

Effects of cannabinoid agonists on the proteome of a human oligodendrocyte culture: possible implications for schizophrenia

Priscilla R. Rumin*, Mariana Fioramonte, Gabriela Seabra, Valéria de Almeida, Daniel Martins-de-Souza.

Abstract

Schizophrenia is a multifactorial psychiatric disorder, which affects about 1% of the world's population. Several studies have demonstrated the involvement of the endocannabinoid system in the pathophysiology of schizophrenia. Studies have shown that endocannabinoids can also affect the function of oligodendrocytes. In order to better understand the mechanisms involved, and to help developing less harmful treatments, we will investigate the effects of endocannabinoids and synthetic cannabinoid agonists on a human oligodendrocyte cell line (MO3.13). In addition, we will verify if these treatments may reverse the effects of the NMDA receptor antagonist MK801 - an *in vitro* model to study schizophrenia. For this, we will use the two-dimensional liquid nanochromatography coupled to *high resolution* mass spectrometry. Data will be processed and analysed using *in silico system biology* tools. Taken together, our approach aims to contribute to the elucidation of the role of activation of cannabinoid receptors in oligodendrocytes and the possible implications for understanding the pathophysiology of schizophrenia.

Key words:

Endocannabinoid System, Proteomics, Glia.

Introduction

Schizophrenia is a severe disorder caused by the interaction of genetic and environmental factors during neurodevelopment¹. Defective neurotransmission have been implicated in the symptoms of schizophrenia. More recently, studies have suggested the involvement of the endocannabinoid system in this disorder.²

Endocannabinoids also play a role in the regulation of glial cells, important components in the pathophysiology of the disease, especially in relation to neuronal differentiation and survival. This is relevant, considering the reduction of the density of oligodendrocytes and white matter in schizophrenia patients, since these cells are responsible for myelination, which is critical to neurodevelopment.³ Thus, alterations that may occur during the proliferation and maturation of oligodendrocyte progenitors may damage neural function related to neurotransmission in schizophrenia.⁴

This work aims to analyze the effect of endocannabinoids and synthetic cannabinoids in the proteome of human oligodendrocytes in culture, in order to identify proteins differentially expressed by these different treatments as well as their interaction networks and altered biochemical pathways, besides possible reversions of effects in a model of glutamatergic hypofunction. Aiming to delineate the role of endocannabinoids at a better understanding of schizophrenia, we present our preliminary results.

Results and Discussion

Cultured oligodendrocytes (cell line MO3.13), were treated with endocannabinoids (anandamide and 2-AG) and synthetic cannabinoids (WIN55,212-2; ACEA and HU308). These drugs will also be used in MO3.13 previously treated with MK801. Next, cells were harvested, proteins were extracted peptides generated by trypsin digestion.

Peptides were analyzed by a large-scale proteomic tool, which consists of two-dimensional liquid chromatography coupled to mass spectrometry. Proteins were identified and quantified using appropriate software and algorithms. Differentially expressed proteins were evaluated in web-based *in silico systems biology* tools such as STRING, DAVID and Reactome, to uncover interactions between these proteins in the different treatments. Also, we aimed to identify biochemical pathways and biological systems in which the differentially expressed proteins are involved.

From the synthetic agonist treatments, we have already obtained some results, which are being analyzed, in order to understand, in the context of schizophrenia, the biological functions, cellular components and biochemical pathways of which these proteins are part.

Conclusions

The use of cellular culture models in association with proteomic analysis has proved to be a fundamental tool for a better understanding of the cellular and molecular roles played by proteins involved in the pathophysiology of the disorder. In this way, this study will allow a deeper understanding of the role of the endocannabinoid system in oligodendrocyte function and point out to potential treatments for schizophrenia.

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² Fernandez-Espejo E., et al. "Role of cannabis and endocannabinoids in the genesis of schizophrenia." *Psychopharmacology*. **2009**. 206(4), 531-549.

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⁴Cassoli J.S., et al. "Disturbed macro-connectivity in schizophrenia linked to oligodendrocyte dysfunction: from structural findings to molecules." *npj Schizophrenia*. **2015**, 1, 15034.