University of Victoria | Graduate Studies

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

of

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BA, BSc (Quest University Canada, 2015)

"Determinants of brain region-specific age-related declines in microvascular density in the mouse brain"

Division of Medical Sciences

Tuesday, January 7, 2020
10:00 A.M.
Medical Sciences Building
Room 150

Supervisory Committee:
Dr. Craig Brown, Division of Medical Sciences, University of Victoria (Supervisor)
Dr. Hector Caruncho, Division of Medical Sciences, UVic (Member)
Dr. Raad Nashmi, Department of Biology, UVic (Outside Member)

External Examiner:
Dr. Julian Lum, Department of Biochemistry and Microbiology, UVic

Chair of Oral Examination:
Dr. Marc Lapprand, Department of French, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

It is emerging that the brain's vasculature consists of a highly spatially heterogeneous network; however, information on how various vascular characteristics differ between brain regions is still lacking. Furthermore, aging studies rarely acknowledge regional differences in the changes of vascular features. The density of the capillary bed is one vascular feature that is important for the adequate delivery of nutrients to brain tissue. Additionally, capillary density may influence regional cerebral blood flow, a parameter that has been repeatedly correlated to cognitive-behavioural performance. Age-related decline in capillary density has been widely reported in various animal models, yet important questions remain concerning whether there are regional vulnerabilities and what mechanisms could account for these regional differences, if they exist. Here we used confocal microscopy combined with a fluorescent dye-filling approach to label the vasculature, and subsequently quantified vessel length, tortuosity and diameter in 15 brain regions in young adult and aged mice. Our data indicate that vessel loss was most pronounced in white matter followed by cortical, then subcortical gray matter regions, while some regions (visual cortex, amygdala, insular cortex) showed little decline with aging. Changes in capillary density are determined by a balance of pruning and sprouting events. Previous research showed that capillaries are naturally prone to plugging and prolonged obstructions often lead to vessel pruning without subsequent compensatory vessel sprouting. We therefore hypothesized that regional susceptibilities to plugging could help predict vessel loss. By mapping the distribution of microsphere-induced capillary obstructions, we discovered that regions with a higher density of persistent obstructions were more likely to show vessel loss with aging and vice versa. Although the relationship between obstruction density and vessel loss was strong, it was clear obstruction rates were insufficient to explain vessel loss on their own. For that reason, we subsequently used *in vivo* two-photon microscopy to track microsphere-induced capillary obstructions and vascular network changes over 24 days in two areas of cortex that showed different magnitudes of vessel loss and obstruction densities: visual and retrosplenial cortex. Surprisingly, we did not find evidence for differences in vessel pruning rates between areas, as we would have expected. Instead, we observed brain region-specific differences in recanalization times and rates of angiogenesis. These findings indicate that age related vessel loss is region specific and that regional susceptibilities to capillary plugging and angiogenesis must be considered to explain these differences.