Epigenetic regulation of CNR1 gene in schizophrenia

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Schizophrenia (SZ) is a chronic, severe, and disabling psychiatric disorder with a prevalence of approximately 0.5 - 1% in the general population. Environmental risk factors, as well as genetic factors, have been identified for their contribution to individual vulnerability in liability to SZ. Many genes have been implicated, although the results are still sparse due to several reasons, such as effect size, phenotype heterogeneity and, most of all, gene-environment interactions and epigenetic mechanisms could have a key role in these interactions.

Among the several neurotransmitter systems implicated, an increasing number of studied indicate the important role of the endocannabinoid system (ECS). We evaluated whether alterations of ECS genes expression might occur in the development and progression of SZ in a gestational rat model (prenatal administration of the mitotoxin methylazoxymethanol acetate (MAM)) as well as in human subjects. Moreover, we evaluated if aberrant phenotypes and gene expression changes are associated to epigenetic modifications of ECS gene promoters, in particular to DNA methylation changes. We observed selective alterations of DNA methylation at the promoter of CNR1, the gene coding for the type-1 cannabinoid receptor, in schizophrenic patients (N=25) with no changes in any other disorder. Lower methylation observed here in younger SZ subjects, when compared to age-matched healthy subjects.

We confirmed the regulation of CNR1 in MAM rats (N=7 per group) where we found, in the prefrontal cortex, a significant increase in CNR1 expression and a consistent reduction in DNA methylation at specific CpG sites of gene promoter. Our finding clearly show a transcriptional regulation of CB1 in SZ via DNA methylation both at preclinical and clinical levels, thus pointing to the evaluation of peripheral CNR1 DNA methylation as a potential biomarker for the disease. SZ typically begins in early adulthood and our findings call for the importance of an early evaluation of DNA methylation, also in the light of the low onset vulnerability for disease development in subjects above 40 years old.