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Cannabinoid CB1 receptor antagonist blockade at birth may be associated with ADHD

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Attention Deficit Hyperactivity Disorder (ADHD) is a condition that becomes apparent in some children in the preschool and early school years, but also appears at adulthood. It is estimated that between 3-5 percent of children have ADHD in USA, and 5-10 percent in the Israel. ADHD is characterized by inattention, impulsivity and/or hyperactivity. A well-known feature of ADHD is the positive response to psychostimulants such as methylphenidate (Ritalin) and D-amphetamine (Adderall), expressed as a reduction in excess motor activity and improved concentration. Although ADHD has been known for over 80 years, the etiology and risk factors for ADHD are still unclear. Importantly, low birth weight may be one of the most important predictive factors of ADHD (Chadapim et al. 2005). Non organic failure-to-thrive (NOFTT) in infants is defined as an abnormally low weight and/or height for age without a known organic cause. In a series of studies performed in neonatal mice we have demonstrated that the cannabinoid CB1 receptor is critically important for feeding and weight gain, apparently caused by an oral-motor dysfunction, similarly to that which characterizes infants suffering from NOFTT (Fride et al., 2001; 2003; 2007). Children who suffered from NOFTT are thought to display behavioral and cognitive dysfunctions in later years. Here we propose that a deficient ECS (endocannabinoid system) at birth may comprise a risk factor for ADHD.

Methods: Male and female pups were administered a single injection of SR141617 (rimonabant, 5, 10 or 20 mg/kg), within 24 hours of birth. At two months of age, mice were tested in an assay for pre-pulse inhibition (PPI) of the acoustic startle response (ASR). At the age of 16 weeks the same mice were examined for motor activity in an open field, immobility (catalepsy) on an elevated ring, for anxiety-like behavior in an 'elevated plus-maze' and in the Porsolt forced swimming test for depressive-like symptoms.

Results: Pups treated with 10 or 20 mg/kg rimonabant showed a reduction in body weight during the first 2 weeks of life. However as adults, all (surviving) mice were of normal weight. Behaviorally, both male and females displayed significant hyperactivity in the open field and on the ’ring’. We also observed a decreased performance in the PPI assay at both doses for the females but only at the 5 mg/kg dose for males. We observed a lower level of anxiety in the plus maze, again primarily in the males which had received 10 mg/kg SR141716. Compatible with this observation, a trend towards a reduced startle response was seen, again mainly in the males. In the forced swimming test, no differences were observed between rimonabant-treated and control mice. Preliminary observations suggest that DL-amphetamine administration (4 mg/kg) normalizes neonatal rimonabant-induced hyperactivity and PPI.

Conclusions: Our observations suggest that brief neonatal blockade of the cannabinoid CB1 receptor at birth precipitates symptoms of ADHD at adulthood as apparent in hyperactivity, impaired sensorimotor gating a tendency toward reduced ‘anxiety’ and the reversibility of these symptoms by amphetamine. In addition, similarly to observations in humans treated for ADHD (Pinckhardt et al., 2009), primary mood regulation was not affected in mice with blocked CB1 receptors at birth. We conclude that at least a subgroup of ADHD may be caused by a developmental deficiency of the endocannabinoid system.