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 re-programming pathological states. There is strong preclinical evidence that learning and memory involve

changes in DNA methylation and histone acetylation (Heyward and Sweatt, 2015). The involvement of DNA methylation and histone acetylation/deacetylation enzymes in learning and memory raises the possibility that they might be targeted to attenuate remote memories for treatment of PTSD(Graff *et al*, 2014). HDAC inhibition enhances cognitive performance in a mouse model of impaired cognition, and CREB pathway-specific selected HDAC inhibitor crebinostat was shown to significantly improve memory (Fass *et al*, 2013). It is unclear, however, whether this approach works in humans. If indeed the clinical data replicates animal studies, isotype-specific HDAC inhibitors should have a large impact on the treatment of cognitive decline and dementia, and perhaps PTSD.

Evidence suggests that addiction is mediated by epigenetic reprogramming in response to drug exposure (Massart *et al*, 2015). Epigenetic therapy might potentially 'reprogram' the addicted state and revert the phenotype to a non-addictive phenotype. Treatment of rats that crave cocaine with the DNA methylation inhibitor RG108 inhibited cocaine craving. Importantly, although the treatment was acute, the effects on blocking addiction persisted up to 60 days, suggesting stable epigenetic reprogramming by the treatment (Massart *et al*, 2015). Epigenetic therapy could potentially erase the epigenetic marks of exposure and exert a long-lasting effect that should persist unless a similar exposure is encountered, in difference from symptomatic therapy, which provides a transient relief.

However, there are critical caveats that need to be addressed. First, epigenetic drugs target general epigenetic processes, how could we guarantee specificity to particular genes? Nevertheless, since epigenetic reprogramming probably involves gene networks (for example, see (Massart *et al*, 2015), perhaps multi-targeted epigenetic drugs might be more potent than other approaches. Second, neurodevelopmental programs involve an organized sequence of epigenetic alterations, how could they be reversed once the neurodevelopmental processes have taken shape? There is genetic evidence that this might be possible; a RETT syndrome phenotype caused by transgenic *mecp2* mutation in mice could be rescued by restoring *MeCP2* gene expression in adult mutant animals (Guy *et al*, 2007). Animal studies have shown that general HDAC inhibitors could reverse learning deficiencies in a neurodegenerative mouse model (Fischer *et al*, 2007), but clinical studies have been limited, used nonspecific HDAC inhibitors, and examined a small number of patients (Sajatovic *et al*, 2008). The main epigenetic drug that is currently in use in psychiatry is valproic acid, a nonspecific HDAC inhibitor. A recent meta-analysis suggests that Valproic acid augmentation might improve treatment of schizophrenia patients (Tseng *et al*, 2016). The question remains, however, whether HDAC inhibitors could reverse behavioral and neuropsychiatric disorders, whether isotype-specific inhibitors would exhibit a more potent reprogramming activity, or whether multi-targeted drugs acting on gene networks rather than single selective agents would exert a more potent clinical benefit, and whether other epigenetic modulators such as DNA methylation inhibitors might elicit stronger responses?

The preclinical evidence for a potential paradigm shift in treatment of mental health conditions using epigenetic modulators has been surprisingly slow in translation to the clinical arena. The clinical studies are sparse, and the selection of epigenetic modulators that cross the blood–brain barrier that are appropriate for clinical studies is limited. Though more work needs to be done, there is vast potential for epigenetic approaches to change the way mental health disorders are treated.

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Ketamine Mechanism of Action: Separating the Wheat from the Chaff

(*R,S*)-ketamine (ketamine) exerts rapid (within hours) and robust (>60% response) antidepressant effects in severely ill-depressed patients who have failed conventional treatments (Zarate *et al*, 2006). This clinical finding has been paradigm-shifting as there is now tremendous hope that very ill-depressed patients can be treated in a matter of hours, rather than many weeks or months required for standard therapies to take effect (if they do at all). However, although the therapeutic potential of ketamine has elicited tremendous excitement in the field, ketamine's use outside of a monitored clinic setting is