



RESEARCH SCHOLAR PROGRAM – 2018

SUPERVISOR & PROJECT INFORMATION FORM

Please complete and return, via email only (crems.programs@utoronto.ca) by **November 3rd 2017** (*forms received after this date will not be posted*).

Supervisor Information

Name: Dr. Margaret Hahn

Email: Margaret.Hahn@camh.ca

Degree: MD, PhD, FRCPC; SGS Appointment (IMS, IHPME, LMP etc.): Associate member, Institute of Medical Sciences, University of Toronto

Academic Rank: Assistant Professor of Psychiatry, University of Toronto

Field of Research: Schizophrenia and metabolic health

Research Institution Affiliation (if applicable): Clinician-Scientist and Co-director of the Mental Health and Metabolic Clinic, Schizophrenia Division, Complex Mental illness, CAMH

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): 1 hour

Project Information

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

Description (max 500 words):

Why do this study? 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. 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.

What will we do? In this study, we want to see if OLA can block the beneficial effects of insulin. 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.

This study would tell us more about how APs cause diabetes, and also why they don't treat cognitive symptoms of schizophrenia.

What will be the impact of this study? The effects of APs on central insulin sensing is a very novel area of investigation; the brain was long considered an insulin-insensitive organ, and we are only beginning to learn about insulin's central effects on not only metabolic, but also mental functioning. This proposed work is the first of its kind and unique as it adopts the work already done in healthy rodents, and moves it into humans. This study aims to enhance our understanding of the mechanisms behind a very serious metabolic adverse effect of AP drugs, risk of type-2 diabetes as well as the potential cognitive impact of APs in the context of central insulin stimulation. Thus, this work has the potential to initiate new streams of work in an area of significant unmet need that intercepts disciplines of physiology, endocrinology and psychiatry and may lead to new therapeutic strategies. For example, evidence of AP-induced central insulin resistance, may advise use of targeted central insulin sensitizers, to address the metabolic and possibly cognitive dysfunction at the earliest stages of the illness.

If human subjects are involved, have Ethics been obtained?

YES

NO

Application Submitted (REB comments addressed)

N/A

Do you expect this work will be published within the 20 months?

YES

NO

Uncertain

Student's roles and responsibilities (please be specific)

Please indicate who will serve as the student's direct report (PI, PhD student, technician etc...)

The student will primarily be involved in screening and recruitment of participants and data collection. He/she can gain expertise and experience in the application of a variety of metabolic assessments such as the oral glucose tolerance tests and pancreatic clamps (the gold standard method of measuring glucose metabolism in humans),

and cognitive assessments such as tests investigating working and spatial memory. Depending on the student's interest, he/she can also participate in data analysis, and manuscript preparation. He/she will also have a chance to present these findings at a conference.

The student will report to my postdoctoral fellow who is taking the lead in running the study.

