CB1-5-HT2A heteromers in schizophrenia patients: human studies in pro-neurons of the olfactory epithelium

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Introduction

Despite multiple clinical and pre-clinical studies investigating schizophrenia, the neurobiological basis of this disease is still unknown. The dysregulation of the serotonergic system, in particular, the 5-HT2A[1] receptor and the endocannabinoid system have been postulated as possible causes of part of the psychotic and cognitive symptoms.

Objectives

The aim of this study is to evaluate the expression of CB1-5-HT2A receptor heteromers in primary cultures of pro-neurons from the olfactory epithelium in schizophrenia patients and control subjects.

Methods

We recruited a group of 15 patients diagnosed with schizophrenia, which were treated with atypical antipsychotics, were clinically stable and had an illness duration range from 1 up to 15 years and 17 healthy volunteers. The patients were diagnosed with schizophrenia from the medical record and confirmed by the Structured Clinical Interview for DSM Disorders. The expression of CB1-5-HT2A receptor heteromers in primary cultures of pro-neurons from the olfactory epithelium was quantified using proximity ligation assays and confocal microscopy [2]. The patients and healthy controls were matched by age and gender. Cognition was assessed with the CANTAB neuropsychological test battery.

Results

- Olfactory epithelium pro-neurons were viable and expressed the neuronal marker, III-β tubulin. We also established the presence and the functionality of CB_1-5-HT_{2A} receptor heteromers in these cells using the proximity ligation and cAMP activity assays, respectively.

Figure 1: Olfactory neuroepithelium cells (antiβIII-tubulin and anti-nestin Immunofluorescent staining) by PLA

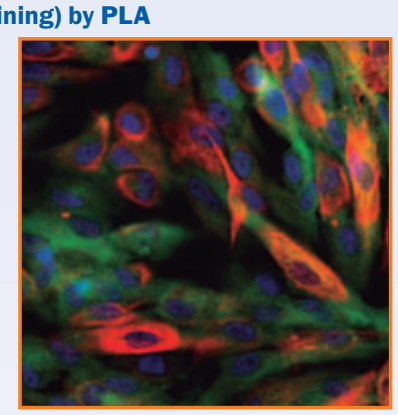
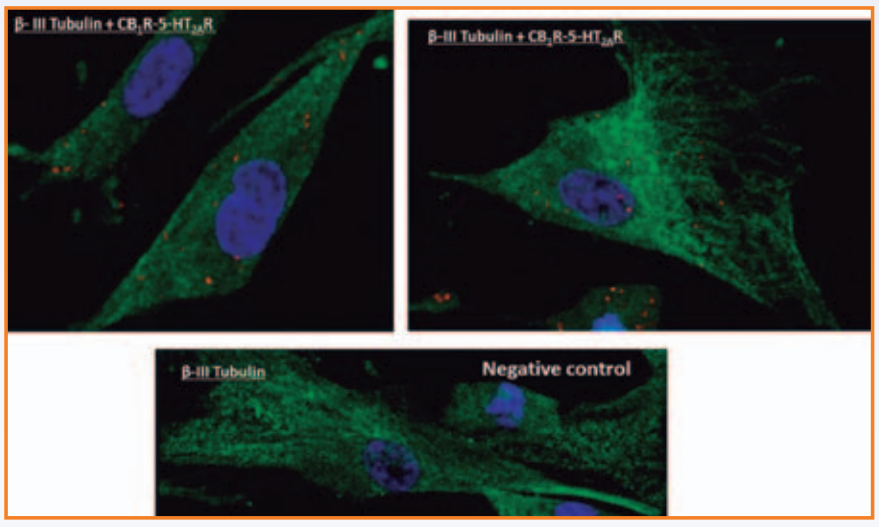
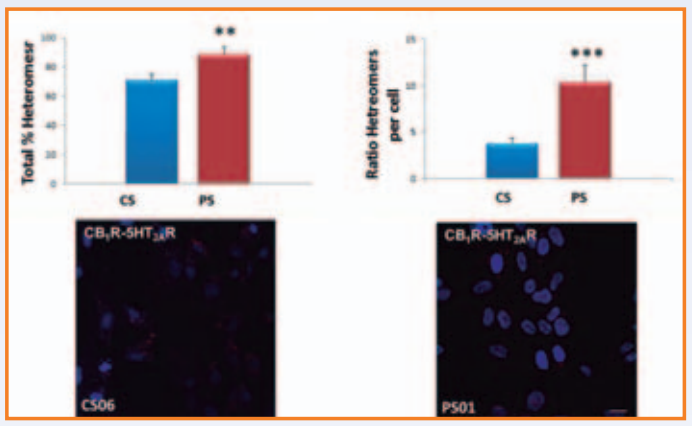


Figure 2: Immunofluorescent staining with β-III-Tubulin and CB1R-5-HT2AR heteromers by PLA



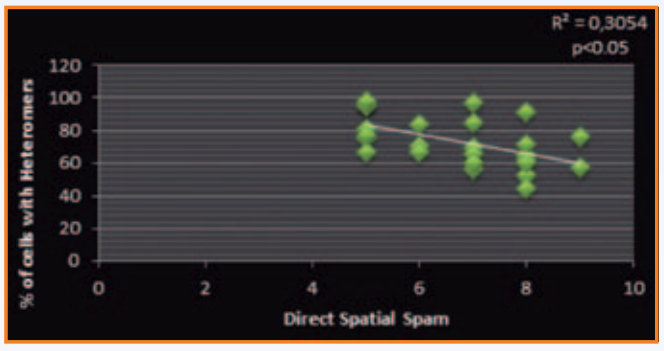
- Heteromer expression was significantly increased in schizophrenia patients with respect to controls

Figure 3: CB1R-5-HT2AR heteromers in control subjects (CS), and patients with schizophrenia (PS) detected by in situ PLAs



- The expression of heteromers (percentage of cells with heteromers) is negatively correlated with the cognitive functions of the patients.

Figure 4: Correlation of Cells with heteromers and Direct Spatial Span



Conclusions

- This highly innovative methodology will allow the non-invasive, low-cost study of new biomarkers for schizophrenia in a model closely related to the central nervous system.
- The presence of CB 1-5HT2a receptor heteromers might be related to cognitive impairment in schizophrenia. Further studies should be performed in schizophrenia in cannabis consumers and non-consumers.

References

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