EFFECT OF ANTIBIOTIC-INDUCED DYSBIOSIS ON ENTEROHEPATIC BILE ACID CYCLING

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Alteration of the intestinal microbiota is considered the key process for the development, but also the mitigation of certain types of intestinal diseases. In addition, the microbiota plays an important role in the intestinal metabolism of bile acids, which are continuously reabsorbed and recycled via the enterohepatic cycling. Both at the intestinal level and in the liver, they exert their function mainly through interaction with FXR and TGR5 receptor. In this study we evaluate whether ciprofloxacin-induced dysbiosis or gut microbiota depletion affect bile acid enterohepatic cycling and their signaling.

This work was performed on C57BL/6J mice (9±1 weeks) treated for 14 days either with ciprofloxacin (CPX mice) to induce dysbiosis or broad-spectrum antibiotics to deplete gut microbiota (ABX mice). We then evaluated the mRNA and protein expressions of the two bile acid receptors FXR and TGR5 in ileum and liver by means of quantitative Real Time-PCR (qRT-PCR) and western blot, the mRNA expressions of two genes that repress Cyp7A1 activity, i.e. FGF15 in the ileum and SHP in the liver, and of the bile acid transporters OSTα in the ileum and BSEP in the liver by means of qRT-PCR.

Dysbiosis and microbiota depletion caused an overexpression of FXR both in the ileum ($p<0.01$ in CPX and $p<0.001$ in ABX mice) and in the liver ($p<0.05$ in CPX and $p<0.001$ in ABX mice). The same significant increase was observed for TGR5 protein expression both in the ileum ($p<0.01$ in CPX and $p<0.001$ in ABX mice) and in the liver ($p<0.05$ in CPX and $p<0.001$ in ABX mice).

In the ileum, the mRNA expression of the repressor FGF15 significantly increased only in CPX mice ($p<0.001$), whereas SHP mRNA expression was significantly higher only in ABX mice ($p<0.001$). The mRNA expression of the bile acid transporter OSTα in the ileum was significantly increased in both groups of treated mice ($p<0.01$ in CPX and $p<0.001$ in ABX mice), whereas mRNA hepatic expression of the transporter BSEP decreased significantly only in ABX mice ($p<0.01$).

Since FXR and TGR5 are involved in the pathogenic mechanism of numerous gut, liver and metabolic diseases, the modulation of gut microbiota represents a promising therapeutic strategy for their management.

Furthermore, the observed downregulation of BSEP, the activity of which is reduced also in liver cholestatic diseases, suggests a key role for gut microbiota in their etiopathogenesis.

References

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