The dual face of the endocannabinoid system in schizophrenia: experimental evidence

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Investigating the association between Cannabis, the endogenous cannabinoid system and schizophrenia must take into account two aspects of major relevance.
On the one hand, Cannabis is the most widely used illegal drug and there is substantial evidence that its consumption has to be classified as an independent risk factor for psychosis that may lead to a worse outcome of the disease. On the other hand, there are several lines of evidence that clearly indicate the presence of a dysregulation in the endocannabinoid system in animal models of psychosis and at least in a subgroup of schizophrenic patients.
Concerning the first point, our recent studies in female rats demonstrated that chronic THC treatment during adolescence induced a complex phenotype in adulthood characterized by the presence of anhedonia, behavioral despair in the forced swim test, reduced sociability as well as significant deficits in spatial working and object recognition memory. Moreover, adolescent THC administration also sensitizes to the locomotor activating effect induced by acute psychostimulant administration in adulthood. This response is consistent with the presence of a psychotic-like phenotype. Thus, the simultaneous presence of pronounced depressive-like behaviors, cognitive deficits as well as psychotic-like signs suggests that adolescent THC exposure had led to a behavioral phenotype in adulthood that reflects the presence of complex schizoaffective-like disorder. Interestingly, when the same protocol of THC exposure was performed in adult animals, no behavioral alterations were observed, thus highlighting the specific vulnerability of the adolescent brain to the long-lasting adverse effects of THC.
The neurobiology of cannabis-induced schizophrenia is still unknown. However, it can be postulated that adolescent exposure to THC alters the endocannabinoid system, ultimately resulting in persistent imbalances of excitatory and inhibitory neurotransmission within specific brain regions. Accordingly, our data demonstrate that the schizoaffective-like disorder associated with adolescent THC exposure in female rats is strictly associated with alterations in the endocannabinoid system in specific brain regions, such as the prefrontal cortex. Moreover, significant alterations in excitatory and inhibitory neurotransmission are present in adult THC-treated rats and are particularly prominent within the prefrontal cortex, a brain region that has been found to be severely affected in schizophrenia.
With regard to the second aspect, there are several lines of evidence that clearly indicate the presence of a dysregulation in the endocannabinoid system in different animal models of psychosis and based on these observations, the pharmacological modulation of the endocannabinoid system has been taken into account as a new therapeutic possibility for psychotic disorders. In line with this, we demonstrated that chronic treatment with the cannabinoid CB1 receptor antagonist, AM251, counteracts the psychotic-like phenotype both in a pharmacological model and in a neurodevelopmental model of schizophrenia in rats. This recovery at behavioral level was paralleled by the normalization of the endocannabinoid system functionality both in terms of endocannabinoid levels and CB1 receptor/G protein coupling in all the brain areas analyzed, possibly suggesting that the ability of AM251 to restore normal endocannabinoid system may account for its antipsychotic action.
As a whole, data reported so far, although preliminary, strongly suggest an association between an altered endocannabinoid tone and the development of psychotic symptoms, thus supporting the exploitation of compounds acting on the endocannabinoid system as new therapeutic agents in the treatment of schizophrenia and related disorders.

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