Role of endocannabinoid system in the adolescent brain maturation: from physiology to pathology

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Adolescence is a time of important neurobiological and behavioral changes, but is also the period in which several mental illnesses emerge, included psychosis and mood disorders, as well as substance abuse such as Cannabis consumption.
During adolescence, the brain undergoes intensive processes of neuronal refinement especially in cortical regions. Adolescent brain maturation involves also a thinning of the gray matter (GM – it contains the cell bodies, dendrites and axon terminals of neurons) as the result of synaptic pruning processes, through which "redundant" synapses overproduced in the early years of life are being eliminated, whereas volumes of white matter (WM – it is made of myelinated axons) increase. Myelin improves neural transmission throughout the brain, contributing to the enhanced brain-regional connectivity and cognitive function that occur during adolescence. Thus, alterations in synaptic refinement as well as in myelination, during this sensitive period, could confer a vulnerability to psychiatric diseases.
Another system that undergoes remodeling of its components during adolescence is the Endocannabinoid System (ECS). In the brain, the ECS is an important neuromodulatory system involved in the regulation of synaptic plasticity mechanisms. So far, many works have been made on the adolescent brain maturation, but the involvement of ECS in the adolescent brain refinement remains to be elucidated.
Our aim is to investigate the role played by the endocannabinoid signaling system on several markers related to plasticity, as well as on myelination during the adolescent window. Through the administration of specific modulators of the ECS, we will investigate the impact of this modulation on markers of plasticity (AMPA and NMDA subunits, PSD95, SAP102) and myelination (MOG and MBP). Specifically, we will administer AM251, a selective antagonist of CB1 receptor, the major cannabinoid receptor in the central nervous system; URB597, an inhibitor of the enzyme fatty acid amide hydrolase (FAAH, the enzyme that catalyzes the intracellular hydrolysis of the endocannabinoid anandamide "AEA"), and JZL184, a selective inhibitor of monoacylglycerol lipase (MAGL, the enzyme that preferentially catabolizes the endocannabinoid 2-arachidonoyl glycerol "2-AG").
With this approach we will be able to elucidate the role played by specific components of the ECS (CB1R, AEA and 2-AG) during adolescent brain maturation. Moreover, we will also understand if adolescent brain vulnerability to long-lasting THC adverse effects could reside, at least in part, in the disruption of the essential role played by this system in the processes characterizing adolescent brain maturation.