

Endocannabinoid system in chronic liver diseases

Summary

The endocannabinoid system (ECS), including endocannabinoids (ECs), cannabinoid receptors and EC degradation enzymes (EDE), mediates a variety of physiological processes not only in the brain, but in the whole human organism. Recent evidence suggests that it is involved in the regulation of hepatic fibrosis, steatosis and the overall modulation of liver inflammation. In this study we will focus on the role of the ECS in alcoholic liver disease (ALD) with the aim to elucidate potentially novel therapeutic mechanisms.

ALD and hepatitis C virus (HCV) infection are among the most frequent causes of chronic liver injury leading to cirrhosis. Recent experimental and clinical data in humans from our and other research groups have found an association of ECs and their corresponding receptors with chronic liver disease progression. For example, it was shown that hepatic cannabinoid receptor 2 (CB2) exerts beneficial effects on fatty liver, inflammation, regeneration and fibrosis, while signaling via cannabinoid receptor 1 (CB1) rather promotes hepatic steatosis, fibrosis, and necroinflammation. However, only few data exist about EC levels and EDE activity in humans with chronic liver diseases, in particular with regard to alcohol or chronic hepatitis virus infection.

The aims of the present project are to determine (1) the levels of ECs and EDE in human ALD and HCV; (2) whether the activity of EDE (i.e. overall regulation of ECS) is affected by external pathogens (alcohol, HCV); (3) whether the ECs may affect the inflammatory and fibrogenic responses in the liver under the alcoholic or viral conditions *in vitro* and *in vivo*. Moreover, we are interested to know whether CB2 activation inhibits inflammation and disease progression in ALD and HCV.

Experimentally, readily available liver biopsies and blood from patients with HCV and ALD will be used for determination of ECs and EDE levels, as well as for isolation of peripheral blood mononuclear cells (PBMC). Primary hepatic stellate cells will be used to study their interaction with PBMC regarding inflammation and extracellular matrix production. *In vivo*, EDE inhibitors will be used to test the effects of endocannabinoids on alcohol-induced liver injury.