Altered signalling in CB_1-$5HT_{2A}$ receptor heteromers in olfactory neuroepithelium cells of schizophrenia patients is modulated by cannabis use

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Schizophrenia (SCZ) is a complex, severe and debilitating mental disorder that causes a substantial clinical, familiar and economic burden, but its aetiology and underlying pathophysiology remain unknown. Dysregulations in the serotonergic and the endocannabinoid systems have been discussed as potential causes of schizophrenia, but the difficulty in obtaining central nervous system tissue samples and cells in living subjects has limited its exploration. Due to its low-invasiveness and high scalability, olfactory neuroepithelium (ON) cell models are becoming a promising surrogate system to explore neuronal biomarkers in schizophrenia, providing a unique opportunity to unveil novel potential molecular targets for psychopharmacology research. Chronic cannabis use induces several deleterious effects including cognitive and mood alterations by acting on the endocannabinoid system, and by modulating the activity of other neurotransmitters in the brain. Recently, we have demonstrated that CB_1 cannabinoid receptor (CB_1R) and serotonergic 2A receptor ($5HT_{2A}R$) heteromers are expressed and functionally active in the brain of mice, where they specifically mediate the memory impairment induced by cannabis (Viñals et al. 2015). Moreover, we revealed the presence of functional CB_1R-$5HT_{2A}R$ heteromers in ON cells of healthy cannabis users (HC/c) and control subjects non-cannabis users (HC/nc), showing a significant negative correlation between the expression levels of this heterodimer and attention and working memory performance (Galindo et al. 2018). In this study, we focused on the ON to investigate CB_1R-$5HT_{2A}R$ heteromer expression and functionality in SCZ patients, and evaluated whether cannabis use in a sub-population of SCZ patients (SCZ/c) modulated these parameters. In addition, we examined possible associations between heteromer expression/functionality and cognitive processes, psychopathological and functional variables in SCZ patients. Finally, we assessed the effects of antipsychotic treatment and its interaction with cannabis use on CB_1R-$5HT_{2A}R$ heteromer functionality. The major finding in this study was that the signalling of CB_1R-$5HT_{2A}R$ heteromers via cAMP and pERK in ON cells is not observed in SCZ/nc, while in SCZ/c the fingerprint of the heteromer is maintained. In addition, we report that clozapine treatment in ON cells of HC/nc also modified the functionality of the heteromer, but not in ON cells of HC/c. These findings point to changes in the molecular conformation of CB_1R-$5HT_{2A}R$ heteromers in treated SCZ patients, which are prevented by cannabis use. Finally, cognitive deficits were present in both SCZ/nc and SCZ/c, suggesting that changes in the functionality of the heteromer may not influence cognitive impairment in SCZ. More studies are needed to further explore the role of CB_1R-$5HT_{2A}R$ heteromer and its clinical significance in the development of SCZ, and in the effects of different antipsychotic medications.

References:

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