University of Victoria | Graduate Studies

Notice of the Final Oral Examination
for the Degree of Doctor of Philosophy

of

MOHAMED GHILAN

BSc Hons (University of Victoria, 2010)

"Functional Dysregulation in Stress-Induced Modulation of Synaptic Plasticity in a Mouse Model of Fragile X Syndrome"

Division of Medical Sciences

Thursday April 16, 2015
9:00 A.M.
Hickman Building
Room 120

Supervisory Committee:
Dr. Brian Christie, Division of Medical Sciences, University of Victoria (Supervisor)
Dr. Craig Brown, Division of Medical Sciences, UVic (Member)
Dr. Raad Nashmi, Division of Medical Sciences, UVic (Member)
Dr. Robert Chow, Department of Biology, UVic (Outside Member)
Dr. Michele Martin, Department of Research Services, UVic (Additional Member)

External Examiner:
Dr. Lori McMahon, Department of Neurobiology, University of Alabama at Birmingham

Chair of Oral Examination:
Dr. George Tzanetakis, Department of Computer Science, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

The fragile X mental retardation protein (FMRP) is an important regulator of protein translation, and a lack of FMRP expression leads to a cognitive disorder known as fragile X syndrome (FXS). Clinical symptoms characterizing FXS include learning impairments and heightened anxiety in response to stressful situations. The *Fmr1-/y* mouse has previously been shown to have deficits in context discrimination and novel object recognition tasks, which primarily rely on the dentate gyrus (DG) region of the hippocampal formation, but not in the Morris water maze (MWM) or the elevated plus-maze tasks, which primarily depend on the *Cornu Ammonis* (CA1) region. Furthermore, previous research has demonstrated *N*-methyl-Daspartate receptor (NMDAR)-associated synaptic plasticity impairments in the DG but not in the CA1. However, the impact of acute stress on synaptic plasticity in the *Fmr1-/y* hippocampus has not been examined. The current study sought to extend previous behavioural investigations in the *Fmr1-/y* mouse, as well as examine the impact of stress on activation of the hypothalamicpituitary-adrenal (HPA)-axis and on hippocampal synaptic plasticity. To further characterize hippocampus-dependent behaviour in this mouse model, the DG-dependent metric change spatial processing and CA1-dependent temporal order discrimination tasks were evaluated. The results reported here support previous findings and demonstrate that *Fmr1-/y* mice have performance deficits in the DG-dependent task but not in the CA1-dependent task, suggesting that previously reported subregional differences in NMDAR-associated synaptic plasticity deficits in the hippocampus of the *Fmr1-/y* mouse model may also manifest as selective behavioural deficits in hippocampus-dependent tasks. In addition, following acute stress, mice lacking FMRP showed a faster elevation of the glucocorticoid corticosterone and a more immediate impairment in longterm potentiation (LTP) in the DG. Stress-induced LTP impairments were rescued by administering the glucocorticoid receptor (GR) antagonist RU38486. Administration of RU38486 also enhanced LTP in *Fmr1-/y* mice in the absence of acute stress to wild-type levels, and this enhancement was blocked by application of the NMDAR antagonist 2-amino-5- phosphonopentanoic acid. These results suggest that a loss of FMPR results in enhanced GR signalling that may adversely affect NMDAR dependent synaptic plasticity in the DG. Finally, synaptic plasticity alterations reported in this work were found to be specific to the DG and were unidirectional, i.e., restricted to LTP, as NMDAR- and metabotropic glutamate receptor (mGluR)-LTD were both unaffected by acute stress in the DG or the CA1 regions. This study offers new insights into synaptic plasticity impairments in the *Fmr1-/y* mouse model, and suggests stress and GRs as important contributors to learning and memory deficits in FXS.