

Schizophrenia is a neurodevelopmental disorder and its aetiology is still debatable. Several findings suggest that both genetic and environmental factors are involved in pathology of schizophrenia. Recent data also indicate that epigenetic regulation mediates the interplay between genes and environment and it is likely to play a significant role in the onset of schizophrenia. Thus, the aim of this project is to investigate a role of epigenetic readers from bromodomain and extraterminal domain (BET) family of bromodomain proteins in the molecular and behavioural aspects of schizophrenia-like abnormalities in an animal model of schizophrenia.

A neurodevelopmental model of schizophrenia based on prenatal administration of environmental factor, antimitotic agent, methylazoxymethanol acetate (MAM) models a dynamic aspect of the illness and BET protein expression will be determined at different stages of brain development. Literature data indicate that adolescence might be a critical period in schizophrenia development and adolescent manipulation might change the course of schizophrenia. Therefore, an inhibitor of BET proteins will be administered during adolescence to determine a role of these proteins in emergence of schizophrenia. Behavioural studies will evaluate some schizophrenia like symptoms in adulthood, i.e., social interactions, memory and sensorimotor gating functions. Moreover, molecular studies (proteomics, gene profiling using RNA-sequencing, Western blot, quantitative real time polymerase chain reaction) will be performed in the medial prefrontal cortex and in the hippocampus to analyse the involvement of BET proteins in expression of genes related to pathophysiology of schizophrenia. Furthermore, the therapeutic utility of BET protein inhibitor will be also evaluated in behavioural tests.

Schizophrenia is a devastating psychiatric disorder affecting about 1 % of the population worldwide and usually produces a lifetime of disability and emotional distress for affected individuals. Apart from personal distress, schizophrenia has a huge socioeconomic burden, mostly in terms of indirect costs like loss of employment and social support and only the better understanding the causes and pathophysiological bases of schizophrenia may improve its prevention and treatment. Moreover, a therapy of schizophrenia is still under investigation, since 10-20 % of schizophrenic patients are resistance to antipsychotic treatment, and recent epidemiological studies indicate that intervention strategies during childhood or early adolescence might prevent schizophrenia development. Thus, a wider knowledge about aetiology and early stages of schizophrenia development might increase a chance of its prevention and show new directions of schizophrenia therapy.