2018 Talent Development Competition Awardees

Title: Effect of antipsychotics on central insulin action in relation to glucose metabolism and cognition in healthy volunteers

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Abstract: Schizophrenia is a severe mental illness that usually begins in the youth. Patients with schizophrenia die 20 years earlier than the general population due to heart disease, adding to the illness burden. Antipsychotics (APs), a prototype of which is olanzapine (OLA), are the mainstay treatment for schizophrenia. However, these medications cause serious metabolism-related side effects, including blood sugar (glucose) problems such as diabetes, and cause reduced sensitivity to the main hormone that regulates glucose, called insulin. This is alarming because patients with schizophrenia already have rates of diabetes that are 3-5 times higher than the general population even without these medications. Therefore, APs can worsen an already difficult situation. However, how APs cause problems in glucose metabolism is largely unknown. APs are also not effective in treating abnormalities related to brain function (cognition) that is a core part of the disability with schizophrenia.The brain is now recognized as having an important role in energy and glucose balance; insulin receptors in the brain are key in regulating glucose production by the liver, and also improving cognition. We have shown in rats that OLA can block the helpful effects of insulin in the brain leading to increased production of glucose by the liver (a main feature of diabetes). In this study, we want to see if OLA can block the beneficial effects of insulin in humans too.To test this, we will give OLA and intranasal insulin to young healthy volunteers, as their age makes them similar to youth with schizophrenia receiving APs for the first time. Glucose metabolism will be measured by a procedure called “pancreatic clamp”. Cognition will be measured by standard tests. We predict that OLA will block the beneficial effects of intranasal insulin on glucose metabolism and cognition. This study would tell us more about how APs cause diabetes, and also why they may not treat cognitive symptoms of schizophrenia.