The Cannabinoid Receptor 1 as a Key Mediator of Adolescent Behavior

Adolescence refers to the behavioral and cognitive transition from childhood to adulthood. This transition phase is a critical period for the emergence of psychiatric disorders (Paus *et al*, 2008). Adolescence is also crucial for the maturation of social skills. Teenagers spend much more time socially interacting with peers than during any other developmental period, and are thus more susceptible to peer-influence. Sensitivity towards social rejection has been reported to be higher during adolescence than in adulthood, and girls are particularly vulnerable to it. Adolescent social rejection by peers negatively affects psychological well-being and can result in severe adverse health outcomes (Williams, 2006). Given that adolescence is a vulnerable phase for the development of psychiatric disorders, social peer-rejection may be seen as an environmental hit that can promote these disorders, and this may be of particular relevance for the emergence of borderline personality (Schmahl *et al*, 2014).

We established a unique experimental approach to model social-rejection in rats where female individuals get excluded from social-play over several weeks during adolescence (Schneider *et al*, 2014; 2016). Those peer-rejected individuals exhibit persistent impairments in social behavior and pain perception, and show specific up-regulation of the cannabinoid receptor 1 (CB1R) in the amygdala and thalamus. Behavioral alterations can be restored by a subthreshold-dose of rimonabant in adult rats. Since CB1R seems to be of importance in mediating long-lasting consequences of social peer-rejection, we suggest that targeting the CB1R in psychiatric conditions and especially in borderline personality would be promising.

The CB1R seems to be also involved in mediating adolescent behavior. We reported recently that core features of

adolescent behavior are regulated by the state of activity of the CB1R (Schneider *et al*, 2015). By introducing a functional point mutation (F238L) into the rat *Cnr1* gene that encodes for the CB1R, a gain-of-function of the receptor was generated. Importantly, mutant rats show only minor compensatory alterations within the endocannabinoid system. This is the first animal model with a gain-of-function of the CB1R, and will hence provide a valuable tool in cannabinoid research in the future. We made an observation that adult mutant rats exhibit an adolescent-like phenotype with typical high-risk seeking, impulsivity, pronounced play behavior, and augmented drug and non-drug reward sensitivity. In further experiments, we showed that the adolescent wild-type control rats were not distinguishable from adult mutant rats at the behavioral level. We further tested whether partial inhibition of CB1R activity in mutant rats would lead to an adult wild-type phenotype. A subthreshold-dose of rimonabant, which did not affect behavior in adult wild-type littermates, normalized augmented reward-seeking behavior and other core features of adolescent behavior in adult mutant rats. This demonstrates a pivotal role for the CB1R in an adolescent brain as a molecular mediator of adolescent behavior.

In conclusion, these new studies show that a better understanding of the molecular underpinnings of adolescent behavior and social peer-rejection during adolescence can yield new intervention strategies for psychiatric disorders, and that the CB1R is a key mediator in this respect.

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Prospects for Medications to Reverse Causative Epigenetic Processes in Neuropsychiatry Disorders

Genome-wide mapping of epigenetic modifications in the brain suggest an important role for epigenetic processes in neurodevelopment (Lister *et al*, 2013). It is hypothesized that epigenetic alterations mediate neurodevelopmental diseases such as schizophrenia or autism, as well as other mental health conditions such as addiction and dementia.

The main appeal of this hypothesis is that, since epigenetic modifications are catalyzed by reversible enzymatic reactions they could be modulated by pharmacological agents, potentially reprogramming pathological states. There is strong preclinical evidence that learning and memory involve