manitoba neuroscience network


# Reversing nerve damage in neuropathic disease: from the dish to the clinic

SEMINAR & VISITING SPEAKER SERIES

DATE
Friday, April 29, 2022
9:00AM

ZOOM LINK
https://us02web.zoom.us/j/83594461654?pwd=cGR6OW96WTVGSkFXRDE5MGRKaDNXZz09

MEETING ID
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PASSCODE
771772

SPEAKER
## Paul Fernyhough, BSc, PhD

Professor, Department of Pharmacology & Therapeutics, University of Manitoba
Director, Division of Neurodegenerative Disorders, St Boniface Hospital Albrechtsen Research Centre
Co-founder WinSanTor Inc

BIO

Dr. Fernyhough was born and educated in East London, UK, and received his bachelor of science degree in biological sciences at the University of Essex. Dr. Fernyhough performed his PhD in biochemistry in the department of biochemistry at University of Sheffield in the UK. He also performed postdoctoral research at Colorado State University, Kings College London and as a Wellcome Trust Postdoctoral Fellow at St. Bartholomew's Medical College. All of these positions spanned 1985-1998. Dr. Fernyhough subsequently worked for over five years (1998-2004) as a fully tenured lecturer in the School of Biological Sciences (now the Faculty of Life Sciences) at the University of Manchester. Dr. Fernyhough's general research interest is in the cell biology underlying neurodegenerative disorders of the peripheral and central nervous systems.

RESEARCH

Distal dying-back of intraepidermal nerve fibers (IENF) is observed in many diseases including diabetic neuropathy, chemotherapy-induced peripheral neuropathy (CIPN), Friedreich ataxia, Charcot-Marie-Tooth disease type 2 and human immunodeficiency virus (HIV)-associated neuropathy. The impact on human health is significant and rising. For example, in Canada 50% of diabetic patients exhibit neuropathy and direct costs for neurological complications are estimated at CA$1-2 bn per annum over the next 10 yrs.

There are no therapies for any of these neuropathies. Our recent studies have revealed a novel therapeutic target for preventing and even reversing diabetes-induced IENF loss. We have found that cholinergic mechanisms endogenous to the skin regulate sensory axonal plasticity, defined as the capacity of sensory axons to sprout and innervate new targets in skin. We have formulated the cholinergic constraint hypothesis, in which acetylcholine acts to suppress axonal plasticity of IENFs (see Calcutt et al, JCI 2017).

During this seminar I will provide an update on pathways utilized by antimuscarinic drugs, selective or specific for the muscarinic acetylcholine type 1 receptor (M1R), to enhance mitochondrial function. The focus will be novel modulation of intracellular calcium homeostasis by M1R blockade in cultured adult sensory neurons. The mechanistic role of AMP-activated protein kinase (AMPK) as a downstream regulator of mitochondrial function will be presented. In addition, I will present novel studies identifying antimuscarinic drugs, such as pirenzepine and muscarinic toxin 7 (MT7), as biased agonists at the M1R. Through this route these drugs activate extracellular signal-regulated kinase (ERK) to elevate neurite outgrowth. Finally, I will provide an update on a recent phase 2 clinical trial completed in Canada using a topical formulation of pirenzepine to treat persons with type 2 diabetes and exhibiting mild-moderate peripheral neuropathy.

OBJECTIVES

1. Mechanisms utilized by antimuscarinic drugs to augment mitochondrial function and drive nerve growth.

2. Molecular pharmacology studies delineating novel antimuscarinic drug action at the muscarinic acetylcholine type 1 receptor.

3. Translation of nerve repair properties of antimuscarinic drugs to human disease: report on phase 2 clinical trial in diabetic neuropathy using a topical antimuscarinic drug formulation.

For more information:

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