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Student: Greimel Theresa

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Bile acid-induced tissue factor activity in hepatocytes correlates with activation of farnesoid X receptor

Theresa Greimel; Jörg Jahnel; Sina Pohl; Tanja Strini; Martin Tischitz; Nathalie Meier-Allard; Sandra Holasek; Katharina Meinel; Victor Aguiriano Moser; Harald Haidl; Siegfried Gallistl; Katrin Panzitt; Martin Wagner; Axel Schlagenhauf

Background Bile acids (BA) have been shown to affect intrahepatic coagulation processes via enhanced tissue factor (TF) decryption and thrombin generation. The exact mechanism of TF decryption within the liver parenchyma and the role of farnesoid X receptor (FXR), a nuclear BA receptor, remain unclear. In this study, the impact of various BA on TF activity and thrombin generation in hepatocytes was investigated and the effects were correlated with activation of FXR-dependent signaling and apoptosis. Methods HepG2 cells and primary human hepatocytes were incubated with chenodeoxycholic acid (CDCA), glycochenodeoxycholic acid (GCDCA), ursodeoxycholic acid (UCDA), the synthetic FXR agonist GW4064 and the FXR antagonist DY268 for 12 and 24 hours respectively. MTT tests were used to determine cell viability. TF activity was tested via factor Xa generation and thrombin generation was measured by calibrated automated thrombography. Quantitative polymerase chain reaction (qPCR) was used to determine FXR activation. Western blotting was used to determine TF protein levels and fluorescence microscopy of stained HepG2 cells to denote upregulation of TF. Cleaved caspase-3 and increased Annexin V binding were tested as apoptotic markers. Results Increased TF activity alongside enhanced thrombin generation was observed with CDCA and GW4064 and in human hepatocytes also with GCDCA. UDCA showed no effect. TF activity was reduced when FXR activation was blocked with DY268. qPCR revealed upregulation of FXR targets only by CDCA and GW4064. Western blot analysis and fluorescence microscopy showed no TF overexpression, arguing for TF decryption. No signs of apoptosis were denoted. Conclusion Exposure of hepatocytes to BA may cause intracellular FXR overstimulation, triggering TF decryption irrespective of the amphiphilic properties of BA. The effect of BA on TF activation correlates with the molecule's ability to activate FXR. TF decryption occurs independently of apoptotic mechanisms.