Cell Calcium 56 (2014) 362–371

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Review

# Calcium signalling in sensory neurones and peripheral glia in the context of diabetic neuropathies

Alexei Verkhratsky[a,b,c,d,*], Paul Fernyhough[e,f,**]

[a] Faculty of Life Sciences, The University of Manchester, Manchester M13 9PT, UK
[b] Achucarro Center for Neuroscience, IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain
[c] University of Nizhny Novgorod, Nizhny Novgorod 603022, Russia
[d] Kazan Federal University, Kazan 420111, Russia
[e] Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, Manitoba, Canada R3E 0T6
[f] Division of Neurodegenerative Disorders, St Boniface Research Centre, Winnipeg, Manitoba, Canada R2H 2A6

ARTICLE INFO

*Article history:*
Available online 1 August 2014

*Keywords:*
Calcium
Diabetes
Diabetic neuropathies
Hyperglycaemia
Insulin
Mitochondria
Neuropathy
Pain
Peripheral nervous system
Satellite glia
Schwann cells
Sensory neurones

ABSTRACT

Peripheral sensory nervous system is comprised of neurones with their axons and neuroglia that includes satellite glial cells in sensory ganglia, myelinating, non-myelinating and perisynaptic Schwann cells. Pathogenesis of peripheral diabetic polyneuropathies is associated with aberrant function of both neurones and glia. Deregulated $Ca^{2+}$ homoeostasis and aberrant $Ca^{2+}$ signalling in neuronal and glial elements contributes to many forms of neuropathology and is fundamental to neurodegenerative diseases. In diabetes both neurones and glia experience metabolic stress and mitochondrial dysfunction which lead to deregulation of $Ca^{2+}$ homeostasis and $Ca^{2+}$ signalling, which in their turn lead to pathological cellular reactions contributing to development of diabetic neuropathies. Molecular cascades responsible for $Ca^{2+}$ homeostasis and signalling, therefore, can be regarded as potential therapeutic targets.



## 1. Calcium signalling and its deregulation in neuropathology

Calcium signalling is fundamental for information processing in the CNS. Highly localised $Ca^{2+}$ signals regulate neurotransmitter release and synaptic plasticity, whereas global $Ca^{2+}$ signals as intracellular $Ca^{2+}$ waves link excitation with energy production (through mitochondrial $Ca^{2+}$ signalling) and gene expression (through numerous $Ca^{2+}$-dependent transcriptional pathways). In neuroglial cells, which can be defined as principal homeostatic cells of the nervous system, $Ca^{2+}$ signals provide the substrate for excitability and are involved in local and long-range signalling, the latter being mediated by $Ca^{2+}$ waves propagating through the glial syncytium.

Molecular cascades that regulate $Ca^{2+}$ movements between cellular compartments and between cells and the environment have primarily evolved to maintain $Ca^{2+}$ homeostasis, which keeps the concentration of free $Ca^{2+}$ steady and distinct in different cell compartments. The concentration gradients created by active transport underlie signalling function, because regulated changes in permeability of plasmalemma or endomembranes result in $Ca^{2+}$ fluxes that rapidly change free $Ca^{2+}$ concentration; these changes in $[Ca^{2+}]$ are decoded by numerous $Ca^{2+}$-sensitive enzymes that act as sensors that trigger or discontinue cellular physiological responses. Molecular cascades of $Ca^{2+}$ homeostasis and signalling, which include $Ca^{2+}$ channels (that mediate transmembrane $Ca^{2+}$ diffusion), $Ca^{2+}$ exchangers, ATP-dependent $Ca^{2+}$ transporters and

* Corresponding author at: Faculty of Life Sciences, The University of Manchester, 1.124 Stopford Building, Oxford Road, Manchester M13 9PT, UK.
Tel.: +44 161 2755414.
** Corresponding author at: Division of Neurodegenerative Disorders, St Boniface Research Centre, Winnipeg, Manitoba, Canada R2H 2A6.
*E-mail addresses:* alexej.verkhratsky@manchester.ac.uk (A. Verkhratsky), PFernyhough@sbrc.ca (P. Fernyhough).

http://dx.doi.org/10.1016/j.ceca.2014.07.005
0143-4160/