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FINAL REPORT

The pathophysiology of pancreatic ductal bicarbonate secretion

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GENERAL REPORT

The overall mortality in acute pancreatitis remains 5-10%, and may increase to 30% or higher if complications develop. This unacceptably high mortality is due to the lack of specific treatments for the disease. In this project we provided experimental justification for the hypothesis that pancreatic ductal bicarbonate secretion has a protective effect for the entire exocrine pancreas during noxious stress such as biliary stones or ethanol abuse. The results of this project may open up the possibility of pharmacological therapy of acute pancreatitis leading to reduced morbidity and mortality (Hegyi et al., Am J Gastro, 2010, Hegyi et al., Gut, 2011).

DETAILED REPORT

Our results showed that (i) a high dose of the non-conjugated chenodeoxycholate (CDC), but not the conjugated gluco chenodeoxycholate (GCDC), causes mitochondrial damage followed by $(ATP)_i$ depletion and (ii) the $(ATP)_i$ depletion by itself can be responsible for the impaired fluid and HCO_3^- secretion. The relationship between mitochondrial function and HCO_3^- secretion and the differences between the effects of conjugated and non-conjugated bile acids needs further investigation (Maléth J et al., Gut, 2011; Hegyi P et al., Gut, 2011) .

We have demonstrated the pathophysiological importance of apical maxiK+ (BK) channels in PDEC. Activation of apical BK channels alone stimulates pancreatic ductal HCO_3^- secretion and importantly, plays a crucial role in the stimulatory effect of CDC on HCO_3^- secretion. Our data suggest that activation of BK channels by

synthetic compounds may represent a new therapeutic approach to protect the pancreas in acute pancreatitis (Venglovecz V et al., Gut, 2011).

In our trypsin study, we showed for the first time that (i) PAR-2 is localized to the apical membrane of the human proximal PDEC, (ii) the localization of PAR-2 in the guinea pig pancreas is identical to the human gland, (iii) trypsin markedly reduces bicarbonate efflux through a dihydro-4,4'-diisothiocyanostilbene-2,2'-disulfonic acid (H_2DIDS)-sensitive apical SLC26 anion exchanger and strongly inhibits CFTR, (iv) that a decrease in pH within the ductal lumen will strongly accelerate the autoactivation of trypsinogen, and (v) trypsin down-regulates PAR-2 expression by PDEC in patients suffering from all forms of pancreatitis (Pallagi P et al., Gastroenterology, in revision).

We characterized a novel model of severe necrotizing acute pancreatitis induced by L-lysine. The results of this study, in combination with our previous data, indicate that basic amino acids, L-lysine, L-arginine and L-ornithine all injure the exocrine pancreas resulting in pancreatitis. Our data demonstrate that L-lysine impairs ATP synthase activity of pancreatic mitochondria. This occurs early in the development of the disease and is followed by trypsinogen and NF-kB activation inflammatory infiltration, and acinar cell death through apoptosis and necrosis. Importantly, L-lysine selectively damages pancreatic mitochondria, it had no effect on liver mitochondria. The data strongly suggest that mitochondrial damage is a cause of pancreatitis induced by L-lysine (Biczo G et al., Antiox & Redox, 2011).

We have also shown evidences that the relationship between the iontransporters and inflammatory disorders are not organ specific and it could be true in the whole GI tract (Yeruva S et al., IBD, 2011; Farkas K et al., IBD, 2011).

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