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Increased cannabinoid receptor expression in the hippocampus drives abstinence from compulsive methamphetamine taking

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Background: Methamphetamine (METH) use disorder (MUD) is characterized by compulsive and repeated drug intake despite negative life consequences. Large intake of METH in humans and animals is accompanied by dysfunctions in learning and memory processes. **Rationale and hypothesis:** The endocannabinoid system (eCB) is known to modulate synaptic plasticity and cognitive functions. In addition, the eCB system has been implicated in substance use disorders. We therefore sought to identify potential changes in various enzymes and the receptors (CB1 and CB2) involved in the eCB system. Herein, we used a model of METH self-administration (SA) that includes a punishment phase (footshocks) that separates rats into a compulsive METH phenotype (compulsive) that continues to take METH and a non-compulsive METH (abstinent) that suppressed or became abstinent in the presence of punishment. We then measured mRNA expression of cannabinoid receptors (*CB/Cnr*), synthetic (*Dagl-a, Dagl-b, Nape-pld*), as well as metabolizing (*Mgll*, *Faah, Cox2*) enzymes of the eCB signaling cascade in various brain regions of rats euthanized two hours after the last METH SA session. **Results.** Abstinent rats exhibited significant increases in the expression of CB1 and CB2 in the hippocampus. mRNA levels for the synthetic enzyme, *Dagl-a*, and the metabolic enzymes, *Mgll, and Faah*, were also increased in the hippocampus, suggesting increased endocannabinoid synthesis and metabolism. There were no significant changes in any of these receptors or enzymes in the nucleus accumbens. **Discussion:** These observations implicate the hippocampal endocannabinoid system in the suppression of METH intake in the presence of adverse consequences. Epigenetic bases for these changes will be discussed.