manitoba neuroscience network

Trans-synaptic allosteric modulators of group III mGluRs in glutamatergic signalling and neurological disease

NEUROSCIENCE GRAND ROUNDS

DATE

Friday, February 16th, 2024

9:00 AM - 10:00 AM

LOCATION
Psychiatry Bldg. 2nd Floor Rm PX236/238

SPEAKER

Henry A. Dunn , PhD

Assistant Professor, Department of Pharmacology and Therapeutics, University of Manitoba

BIO

Dr. Henry A. Dunn is an assistant professor in the Department of Pharmacology and Therapeutics at the University of Manitoba, and a principal investigator at St. Boniface Hospital Albrechtsen Research Centre where he leads the Molecular Pharmacology and Neuropsychiatric Disease Lab. Dr. Dunn is best known for his work on G protein-coupled receptors (GPCRs): particularly, delineating molecular mechanisms of stress-induced anxiety and depression, and illuminating a novel trans-synaptic pharmacological regulation mechanism with relevance to attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and epilepsy. These seminal studies have led to a keen interest in the interplay between synaptic adhesion molecules and synaptic GPCRs, including: (1) how these relationships are utilized in synaptic connectivity, neurotransmission and intracellular signalling, and (2) how these interfaces can be exploited for novel drug design in neurodevelopmentaland neuropsychiatric disease.

ABSTRACT

The functional characterization of the GPCR interactome has predominantly focused on intracellular binding partners; however, the recent emergence of transsynaptic GPCR complexes represents an additional dimension to GPCR function that has previously been unaccounted for in drug discovery. Herein, we pioneer a new assay platform facilitating the discovery of ELFN1 as the first trans-syanptic allosteric modulator of a GPCR: critically altering the accepted pharmacological concepts of the pharmaceutical target of ~35% of FDA-approved drugs. Furthermore, we characterize ELFN1 paralog ELFN2 as a novel postsynaptic adhesion molecule with a distinct expression pattern throughout the brain and a selective binding with group III metabotropic glutamate receptors (mGluRs) in trans: homeostatic regulators of excitatory glutamatergic neurotransmission. Using our transcellular GPCR signaling platform, we report that ELFN2 critically alters group III mGluR secondary messenger signaling by directly altering G protein coupling kinetics and efficacy. Loss of ELFN2 in mice results in the selective downregulation of group III mGluRs and dysregulated glutamatergic synaptic transmission. Elfn2 knockout (Elfn2 KO) mice also feature a range of neuropsychiatric manifestations including seizure susceptibility, hyperactivity, and anxiety/compulsivity, which can be rescued by pharmacological augmentation of group III mGluRs. Thus, we conclude that extracellular transsynaptic scaffolding by ELFN2 in the brain is a cardinal organizational feature of group III mGluRs essential for their signaling properties and brain function: with ELFN1/2 exhibiting correlative and pathogenic relevance to neurodevelopmental and neuropsychiatric disease.

Zoom Link: https://us06web.zoom.us/j/83267302150

Meeting ID: 832 6730 2150

Passcode: 748222

OBJECTIVES

1. Introduction to GPCRs as highly viable drug targets within the neurological disease

2. Discovery of novel trans-synaptic regulatory mechanisms in GPCR pharmacology

3. Implications towards new synaptic targets, interfaces, and strategies for neurological disease

Social Media: @GPCRHenry

For more information
T: 204-235-3939
E: info@manitobaneuroscience.ca

Hôpital St-Boniface Hospital
RECHERCHE • RESEARCH
Division of Neurodegenerative Disorders

Health Sciences Centre Winnipeg

University of Manitoba