



PROJECT

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1) Project title: Investigating the metabolic dysfunctions associated to atypical antipsychotic drugs using *Drosophila melanogaster*

2) Abstract (max 500 words)

Antipsychotic (AP) drugs are considered as the first line of treatment to manage psychosis, and principally used in schizophrenia and bipolar disorder. There is no doubt that antipsychotic drugs have provided relief and symptom control for a substantial proportion of people with schizophrenia and related psychotic disorders, however, along with the increased use of the second generation antipsychotics has come an increasing awareness of an important and limiting adverse effect, that of weight gain and its metabolic consequences. Excessive appetite, weight gain, obesity and obesity-related metabolic disorders such as insulin resistance and hyperglycemia are the most severe side effects in most patients treated with antipsychotic drugs. In fact, the long-term administration of APs during psychiatric rehabilitation or maintenance therapies, increases the risk of developing type 2 diabetes mellitus and/or a metabolic syndrome. The patients receiving antipsychotic medications show a wide variability in drug response and drug induced side effects which could be attributed to genetic or non-genetic components influencing drug response. The main explanation is that APs act through the modulation serotonin, histamine and acetylcholine receptors, increasing appetite and decrease activity. A complementary explanation for AP-induced metabolic dysfunctions is that APs exert a yet uncharacterized action on lipid and cholesterol metabolism and trafficking. Being amphiphilic weak bases, antipsychotics can disrupt lysosomal function, affecting cholesterol trafficking; moreover, by chemical mimicry, antipsychotics can inhibit cholesterol biosynthesis.

In this project *Drosophila* will be used to explore the direct effects of antipsychotics on metabolism and develop an accurate investigation on metabolic parameters and intracellular trafficking changes. *Drosophila* is one of the most used model for studies of mechanisms implied in human pathologies and in the last years Its use in pharmacological screening is growing up. *Drosophila* model of obesity, type 2 diabetes mellitus, cholesterol metabolism has been generated and demonstrated that fruit flies is a good model to study metabolic syndromes. The opportunity to analyzed biological process in a whole organism maintaining the complexity and interplay between tissues and organs is indispensable for antipsychotic induces metabolic dysfunction analysis. A combined approach using molecular biology, confocal imaging and genetic techniques as well as behavioral tests will be used to study the molecular mechanisms of different APs in various genetically modified flies. *Drosophila* mutant lines affecting serotonin, histamine and acetylcholine pathways and/or mutations affecting receptor recycling, such as dysbindin mutant flies, will be used to investigate the effects of different APs at behavioral, cellular and molecular level.

