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CONFIRMATION OF ABSTRACT SUBMISSION

The following abstract has been successfully submitted to the Combined EPC & IAP Meeting.

Abstract No:	768
Date of submission:	03.04.2014
Section:	Basic science - Acute pancreatitis
Preferences:	Oral or Poster
EPC Travel scholarship request for the first author:	Yes

CFTR loss of function after alcohol consumption and in alcoholic pancreatitis

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Background: Excessive ethanol consumption is one of the most common causes of acute and chronic pancreatitis. It is also documented that genetic defects of CFTR can lead to pancreatitis, however the effects of alcohol consumption on CFTR function in the pancreas is not known.
Aim: Our aim was to investigate the role of CFTR in the pathogenesis of alcohol-induced pancreatitis.
Materials & methods: The effects of ethanol, fatty acids and fatty acid ethyl esters on CFTR function and expression were examined in human (volunteers, patients and cell lines) and in animal models (guinea pigs and CFTR-/- mice).
Results: Sweat chloride concentration was increased in alcohol intoxicated patients but not in healthy volunteers, indicating impaired CFTR function. Loss of CFTR expression was found in pancreas specimens from patients with acute or chronic alcohol-induced pancreatitis. In functional studies, we detected strong inhibitory effects of alcohol and fatty acids on CFTR activity and HCO3- secretion in pancreatic ductal epithelial cells. The inhibition was mediated by intracellular calcium overload, decreased cellular cAMP levels and ATP depletion. We reproduced the alcohol-induced decrease in CFTR expression in cultured pancreatic epithelial cells and in vivo in guinea pigs, which was caused by a combination of reduced CFTR mRNA levels, decreased cell surface stability and folding defect of CFTR. Finally, genetic deletion of CFTR lead to more severe pancreatitis in CFTR

knock-out mice induced by ethanol and fatty acids.
Conclusion: The findings indicate that alcohol-induced loss of CFTR function is critical in the development of alcoholic pancreatitis; therefore, correcting CFTR function should offer therapeutic benefit.