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PANCREATITIS

Mislocalization of CFTR by alcohol promotes pancreatitis

According to new research published in *Gastroenterology*, the expression and cellular localization of the ion channel cystic fibrosis transmembrane conductance regulator (CFTR) is disrupted by ethanol, which in turn promotes pancreatitis.

The group decided to investigate the role of CFTR in alcohol-induced pancreatitis because mutations in *CFTR* are known to cause pancreatic damage. "We hypothesized that alcohol may exert its detrimental effect [on the pancreas] through affecting CFTR function," remarks corresponding author Peter Hegyi.

Using the cystic fibrosis 'sweat test' (used to screen for CFTR activity), the authors showed that CFTR activity was decreased in patients after acute alcohol consumption ($n = 49$), as indicated by higher concentrations of Cl^- in sweat from these patients than in sober volunteers ($n = 26$). Chronic alcohol consumption was found to have a lasting, detrimental effect on CFTR activity. Patients who had not consumed alcohol a week prior to the test but who did have a history of alcohol abuse ($n = 15$), had elevated Cl^- sweat concentration compared with controls.

Analysis of pancreatic tissue from patients with alcohol-induced acute pancreatitis showed decreased CFTR mRNA levels and protein expression. By contrast, patients with alcohol-induced chronic pancreatitis had elevated CFTR mRNA levels and protein expression; however, CFTR protein at the plasma membrane of pancreatic duct epithelial cells (PDECs) was substantially reduced. This data led the authors to believe that alcohol damages CFTR protein folding and/or trafficking to the cell membrane, thereby reducing its function.

To test this hypothesis, guinea pigs were injected with ethanol and the intracellular localization of CFTR in PDECs was assessed. Cytoplasmic CFTR levels were elevated after 3 h but apical membrane localization was substantially decreased at 12–24 h after treatment. This data supports the theory that alcohol damages CFTR trafficking in PDECs.

MDCK-II cells overexpressing CFTR were used as a model of epithelial cell polarity to further study the potential defects in CFTR trafficking caused by alcohol. Treatment with ethanol or products of pancreatic ethanol metabolism (palmitoleic acid and palmitoleic acid ethyl ester) caused a ~15–40% reduction in CFTR expression at the apical membrane and reduced the efficiency of CFTR protein folding by ~4–7% compared with untreated cells.

Owing to the role of CFTR in alcohol-induced pancreatitis demonstrated by these experiments, "correcting and/or potentiating CFTR function should offer therapeutic benefit," remarks Hegyi. To better treat pancreatitis, the group intend to develop colloidal nanovectors for targeted drug delivery.

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Original article Maléth J. *et al.* Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis. *Gastroenterology* doi:10.1053/j.gastro.2014.11.002

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