CANNABINOID INVOLVMENT IN THE DEVELOPMENT OF SCHIZOPHRENIA BEHAVIORAL PHENOTYPES

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Cannabis is among the most worldwide used psychoactive drugs, with an estimates 125-227 million consumers all over the world (World Drug Reports, 2014). The most powerful component of cannabis is the Δ9- Tetrahydrocannabinol (Δ9-THC), which acts as agonist on cannabinoid receptor 1 (CB1R) modulating several functions such as learning (Lee et al., 2016), memory (Qin et al.,2015), cerebral development (Galve-Roperth et al.,2009), social and emotional memories (Busquéts-Garcia et al., 2016). Mounting evidence from human and animals studies suggest a strong relationship between cannabis consumption and the development of psychosis, with particular genetic variations conferring a vulnerable background (Henquet et al., 2008). For example, individuals carrying the COMT Val allele (which induce an increased COMT activity) appeared to be the most sensitive to the effects of adolescence cannabis exposure on the development of psychotic symptoms (Caspi et al., 2005). In order to investigate how the interaction between genetic polymorphism and cannabis use may affect the development of psychiatric disorders, humanized COMT Val tg mice and their control littermates were injected with increasing doses of Δ9-THC (1.25-5mg/kg i.p.) or vehicle during adolescence (pnd 29-44) and then tested during adulthood (pdn~110). To control for the developmental effects of Δ9-THC treatment another cohort of COMT Val-tg and control littermates were treated with the same increasing doses (1.25-5 mg/kg ip) of Δ9-THC or vehicle only during adulthood (pdn75-90) and then tested after a 20 days of washout. Both groups of adolescence Δ9-THC e adult Δ9-THC were assessed during adulthood for behavioral phenotypes relevant to schizophrenia, using different behavioral tasks: Prepulse Inhibition (PPI), Locomotor Activity (LMA), Psychostimulant Sensitization and Social interaction (SI). Moreover, since social abilities impairment is a core feature in schizophrenia patients, we also analyzed the effect of an Δ9-THC acute treatment (2.5 mg/kg i.p., 30 minutes before the test) using novel protocols for SI and emotion recognition tasks. Δ9-THC exposure produced divergent behavioral effects depending on its presentation in different stages of life. For instance, it decreased startle reaction in control and COMT Val tg mice treated during adolescence, but it increased the startle reaction in mice treated during adulthood. Moreover, Δ9-THC treatment, both in adolescence and adulthood, did not affect the LMA, but it altered psychostimulant sensitization in male COMT Val tg treated during adulthood. In addition, Δ9-THC chronic treatment impaired social interaction in control and COMT Val mice reducing the total interaction time. Furthermore, preliminary data in adult mice acutely injected with Δ9-THC demonstrated deficit in social abilities decreasing the interaction time in both SI and emotion recognition tasks. Our findings highlight how the COMT Val genetic background might differentiate individuals to a higher susceptibility to the detrimental effects of cannabis exposure and establish our model as a valid experimental tool to address individual differences in cannabis responses.

References:

United Nations Office on Drugs and Crime. World Drug Report (2014)

Lee et al. (2016). Genes, Brain and Behavior (2016) 15: 108–124

Qi et al. (2015). Behavioural Brain Research 291 (2015) 164–171

Galve- Roperth et al. (2009). Eur Arch Psychiatry Clin Neurosci (2009) 259:371–382

Busquéts-Garcia et al. (2016). F1000Research 2016, 5(F1000 Faculty Rev):990

Henquet et al. (2008). Schizophrenia Bulletin vol. 34 no. 6 pp. 1111–1121, 2008

Caspi et al. (2005). Biol Psychiatry. 2005 May 15;57(10):1117-27.