Notice of the Final Oral Examination
for the Degree of Master of Science

of

CONSTANCE SOBSEY

BA (University of Alberta, 2007)

“Metabolomics of Chronic Stress”

Department of Biochemistry and Microbiology

Wednesday, March 9, 2016
12:00 P.M.
Clearihue Building
Room A202

Supervisory Committee:
Dr. Christoph Borchers, Department of Biochemistry and Microbiology, University of Victoria (Supervisor)
Dr. Caren Helbing, Department of Biochemistry and Microbiology, UVic (Member)
Dr. Scott McIndoe, Department of Chemistry, UVic (Outside Member)

External Examiner:
Dr. Leonard Foster, Biochemistry and Molecular Biology, University of British Columbia

Chair of Oral Examination:
Dr. Rosaline Canessa, Department of Geography, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies
Abstract

The World Health Organization has called stress-related illness “the health epidemic of the 21st century.” While the biochemical pathways associated with the acute stress response are well-characterized, many of the pathways behave differently under conditions of chronic stress. The purpose of this project is to apply high-sensitivity mass spectrometry (MS)-based targeted and untargeted metabolomics approaches to generate new insights into the biochemical processes and pathways associated with the chronic stress response, and potential mechanisms by which chronic stress produces adverse health effects.

Chapter 1 describes the application of a set of targeted and untargeted metabolomics approaches to analyze serum samples from a human epigenetic model of chronic stress in order to identify potential targets for further analysis. To test the resulting hypothesis that oxidative stress is a key feature of chronic stress, a new targeted multiple reaction monitoring (MRM)-MS assay was developed for the accurate quantitation of aldehyde products of lipid peroxidation, as described in Chapter 2. In Chapter 3, the validated method for quantitation of malondialdehyde (MDA) was then applied to mouse plasma samples from a model of chronic social defeat stress to determine whether animals exposed to acute stress show increases in oxidative stress. Mouse plasma samples from this model were also analyzed by untargeted metabolomics using Fourier-transform (FT)-MS to identify other important metabolite features, particularly those that overlap with metabolites identified in the human epigenetic model.

Analysis of metabolomic data from two very different models of chronic stress supports the consistent detection of a metabolomic phenotype for chronic stress that is characterized by the dysregulation of energy metabolism associated with decreased concentrations of diacyl-phospholipids in blood. Increased blood concentrations of fatty acids, carnitines, acylcarnitines, and ether phospholipids were also observed. In addition to metabolites associated with energy metabolism, chronic stress also significantly influenced metabolites associated with amino acid metabolism and cell death. This characteristic pattern of differences in metabolite concentrations was observed in the plasma of mice exposed to chronic social defeat stress, irrespective of whether or not they displayed outward signs of a chronic stress response; in fact, mice that were “resilient” to the behavioural effects of chronic social defeat stress displayed an exaggerated phenotype over mice that showed depressive-like symptoms following chronic stress exposure.

This may suggest that the observed changes in fatty acid composition are protective against stress. However, changes in fatty acid composition are also known to be associated with a wide variety of pathologies including heart disease, neurodegenerative diseases, and mood disorders, so the lipidomic changes associated with chronic stress may also contribute to its health impact. Overall, the results provide further evidence that changes in energy metabolism are a central part of allostatic adaptation to chronic stress.