandez-Salazar et al., 2004). One solution is that a primary pump could be involved, such as the vacuolar type H^+ -ATPase (V- H^+ -pump), to pump H^+ out to interstitium and leave HCO_3^- for the luminal transport. In one study, such vacuolar H^+ pump on the basolateral membrane was proposed (Villanger et al., 1995) and detected immunohistochemically (Roussa et al., 2001). Several functional studies gave contradictory findings (Zhao et al., 1994; Ishiguro et al., 1996; de Ondarza and Hootman, 1997). Taking an inspiration from gastric glands, the colon and kidney distal tubules, we considered whether pancreatic ducts express H^+ - K^+ -ATPases. Indeed, we found that rodent ducts express both the gastric and non-gastric (colonic) types H^+ - K^+ -ATPases (Novak et al., 2011). Inhibition of these with proton pump inhibitors reduced pH_i recovery in response to acid loads; more importantly, they reduced secretion in isolated pancreatic ducts. Thus, these functional studies support the theory that pancreatic ducts resemble gastric glands—just working in reverse, expelling H^+ toward the blood side

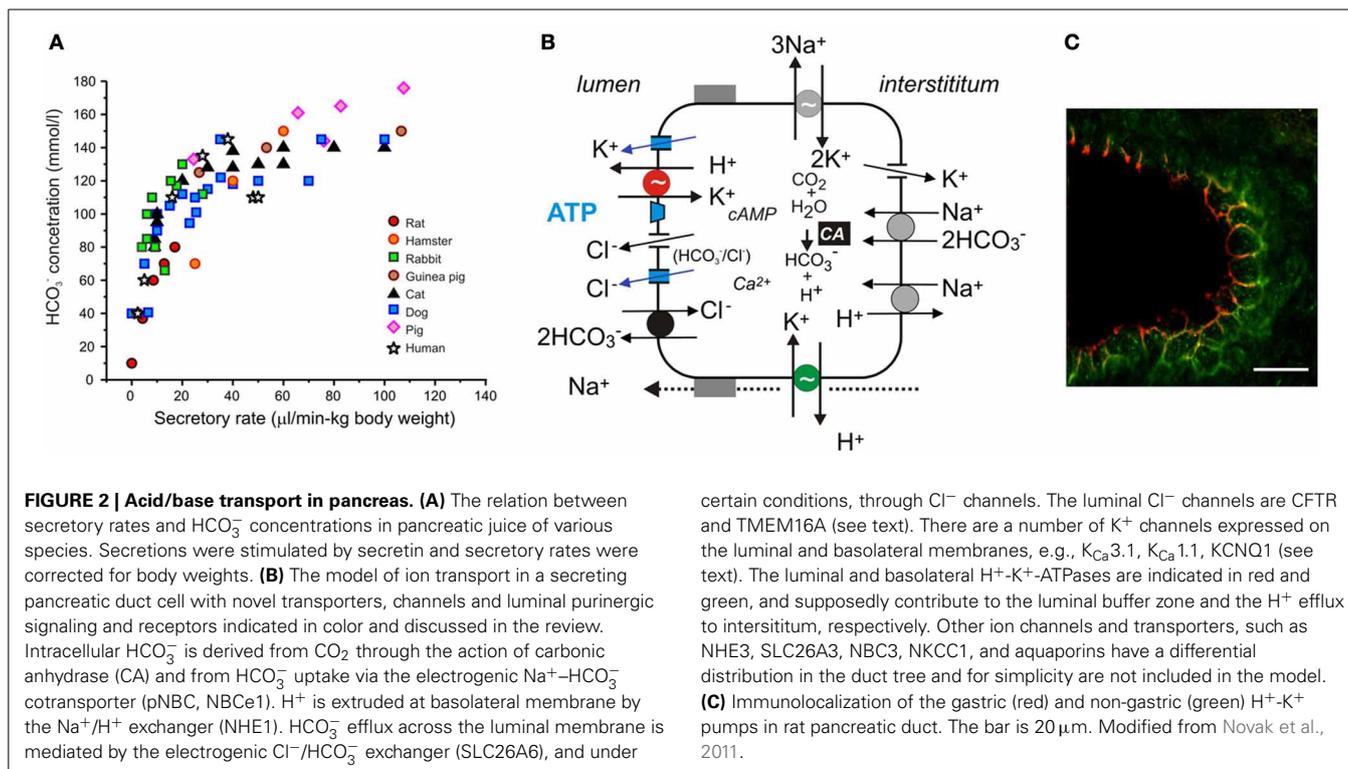


FIGURE 2 | Acid/base transport in pancreas. (A) The relation between secretory rates and HCO₃⁻ concentrations in pancreatic juice of various species. Secretions were stimulated by secretin and secretory rates were corrected for body weights. **(B)** The model of ion transport in a secreting pancreatic duct cell with novel transporters, channels and luminal purinergic signaling and receptors indicated in color and discussed in the review. Intracellular HCO₃⁻ is derived from CO₂ through the action of carbonic anhydrase (CA) and from HCO₃⁻ uptake via the electrogenic Na⁺-HCO₃⁻ cotransporter (pNBC, NBCe1). H⁺ is extruded at basolateral membrane by the Na⁺/H⁺ exchanger (NHE1). HCO₃⁻ efflux across the luminal membrane is mediated by the electrogenic Cl⁻/HCO₃⁻ exchanger (SLC26A6), and under

certain conditions, through Cl⁻ channels. The luminal Cl⁻ channels are CFTR and TMEM16A (see text). There are a number of K⁺ channels expressed on the luminal and basolateral membranes, e.g., K_{Ca}3.1, K_{Ca}1.1, KCNQ1 (see text). The luminal and basolateral H⁺-K⁺-ATPases are indicated in red and green, and supposedly contribute to the luminal buffer zone and the H⁺ efflux to interstitium, respectively. Other ion channels and transporters, such as NHE3, SLC26A3, NBC3, NKCC1, and aquaporins have a differential distribution in the duct tree and for simplicity are not included in the model. **(C)** Immunolocalization of the gastric (red) and non-gastric (green) H⁺-K⁺ pumps in rat pancreatic duct. The bar is 20 μm. Modified from Novak et al., 2011.

and leaving HCO₃⁻ for the luminal transport (Figure 1B). The immunohistochemical study showed that the H⁺-K⁺-ATPases (mainly colonic type) are localized to the basolateral membrane (Figure 2C).

However, H⁺-K⁺-ATPases, especially the gastric form, are also localized at or close to the luminal membrane (Figure 2C) (Novak et al., 2011). It seems counterintuitive to place H⁺ pumps on the HCO₃⁻ secreting luminal membrane. Nevertheless, there are epithelia that are high HCO₃⁻ secretors and yet express H⁺ pumps on the luminal membranes. For example, insect midgut and marine fish intestine have functional V-H⁺-ATPase on the luminal membranes (Wieczorek et al., 2009; Wood et al., 2010; Guffey et al., 2011). Also other epithelia, which are not high HCO₃⁻ secretors (HCO₃⁻ <25 mM), express various H⁺ pumps on the luminal membranes. For example, airway epithelia transport both base and acid, and the airway fluid layer is slightly acidic (Fischer and Widdicombe, 2006). Some studies provide evidence for the presence of bafilomycin A sensitive V-H⁺ pump (Inglis et al., 2003; Fischer and Widdicombe, 2006; Shan et al., 2012); other studies show that transport is sensitive to SCH28080, an inhibitor of gastric (and also non-gastric) H⁺-K⁺ pumps (Smith and Welsh, 1993; Poulsen and Machen, 1996). The non-gastric, ouabain-sensitive H⁺-K⁺-pumps were also demonstrated in some studies (Coakley et al., 2003; Krouse et al., 2004; Shan et al., 2012).

Coming back to the pancreatic luminal H⁺-K⁺ pumps, let us speculate what their function may be. They could help to defend the cell against intracellular acidification, although there is a redundancy of acid/base transporters including several NHEs, NBCs, and Cl⁻/HCO₃⁻ exchangers (Figure 2B). Our proposal

is—these luminal pumps are safeguarding luminal cell surface with acid secretions to protect against the bulk alkaline secretions, which at pH >8 would be caustic to cells. Thus, pancreatic ducts would have protective buffer (and mucus) zone, which is reminiscent to the buffer zone in the stomach, though achieved by H⁺ rather than HCO₃⁻ secretion (Figures 1A,B). In addition, the luminal H⁺-K⁺ pumps would recirculate K⁺ extruded by the luminal K⁺ channels (Figure 2B). Lastly, luminal H⁺-K⁺ pumps in distal ducts would by virtue of H⁺ secretion have more impact on pancreatic juice composition at low flow rates and minor at high flow rates, thus, explaining excretory curves for HCO₃⁻ (Figure 2A).

Ca²⁺-ACTIVATED Cl⁻ CHANNELS

In addition to CFTR-dependent secretion, a number of studies showed that agonists acting via Ca²⁺-signaling stimulate Ca²⁺-activated Cl⁻ channels (CaCC) and thus, could support duct secretion (Gray et al., 1989; Pahl and Novak, 1993; Winpenny et al., 1998; Szalmay et al., 2001; Pascua et al., 2009) (Figure 2B). The molecular identity of CaCC channels has been difficult to pinpoint [see (Duran et al., 2010)]. After suggestions of CCl-2 and bestrophins, the TMEM16/ANO family was discovered (Caputo et al., 2008; Schroeder et al., 2008; Yang et al., 2008), and especially TMEM16A/ANO1 became a CaCC favorite. Recent studies show that human duct cell lines express TMEM16A, which re-localizes from cytosol to the luminal membrane upon purinergic stimulation and gives rise to secretory potentials (Wang and Novak, 2013; Wang et al., 2013). In human pancreatic samples immunohistochemistry shows TMEM16A in centro-acinar and small ducts cells (Bergmann et al., 2011).

It is relevant to ask whether TMEM16A and/or Ca^{2+} signaling pathways lead to HCO_3^- secretion. There are a few studies in support of this notion. For example, Ca^{2+} signaling via IRBIT stimulates NBCe1 (Shirakabe et al., 2006; Yang et al., 2009). A recent study on TMEM16A anion permeability shows that in HEK293 cell expression system and mouse salivary acinar cells the channel is directly modulated by calmodulin, which increases its HCO_3^- permeability (Jung et al., 2013). This is supported by a study on *ex vivo* salivary glands stimulated with acetylcholine, which induced production of HCO_3^- rich pancreatic-like secretion when Cl^- transport was inhibited (Novak and Young, 1986). Nevertheless, it cannot be excluded that there are other molecular candidates for CaCC, or that CFTR can convey part of the Ca^{2+} -activated Cl^- currents. The latter mechanism could involve Ca^{2+} sensitive adenylate cyclases and tyrosine kinases (Src2/Pyk complex), both of which could alter activity of CFTR, as shown for other epithelia (Billet and Hanrahan, 2013; Billet et al., 2013). Another effect at the CFTR level could be priming of some PKC isoforms that enhance CFTR activity [see (Billet and Hanrahan, 2013)]. Lastly, it is highly unlikely that Ca^{2+} mediated signaling stands alone, rather the two major signaling pathways of Ca^{2+} and cAMP/PKA act synergistically in pancreatic ducts, e.g., via IRBIT regulation of CFTR and SLC26A6 (Park et al., 2013).

K⁺ CHANNELS

The driving force for Cl^- or HCO_3^- exit is maintained by hyperpolarizing membrane potential created by opening of K^+ channels, and G_κ is both present on the basolateral and luminal membranes (Novak and Greger, 1988, 1991). Equivalent-circuit analysis has shown that stimulation of luminal K^+ channels contributes with at least with 10% to the total conductance. Modeling in salivary glands confirms that such ratio of luminal to basolateral K^+ channels would optimize secretion without destroying the transepithelial potential and transport (Cook and Young, 1989; Almasy et al., 2012). Furthermore, luminal K^+ channels could contribute to secreted K^+ , as pancreatic juice contains 4–8 mM K^+ (Sewell and Young, 1975; Cafilisch et al., 1979; Seow et al., 1991). The molecular identity of some K^+ channels in pancreatic ducts is known, however, the exact localization and function remains to be verified [see (Hayashi and Novak, 2013)]. The $\text{K}_{\text{Ca}1.1}$ channels (maxi-K, BK, coded by *KCNMA1*) are present in pancreatic ducts (Hede et al., 2005; Venglovecz et al., 2011). The latter study proposes that these channels are expressed on the luminal membrane and activated by low concentrations of bile acids. However, earlier patch-clamp studies indicated that these channels were also located basolaterally (Gray et al., 1990; Hede et al., 1999). The $\text{K}_{\text{Ca}3.1}$ channel (IK, SK4, coded by *KCNN4*) was demonstrated in pancreatic ducts (Hede et al., 2005; Jung et al., 2006; Hayashi et al., 2012). Immunolocalization indicates that $\text{K}_{\text{Ca}3.1}$ is expressed on both membranes, though stronger on the luminal one (Figure 2B). Interestingly, the channel activator EBIO enhanced secretion potentials (Hayashi et al., 2012; Wang et al., 2013). Recent studies on pancreatic ducts offers molecular identities of several K^+ channels, including KVLQT1, HERG, EAG2; Slick, and Slack (Hayashi et al., 2012), and interestingly the pH sensor TASK-2 (Fong et al., 2003). However, the function and regulation of these channels in pancreas physiology needs to be explored.

PURINERGIC SIGNALING

Pancreatic secretion regulated by hormonal and neural systems is well documented (Lee et al., 2012; Wilschanski and Novak, 2013). Paracrine regulation is less explored, but it is highly relevant as it allows regulation within the gland and integration of acinar and ductal responses. Pancreatic ducts can be regulated by acinar factors (trypsin, guanylin, ATP) as well as retrograde factors (bile acids) (Kulaksiz et al., 2001; Alvarez et al., 2004; Venglovecz et al., 2008; Pallagi et al., 2011; Wang and Novak, 2013). Here we concentrate on purinergic signaling and present evidence that this signaling could fine-tune and coordinate pancreatic secretion on several fronts. Pancreatic ducts express several types of purinergic receptors including members from the G-protein coupled receptor families (adenosine, P2Y) and ligand-gated ion channels (P2X receptor) families (Novak, 2008, 2011) that can potentially stimulate a variety of intracellular signaling pathways (Burnstock, 2007; Surprenant and North, 2009; Lenertz et al., 2011; Wiley et al., 2011; Bilbao et al., 2012). These receptors regulate pancreatic duct ion transport, mucin secretion, and survival of fibrogenic pancreatic stellate cells (Jung et al., 2004; Haanes et al., 2012). ATP originates from ZG where it is accumulated by the vesicular nucleotide transporter VNUT (Haanes and Novak, 2010), and in addition ATP is presumably released by nerves and ductal epithelium (Bodin and Burnstock, 2001; Novak, 2011; Burnstock and Novak, 2012). Various ecto-nucleotidases are expressed and secreted, and potentially ATP/ADP and adenosine are effective regulators of ductal functions (Sørensen et al., 2003; Kittel et al., 2004; Yegutkin et al., 2006; Burnstock and Novak, 2012).

ATP and UTP via P2 receptors have effects on intracellular Ca^{2+} , intracellular pH, and transepithelial transport in both isolated ducts and *in vivo* pancreas (Ishiguro et al., 1999; Novak et al., 2010). The physiological response to nucleotides is side specific. Basolateral UTP inhibits secretion, most likely due to inhibition of $\text{K}_{\text{Ca}1.1}$ channels, presumably to prevent overextension of ducts. In contrast, luminal UTP/ATP application causes duct secretion and activation and Cl^- and K^+ channels (Hede et al., 1999; Ishiguro et al., 1999; Wang et al., 2013). In particular $\text{K}_{\text{Ca}3.1}$ channel activation potentiates secretion (see above). It is well documented that purinergic receptor stimulation activates CFTR, $\text{Cl}^-/\text{HCO}_3^-$ exchangers and TMEM16A on the luminal membrane (Namkung et al., 2003; Wang et al., 2013). Furthermore, P2 receptors activate CaCC and CFTR interdependently and synergistically, though exact receptors and signaling pathways remain to be elucidated (see above). In addition, some effects can be due to stimulation of $\text{A}_{2\text{A}}$ and $\text{A}_{2\text{B}}$ receptors, which stimulate CFTR (Novak et al., 2008).

A number of processes in purinergic signaling are pH sensitive, and this must be of relevance in pancreatic duct lumen. For example, nucleotidase activities, CD39 and CD73 types, are stimulated at alkaline pH 8–9 (Leal et al., 2005; Rucker et al., 2008), thus, favoring conversion of ATP to adenosine in duct lumen. Furthermore, purinergic receptors are also pH sensitive. From other preparations we know that extracellular acidification enhanced the potency of UTP up to 10 fold on the rat P2Y4 but not P2Y2 receptors (Wildman et al., 2003), and the P2X2 receptors was activated by acid pH (King et al., 1996). Extracellular alkalization enhances activity the P2X4 and P2X7 receptors (Clarke et al., 2000; Liu et al., 2009). Several types

of these receptors are expressed in duct lumen including the P2Y2 and P2X7 receptors, and these enhance pancreatic secretion and integrate acini-to-duct signaling (Novak, 2008; Novak et al., 2010).

SUMMARY AND PERSPECTIVES

The original cellular model for pancreatic HCO_3^- secretion has been supplemented with molecular identities for many ion transporters/channels. The present review challenges present concepts by including active H^+ pumps in the model, and by comparing basic processes in pancreas and stomach. Furthermore, we present new additions to the model— Ca^{2+} -activated Cl^- and K^+ channels, and propose that they work in synergy to regulate secretion. On the organ level, acini, and ducts integrate their function in acid/base transport and regulation, the latter exemplified by purinergic signaling. Further challenges lay in understanding dysregulation of acid-base transport in pancreas pathophysiology. In CF patients and animal models, pancreatic juice pH decreases from values >8.1 to <6.6 , and pancreas contributes to duodenal hyperacidity (Freedman et al., 2001; Uc et al., 2011) [see (Wilschanski and Novak, 2013)]. It is not clear whether the problem relates to ductal and/or acinar secretion. In acute pancreatitis, which has complex etiologies, it is now appreciated that defective pancreatic duct secretion can be the initiating factor (Lee and Muallem, 2008; Hegyi et al., 2011b). Finally, in several cancer types, various acid-base transporters and associated ion channels, such as NHE1, NBCn1, CAIX, TMEM16A, $\text{K}_v10.1$, and $\text{K}_{Ca}3.1$, change expression or function [see (Pedersen et al., 2013)]. Our knowledge about the role of acid-base transporters in pancreatic ductal adenocarcinoma clearly needs to be expanded, in order to provide potential diagnostic and therapeutic approaches.

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