manitoba neuroscience network

How to disrupt excitotoxic cascades in Alzheimer's disease

NEUROSCIENCE GRAND ROUNDS

SPEAKER

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DATE

Friday, May 19th, 2023

9:00 AM - 10:00 AM

LOCATION

Apotex Centre 050

Zoom Meeting ID: 652 1527 2385

Passcode: 642549

BIO

Dr. Jackson joined the Department of Pharmacology & Therapeutics at the University of Manitoba in 2013. His laboratory is located at the PrairieNeuro Research Center in the Kleysen Institute for Advanced Medicine (KIAM). Dr. Jackson obtained his PhD from McGill University in the Department of Pharmacology and completed postdoctoral training at the University of Toronto in the Department of Physiology. Before joining the University of Manitoba, he was a Research Scientist at the Robarts Research Institute and Adjunct Professor in the Department of Physiology and Pharmacology at Western University. A major focus of his research program is to understand how families of Ca2+-permeable channels, contribute to Ca2+ dysregulation, impaired excitatory transmission and synaptic plasticity in Alzheimer's disease. At the cellular and network level, the integration of excitatory synaptic activity forms the basis of human cognitive abilities, including consciousness, perception, thinking, judgment and memory. Whether as a cause or consequence of disease, mental health and neurodegenerative disorders are recognized to be associated with changes in connectivity at the level of individual synapses and neural circuits and are thus increasingly understood to represent connectopathies. Dr. Jackson's research seeks to identify molecular and cellular mechanisms that cause altered neuronal connectivity in disease. A central theme of past and present work is to understand signalling mechanisms initiated in response to aberrant NMDA receptor (NMDAR) activity and establish in turn how these signalling events alter excitatory transmission, synaptic plasticity and metaplasticity.

ABSTRACT

Accumulation of soluble amyloid beta oligomers (AβOs) is closely linked to cognitive decline in Alzheimer's disease (AD). Our research program is focused on identifying molecular mechanisms through which AβOs disrupt the function and plasticity of glutamate excitatory synapses and thus precipitate cognitive decline. AβOs are known to provoke accumulation of glutamate, associated with excitotoxic stimulation of Ca2+ permeable NMDA-type glutamate receptors (NMDARs). Notably, partial block of NMDARs is responsible for the beneficial (though modest) response in patients treated with memantine/Ebixa, a "weak" NMDAR blocker.

As more potent NMDAR blockers are associated with intolerable side effects, our research seeks to identify downstream effectors of NMDAR-initiated excitotoxic cascades. The research presented will highlight our recent and ongoing research focused on identifying signalling cascades recruited as a consequence of NMDAR activation, with emphasis on identifying secondary routes of Ca2+ entry recruited as a consequence of aberrant NMDAR activation. Our research has identified distinct Ca2+ permeable non-selective cation channels, including TRPM2 and Panx1, that are activated in response to NMDAR stimulation. Elucidating cell-specific and context-dependent actions of these channels represents two central themes of our research program.

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