Neuroendocrine characterization of the intestine of F508del CFTR mice

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We previously found hypertrophy of the gut in F508del homozygous mice. Objectives: To characterize the neuroendocrine and innervation pattern in the intestines of wt, homo- and heterozygous F508del CFTR mice.

Methods: Specimens from the gastrointestinal tract were studied by immuno- cytochemistry (ICC) for VIP, galanin, NPY, CORT, CART, VAcHT as well as NOS in situ hybridization (ISH) for VIP and CART mRNA. Enzymes involved in the formation and degradation of S-1-P and C-1-P were studied by isotope-assays. The muscle layer of the small intestine was thickened 4 times with hypertrophy of both the circular and longitudinal layer. In nerve fibres in the circular muscle VIP immunostaining was more intense in CF than in wt mice. Other neuropeptid/peptide markers appeared unchanged. Furthermore, the submucosal VIP neurons (lacking both the circular and longitudinal layer) and VIP-containing fibres in the circular muscle and submucosal layer of the small intestine were more frequent and intensively immunoreactive. The relevance to the enteric nervous system and its function in CF needs further studies on humans.

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9. Gastrointestinal/Liver Disease/Metabolic Complications of CF/Nutrition

includes function studies in CF with or without genetic correction. The relevance to the enteric nervous system and its function in CF needs further studies on humans.

Pancreatic and biliary secretion differ in cystic fibrosis and wild-type pigs

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Objectives: The hallmark feature of pancreatic disease in cystic fibrosis (CF) is the production of viscous, low-volume and acidic fluid. Because pancreatic function studies in humans are done by sampling the jejunal fluid, it is not known whether pancreatic or biliary secretions are equally affected in CF. With a pancreatic histopathology similar to humans with CF and separate biliary and pancreatic duct openings into the intestine, the pig model offers an opportunity to examine pancreatic and biliary fluids separately.

Methods: Four WT, 3 CFTR−/− and 2 CFTRΔF508/ΔF508 newborn pigs were studied. Bile and pancreatic juice were collected from blind intestinal loops at baseline and 30 min after secretin. Results: Compared to WT pigs, pancreatic juice volume and pH were low in CF pigs (8.4±0.1 in WT vs. 5.7±0.1 in CF). Contrary to WT, pancreatic juice volume and pH did not increase in CF pigs following secretin. Bile volume and pH were not significantly different between WT and CF pigs, but bile volume did not increase after secretin in CF pigs. The differences between the pancreatic and biliary secretion may have important implications in the pancreaticobiliary disease pathogenesis in CF.

TGF-β and SMAD proteins participate in the fibrotic process of liver disease in cystic fibrosis

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Focal biliary fibrosis may occur early in cystic fibrosis (CF). TGF-β is a cytokine that regulates proliferation and differentiation of a wide spectrum of cells. TGF-β signal through transmembrane threonine-kinase receptors, activating intracellular mediators, called SMADs, which modulate the transcription of target genes. The aim of this study was to investigate the contribution of TGF-β and other cytokines to the hepatic fibrosis in CF.

Methods: LD was demonstrated in 12 CF patients, who had a mean age of 12.5 years and underwent percutaneous liver biopsy with the biopsy needle directed to the site of the lesion with the aid of CT scan. Hepatic tissue mRNA levels of TGF-β1, TGF-β2, TGF-β3, CTGF, ALK-5 and Smad-2, -3, -4, -7 were estimated by quantitative real-time RT-PCR.

Results: Strong correlation between the expression of TGF-β1, ALK-5, Smads and CTGF at the fibrosing process was observed (TGF-β1/ALK-5: p < 0.01, Smad-2/ALK-5 p < 0.001, Smad-3/ALK-5: p < 0.01, Smad-3/Smad-2: p = 0.003, Smad-7/Smad-4: p = 0.0102, Ctgf/Smad-7: p = 0.0006, ALK-5/TGF-β1: p < 0.0001, ALK-5/TGF-β3: p = 0.0045, Smad-3/TGF-β3: p = 0.0114, Smad-7/TGF-β1: p = 0.0032, Smad-7/TGF-β3: p = 0.0139, Smad-7/ALK-5: p = 0.0001, Smad-7/Smad-2: p = 0.001, Smad-7/Smad-3: p = 0.0026, Ctgf/TGF-β1: p = 0.0034, Ctgf/TGF-β2: p = 0.0261, Ctgf/Smad-5: p = 0.0114, Ctgf/Smad-2: p = 0.0005). Significant correlation between fibrosis and inflammation grade was also demonstrated (p < 0.007).

Conclusion: The pathway of TGF–SMADs contributes to the fibrosing process of CFD. There is an increase of the degree of inflammation in association with fibrosis. Thus, the measurement of tissue cytokines may be helpful in the assessment of the degree of the reactive fibrosing process in CFD.