Antipsychotics Modulate the Metabolic Proteome of Adipocytes

Bradley Joseph Smith[1], Daniel Martins de Souza[1]

[1.] UNICAMP, Universidade Estadual de Campinas, Instituto de Biologia, Rua Monteiro Lobato, 255, Cidade Universitária, Campinas - SP, 13083-859;

Metabolic dysregulations such as weight gain, high cholesterol, and altered fasting blood glucose are common side effects of antipsychotics, the principal treatment option for psychiatric disorders such as schizophrenia. While a portion of these effects can be attributed to changes in mood, behavior, and homeostasis within the brain, there is evidence that antipsychotics can have direct and deleterious effects on the periphery, including modulations in adipocytes. In this study, human pre-adipocytes (cell line A41) were differentiated into mature white adipocytes before being exposed to 6 antipsychotics with a range of severity of inducing metabolic side effects in patients. These samples were multiplexed (16-plex) with TMTPro, each plex containing all 3 control conditions to maintain intra-injection comparisons, prefractionated into 8 fractions by reversed phase separation, and injected into a Thermo Scientific Orbitrap Eclipse mass spectrometer for analysis. All conditions were executed with technical triplicate, and two passages were utilized as biological pseudoreplicates. A vehicle condition was used as a comparative negative control, and cells that had just finished undergoing maturation induction were collected early as a metabolically active control. Data were processed using Proteome Discoverer v2.5, identifying over 6000 proteins per plex. Filters revealed approximately 4500 quantified proteins per plex, and statistical analyses revealed differentially expressed proteins in each comparison. Distinct dysregulations were seen among different antipsychotics. Pathway and gene ontology overrepresentation analyses revealed few terms, partially in agreement with previous literature, suggesting that post-translationally modified protein activity may have more of an effect on antipsychotic-induced lipid dysregulation than the levels of individual proteins.

Agradecimentos: We would like to thank the laboratory of Dr. Matthew MacDonald of the University of Pittsburgh Medical Center and his students Jordan Gilardi, Akayla Lewin, and Andrew Demarco for their training and assistance with TMTPlex preparation and LC-MS runs. We also thank Dr. Aline Valença, Julia Crisostomo, and Dr. Raissa Ludwig for their assistance in establishing and maintaining the human adipocyte cell line in our laboratory. Finally, we thank Licia Costa for her unwavering support with logistics and overall assistance.