ABSTRACT

Huntington disease (HD) is a progressive disorder characterized by involuntary movements, emotional disturbances, and memory loss. The cardinal neuropathological feature of HD is loss of medium spiny neurons within the striatum. There is currently no cure for HD and the disease is ultimately fatal. Accumulating evidence has implicated excitotoxicity, a process in which excessive signaling via the glutamate receptors results in neurotoxicity, in the selective neuronal loss in HD. The main aim of the studies presented was to evaluate the potential of small molecule therapeutics known to target excitotoxicity-related pathways in the YAC128 transgenic mouse model of HD. Induction of a heat shock protein (HSP) response has been shown to be neuroprotective in acute excitotoxicity models and in models of polyglutamine-induced neurodegenerative disease. We examined whether treatment with arimoclomol, a compound shown to enhance the HSP response by prolonging the activation of heat shock factor 1 (Hsf-1), can improve the phenotype of the YAC128 HD mice. Our findings demonstrate that treatment with arimoclomol does not lead to up-regulation of an HSP response or rescue of the behavioural and striatal deficits in the YAC128 HD mice. We next examined whether treatment with memantine, a clinically well-tolerated NMDA receptor antagonist currently used to treat patients with moderate to severe Alzheimer’s disease, can improve the phenotype of YAC128 HD mice. We demonstrated that treatment with memantine results in improvements in motor function and rescues the striatal deficits in a dose-specific manner. Rasagiline is a selective inhibitor of monoamine oxidase type B (MAO-B) clinically approved for the treatment of Parkinson’s disease that has been shown to protect against a number of neurotoxic stimuli. We demonstrate that treatment with rasagiline protects against striatal lesioning in acute models of excitotoxicity and improves the motor function of the YAC128 HD mice. Finally, we demonstrate that treatment with a combination of memantine and rasagiline yields greater benefit than obtained with either compound alone, providing early and sustained improvements in motor function and rescuing striatal deficits in the YAC128 HD mice. Our findings suggest that targeting excitotoxicity may be a viable therapeutic approach in HD.

BIOGRAPHICAL NOTES

Born: September, 14, 1979, Kuwait
Academic Studies: B. Sc. (Honours) McMaster University, 2001 M. Sc. McMaster University, 2004

GRADUATE STUDIES

Field of Study: Translational research on excitotoxicity as a therapeutic target for Huntington disease

Courses

- MEDG520 Advanced Human Molecular Genetics
- MEDG530 Advanced Human Genetics
- MEDG545 Current Topics in Medical Genetics
- MEDG548 Directed Studies

Instructors

- Dr. A. Brooks-Wilson & Dr. C. Brown
- Dr. J. Friedman
- Dr. W. Robinson
- Dr. M.R. Hayden

AWARDS

2010 Ripples of Hope Award in Biotechnology & Entrepreneurship
2009 Canadian Institutes of Health Research Brain Star Award
2009 CHDI HD Therapeutics Conference Oral Presentation Prize
2008 UBC Medical Genetics Research Day Senior Poster Prize
2007 UBC Medical Genetics Research Day Senior Poster Prize
2004-2008 Canadian Institutes of Health Research Doctoral Research Award
2006-2007 Michael Smith Foundation for Health Research Doctoral Trainee Award
2004-2007 University of British Columbia PhD Tuition Award

SELECTED PUBLICATIONS


Graham RK, Pouladi MA, Joshi P, Lu G, Deng Y, Wu NP, Figueroa BE, Metzler M,


* These authors contributed equally to this work.

SELECTED PRESENTATIONS


SUPERVISORY COMMITTEE

Dr. Michael R. Hayden, Research Supervisor (Medical Genetics)
Dr. Yu Tian Wang (Neuroscience)
Dr. Jon Stoesl (Neuroscience)
Dr. Lorne Clarke (Medical Genetics)