

ALTERED EXPRESSION OF FIBROBLAST GROWTH FACTOR 15 IN ACUTE PANCREATITIS: POTENTIAL CONSEQUENCES FOR BACTERIAL TRANSLOCATION AND INFECTION RISK

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INTRODUCTION: Intestinal bile salts protect against bacterial overgrowth and translocation through activation of the ileal bile salt nuclear receptor Farnesoid X Receptor (FXR) and upregulation of target genes angiogenin 1 (ANG1), iNOS, CAR12 and IL-18 that are involved in antibacterial defence. Additionally, FXR activation induces expression and secretion of ileal hormone fibroblast growth factor 15 (FGF15; human orthologue FGF19), which probably signals the end of postprandial state with inhibition of pancreatic secretion. Since in acute pancreatitis (AP), the enterohepatic bile salt circulation may be altered, we explored potential changes of the FXR-FGF15 axis in complementary mouse and human models.

AIMS & METHODS: AP was induced in male C57BL/6 mice by hourly intraperitoneal injections of cerulein (50 µg/kg, for 10 hours). Control mice (n=10) were injected with saline. Mice were terminated 24 hours (early phase, n=10) or 72 hours after start of induction (late phase, n=10). To confirm AP, histology of pancreas samples was done. Decreased integrity of mucosal barrier in the ileum was assessed by Ussing chamber experiments. Ileum mRNA expression of FXR and FXR-target genes was assessed by real-time PCR. Plasma FGF19 levels were determined by ELISA in 15 predicted severe AP patients during continuous enteral nutrition and compared to 28 healthy volunteers.

RESULTS: In the mouse model, both FGF15 and FXR-intermediate SHP expression were decreased more than twofold (P=0.004 and P=0.009 respectively) in the early but not late phase of AP. ANG1 was down regulated in early phase (P=0.001). No change in expression of FXR or target genes IL18, iNOS, and CAR12 was found. Histology confirmed AP in the early phase, and the late phase showed clear signs of recovery. Electrical resistance of the ileum was decreased in the early phase (22 ± 7 vs. controls: 44 ± 8 Ω/cm², P<0.001). Plasma levels of FGF19 in AP patients were significantly lower than in healthy volunteers in the postprandial state (0.39 vs. 0.71 ng/ml, P=0.001).

CONCLUSION: In the mouse model, ileal FGF15, SHP and ANG1 are decreased in the early phase of AP. Similarly, FGF19 plasma levels are decreased in AP patients. These results indicate a potential role of FXR and FXR target genes in severity of AP and the occurrence of bacterial translocation and subsequent infectious complications in AP.