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Review

Bicarbonate in cystic fibrosis

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Abstract

Background: Cystic fibrosis (CF, mucoviscidosis) is caused by mutations in the gene encoding CF transmembrane conductance regulator (CFTR), which is a chloride and bicarbonate channel necessary for fluid secretion and extracellular alkalization. For a long time, research concentrated on abnormal Cl^- and Na^+ transport, but neglected bicarbonate as a crucial factor in CF.
Methods: The present short review reports early findings as well as recent insights into the role of CFTR for bicarbonate transport and its defects in CF.
Results: The available data indicate impaired bicarbonate transport not only in pancreas, intestine, airways, and reproductive organs, but also in salivary glands, sweat duct and renal tubular epithelial cells. Defective bicarbonate transport is closely related to the impaired mucus properties and mucus blocking in secretory organs of CF patients, causing the life threatening lung disease.
Conclusions: Apart from the devastating lung disease, abrogated bicarbonate transport also leads to many other organ dysfunctions, which are outlined in the present review.

Keywords: Mucoviscidosis; Cystic fibrosis; Bicarbonate; Mucus; Cystic fibrosis transmembrane conductance regulator; CFTR

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1. Mucoviscidosis, a historical perspective

Clinical, biochemical and physiological findings on mucoviscidosis (cystic fibrosis) were obtained long before the discovery of the disease causing gene cystic fibrosis transmembrane conductance regulator (CFTR) in 1989 [1–4]. In 1936 the

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Swiss pediatricians Fanconi and his colleagues described the "coeliac syndrome", with congenital fibrosis of the pancreas and lung bronchiectasis [5]. This was followed by a more precise description of the disease, coining the term cystic fibrosis [6]. In a cooperative study, the clinician Harry Shwachman and pathologist Sydney Farber described the abnormally high viscosity of intestinal contents which they called mucoviscidosis [7].

Di Sant Agnese's description of sweat abnormalities in cystic fibrosis (CF) in 1953 pointed to a membrane transport defect for anions, which they confirmed later in technically more sophisticated experiments [8]. It took another 15 years for a better characterization of the transport defect in sweat glands by micropuncture of single human glands. Unfortunately, these results were not published in common scientific journals and therefore received little attention [9,10]. In the same year, deficient pancreatic secretion upon stimulation with secretin was observed by Johansen, Hadorn and Anderson, defining a primary generalized disturbance of fluid and bicarbonate secretion in CF [10]. Paul Quinton's groundbreaking work on the sweat duct finally brought the anion transport defect to everybody's attention [11–14]. Eventually defective single channel chloride currents were demonstrated in cells from CF patients, although with some confusion regarding the biophysical properties of the channel [15–18]. These impressive scientific achievements were crowned by identification of CFTR as a cAMP regulated chloride channel, which unleashed a powerful research activity that lasts until today [2–4].

Yet it was still unclear how dysfunctional CFTR leads to abnormal mucus in lungs, intestine, and reproductive organs of CF patients. CFTR was shown to inhibit epithelial Na^+ channels (ENaC) *ex vivo* and to decrease transport by electroneutral Na^+/H^+-exchangers (NHE3) in airways and intestine, which explained enhanced Na^+ absorption in the absence of functional CFTR [19,20]. Hyperabsorption of NaCl with thinning of the airway surface liquid (ASL) layer due to hyperactive epithelial Na^+ channels (ENaC) was blamed as the cause of dehydrated mucus with poor rheological properties [21–24]. However, there was no evidence for Na^+ hyperabsorption in CF sweat ducts or pancreas, while other findings argued against Na^+ hyperabsorption in CF airways and found enhanced salt content in CF ASL [25–27]. Moreover chronic inflammation, either intrinsic or due to infection, was discussed as major cause for mucus hypersecretion [28–32]. In contrast a possible impact of defective bicarbonate secretion had not been further studied until Quinton and others provided evidence that bicarbonate was essential for proper mucus release and viscosity [33,34].

2. Exocrine pancreas

Altered viscosity of the duodenal content in mucoviscidosis had been recognized early by Shwachman and colleagues, but it took another 15 years until Rick detected strongly compromised pancreatic bicarbonate secretion during stimulation with pancreozymin-secretin [31,35]. We adapted the test to measure pancreatic output of enzymes and bicarbonate upon hormonal stimulation in children, and applied the test to study the output of enzymes, volume and bicarbonate in adolescent CF patients with residual exocrine function [36]. Typical results from a CF patient and a healthy volunteer are shown in Fig. 1. In addition to a severe volume reduction, the concentration of bicarbonate was extremely low in the pancreatic juice, while the chloride concentration remained high. Moreover, the apparent viscosity was high in the patient but decreased rapidly even with small amounts of bicarbonate being excreted following stimulation. Fig. 2 demonstrates the discrepancy between chymotrypsin and bicarbonate in patients with residual function [36,37]. Due to the small volume of the pancreatic juice, enzymes were found to be very concentrated. These results were confirmed in subsequent studies [38–40].

After identification of CFTR and invention of the patch clamp technique, secretin, i.e. cAMP-regulated chloride channels were identified in epithelial cells of normal pancreatic ducts that were absent in cells lacking expression of functional CFTR [41,42]. Subsequent studies recognized the importance of functional CFTR in driving basolateral HCO_3^- uptake and luminal HCO_3^- secretion in the pancreatic duct [43–45] (Fig. 8A). Bicarbonate accumulates in the distal pancreatic duct at very high concentrations, which is due to the high rate of uptake by basolateral transporters and luminal exit through CFTR. After identifying pancreatic HCO_3^- transport through CFTR in the groundbreaking work by Muallem and coworkers, abnormal HCO_3^- transport in CF finally received the well-deserved attention [33,34]. CFTR

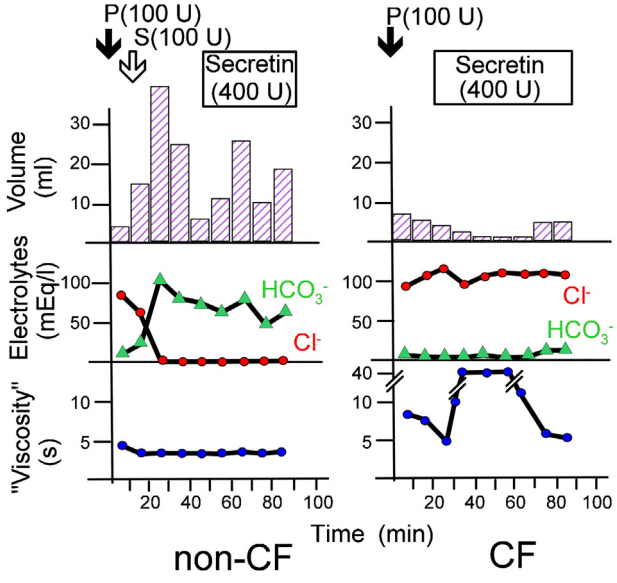

Fig. 1. Pancreozymin-secretin test in non-CF and CF. Modified pancreozymin secretin test in a normal young adult aged 27 years (left) and in a patient with cystic fibrosis aged 15 years (right). Arrows represent single injections of 100 units pancreozymin and secretin, while "secretin 400 U" indicates continuous infusion of 400 U. In the normal adult, bicarbonate content of duodenal and pancreatic secretion (green triangles) increases after the stimulus, while chloride (red circles) shows a rapid fall ending with unmeasurable values. In contrast, in the CF patient, single injection of secretin has no effect on bicarbonate excretion and chloride remains high at ca. 100 mEq/l. After the augmented dose, there is only a small increase of bicarbonate excretion in the CF patient. This is nevertheless associated with a decrease of apparent viscosity, as measured by a modified Ostwald-type viscosimeter. With permission [36]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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