

Schizophrenia is a debilitating psychiatric disorder that affects 1% of the worldwide population. It is a complex and heterogeneous disease with multiple domains of symptoms, e.g. positive symptoms like hallucinations and delusions, negative symptoms like emotional apathy and lack of motivation as well as and cognitive deficits like impaired memory, thinking and concentration. In addition to these symptoms, depression and anxiety commonly accompany schizophrenia. Many of currently available antipsychotic drugs have shown their limitations in terms of efficacy against cognitive impairments associated with schizophrenia and co-morbid depression and anxiety and are affected by metabolic side effects as significant weight gain, dyslipidemia and hyperglycemia, which increase the risk for diabetes and cardiovascular disease. There is a large body of evidence indicating that serotonin 5-HT<sub>6</sub> receptor ligands, both agonists and antagonists, displayed improving memory, antidepressant and anxiolytic properties and are active in body weight reduction, thus they seem to be promising supplement to antipsychotic treatment.

The aim of the proposed research is to assess the influence of the combined use of antipsychotic drugs and selective 5-HT<sub>6</sub> receptor ligands (an antagonist and an agonist) on metabolic side effects caused by neuroleptics, selected cognitive impairments associated with schizophrenia, depression and anxiety symptoms.

All the experiments will be conducted on Wistar rats. The following agents are selected for the investigations of combined acute and chronic treatments: three antipsychotic drugs with different receptor, pharmacological and side effects profiles and two 5-HT<sub>6</sub> receptor ligands (agonist and antagonist). Each antipsychotic drug will be combined with both an agonist and an antagonist, and the reference groups will be vehicle, respective antipsychotic and respective 5-HT<sub>6</sub> ligand treated groups.

*In vivo* behavioral studies will include:

- the influence of the combined treatment of antipsychotic drugs and 5-HT<sub>6</sub> receptor ligands on the weight gain and food intake,
- pharmacological evaluation of potential procognitive effects of the combined treatment of antipsychotic drugs and 5-HT<sub>6</sub> receptor ligands using common screening tests: the novel object recognition test, the Y-maze test and the social interaction test,
- pharmacological evaluation of potential antidepressant and anxiolytic activity of the combined treatment of antipsychotic drugs and 5-HT<sub>6</sub> receptor ligands using common screening tests: the forced swim test, the Vogel conflict drinking test and the elevated plus maze test.

*Ex vivo* biochemical and molecular studies will include:

- the determination of the lipid profile, glucose level and leptin, ghrelin, insulin, adiponectin concentrations in the blood using enzyme immunoassays tests,
- the determination of proteins and genes of neuropeptides and their receptors involved in the regulation of food intake and body weight using Western blot and RT-qPCR molecular methods.

The obtained, during this research project, results can be used to increase the efficacy and safety in the management of schizophrenia and may contribute to improving the psychiatric patients' compliance. An important result, that will affect the development of the science, will also be determination of the influence of combined therapy on the selected factors that regulate food intake and body weight, which may help to explain the mechanism of this action.