cognitive functions, affective and hedonic behaviours. Thus, mice lacking the neuronal cannabinoid CB1 receptor show a striking acceleration of the age-related cognitive decline, accompanied by an enhanced neuronal loss and increased neuroinflammation. A similar phenotype was also observed in mice lacking CB1 specifically on GABAergic neurons. The role of endogenous cannabinoids in age-related changes will also be addressed using knockout mouse models with deletions in endocannabinoid synthesizing and degrading enzymes.

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Cannabinoid modification of cocaine action
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The endocannabinoid (eCB) system includes endogenous lipid molecules, such as anandamide and 2-arachidonoylglycerol (2-AG), the type 1 and type 2 cannabinoid (CB) receptors and several specific membrane-bound biosynthetic and degradative enzymes. This system is involved in a host of homeostatic and physiologic functions including synaptic transmission, neuronal firing and neurotransmitter release [Di Marzo, Proc Natl Acad Sci USA, 2011]. It also mediates goal-maintained behaviors and pathologies affecting these processes. More recent evidence suggests that the CB transmission may control drug addiction, however, the literature regarding CB effects on the actions of drugs of abuse remains contradictory [Filip et al., Pharmacol Rep, 2006; Olière et al., Front Psychiatry, 2013; Panillio et al., Pharmaco Ther, 2013].

We addressed the role of the CB receptors in the expression of cocaine-induced rewarding and seeking behaviors in intravenous self-administration and a drug-free extinction training procedures in rats. With using selective pharmacological tools at CB1 (AM 251, an antagonist) and CB2 (SR144528, an antagonist) receptor sites, we found that constitutive activation of CB receptors does not maintain cocaine reinforcement. We also show inhibitory effects of CB1 and CB2 receptor antagonists on drug-prized cocaine-seeking behavior. In contrast to CB1 receptors, CB2 receptors do not affect cue-induced reinstatement of cocaine-seeking behavior. Neuroadaptive changes in the eCB system following repeated i.v. cocaine and its withdrawal were determined ex vivo in autoradiographic (CB1 receptor binding measurements with [3H]JCP 55,940) and neurochemical (the tissue eCB concentrations analyzed via an LC–MS/MS method) studies. With using the same experimental protocols as in behavioral pharmacological studies and a “yoked” procedure to separate pharmacological vs. motivational effects of cocaine, we demonstrated selective CB1 receptor control over motivational and cognitive processes. In some rat brain regions we found alterations in levels of anandamide and 2-AG that were maintained over a long-lasting extinction period. Our findings support the evidence that the eCB system is involved in reinforcement and extinction of reinforced behaviors and that the lipid-derived molecules may represent promising targets for the development of new treatments for cocaine addiction.

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Cannabinoids and adolescent behaviour
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Adolescence, the transitional stage between childhood and adulthood, is characterized by drastic processes of neuronal and behavioural adjustment. These developmental alterations are essential across species to allow the transition from an immature individual toward an independent adult, capable of reproduction. At the same time, adolescent neurodevelopment also comprises a critical period of vulnerability for unintentional self-harm, suboptimal choices and behaviours, and the emergence of neuropsychiatric disorders. Detailed mechanisms of adolescent brain development and concomitant behavioural changes are still largely unknown. Adolescent behavioural characteristics can be observed in various mammalian species during development (e.g. humans, non-human primates, rodents, elephants). Among these behavioural features, enhanced reward processing may represent one of the key features triggering other behaviors, such as risky choices, impulsivity and the vulnerability toward drug use/abuse. It is well known that reward processing and the sensitivity towards drug and natural rewards are subjected to considerable changes throughout lifetime and we have recently shown that reward sensitivity peaks during mid-adolescence [Friemel et al., Front Behav Neurosci, 2010]. This peak in reward sensitivity is closely linked to pronounced neuronal processing of reward-related stimuli in the dorsal striatum. Enhanced signalling of endogenous opioids and/or endocannabinoids (ECB) might be involved in augmented reward sensitivity during mid-adolescence. However, our and other results show the involvement of the endogenous opioid system in the mediation of hedonic properties rather than motivational aspects of reward processing [Schneider et al., Behav Brain Res, 2010]. Furthermore, enhanced ECB signalling has been reported to occur as a transient state during adolescent brain development. Hence, cannabinoid receptor 1 (CB1) matures slowly during postnatal development, with peak levels of receptor binding, protein levels and levels of the endogenous ligand N-arachidonylethanolamide (AEA) being reached around early/mid-adolescence. Since the ECB system represents a crucial mediator of various processes of neuroplasticity, the transient boost in ECB signalling which appears to occur during adolescence, may provide increased plasticity and behavioral flexibility required specifically during this developmental stage. We therefore hypothesized that enhanced ECB signalling is critical involved in the peak of reward sensitivity during adolescence. By the use of a novel rat model with enhanced ECB signalling we demonstrate that this is indeed the case. Adult rats with enhanced ECB signalling are much more sensitive to natural and drug rewards. For example, these mutant rats show increased development and expression of cocaine sensitization and acute stimulatory effects of cocaine were also much more pronounced in mutant than wild-type rats. We further show that other behavioural features of adolescent behaviour are also mediated by enhanced ECB signalling. In conclusion, the adolescent state comprises a complex behavioural phenotype that bears many vulnerability factors for psychiatric disorders. Increased reward processing during adolescence appears to represent a key feature in mediating this heightened susceptibility and enhanced ECB signalling seem to be critical for initiating and mediating augmented reward processing and other behavioural features of adolescence.

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