The endocannabinoid system and substance use disorders: acute and chronic endocannabinoid levels in alcohol dependent users

3.2 Summary

BACKGROUND: Alcohol use disorder is a major public health issue in Switzerland and worldwide. Especially alcohol use relapse rates are reported with up to 90%. Therefore, we must ask: **what are the reasons to maintain alcohol use and what are their underlying neurobiological mechanisms?** Recent addiction models indicate stress as a key risk factor for developing drug addiction and for relapse, maintaining the vicious circle of drug addiction. A growing body of work indicates that the endocannabinoid (eCB) system plays a crucial role in the regulation of stress response. Recently, the eCB system attracted increased attention also in addiction research due to its stress buffering effects in animals and humans. Therefore, eCB levels in bio-samples such as plasma and hair might give important information about dysfunctional stress responses, which are likely drivers of stress-induced craving and relapse as well as drug addiction in general. However, mainly animal studies have yet investigated the link between the eCB system and addiction. Therefore, **the overall aim of the present project is to establish the major influence of the eCB system on alcohol use disorder in humans.** The *central hypothesis* is that eCB transmission is altered in patients with alcohol use disorder, which leads to inadequate stress responses resulting in increased craving and drug relapse.

METHODS: Hair and plasma eCB levels of individuals diagnosed with a DSM 5 alcohol use disorder (N=50) will be collected at the Centre for Addictive Disorders (ZAE) of the Psychiatric Hospital of the University of Zurich (PUK) to investigate basal eCB levels on an acute (plasma concentration) and chronic (hair concentration) level. As a control group healthy volunteers (N=50) will be recruited from the community in order to address our main objective: **To determine if alcohol dependent users show differences in acute and chronic eCB levels.** We will test this by comparing baseline eCB plasma and hair levels between drug-naïve healthy controls and alcohol dependent users. In additional exploratory analyses, we will determine associations between hair concentrations of ethyl glucuronide (EtG) as a reliable biomarker of chronic alcohol use and eCB levels in plasma and hair, which will give additional valuable information about potential dose-dependent effects of alcohol use on acute and chronic changes in the eCB signaling system. Moreover, results from our recent hair and plasma analyses of eCBs in cocaine users will enable us to compare eCB levels between different substance user groups (alcohol vs cocaine).

IMPACT: In sum the project aims to achieve a breakthrough in our **understanding of the underlying mechanism of the eCB system in alcohol use disorder**. The mechanistic understanding arising from this project could have profound implications for addiction resarch, as well as for the development of novel and improved treatments for alcohol relapse and abstinence by targeting the eCB system, specifically anandamide (AEA), in a pharmaco-therapeutic setting. The fatty acid amide hydrolase (FAAH) inhibitor, which increases AEA levels and is currently tested in a clinical trial for treatment of post-traumatic stress disorder (PTSD), might be a promising pharmacological target to reduce stress-induced drug craving and relapse also in alcohol use disorder.