DIABETIC NEUROPATHY

Background

Diabetic painful neuropathy affects over 40% of adult diabetic patients. The pathology has been associated with a number of modifiable and non-modifiable risk factors, including the degree of hyperglycemia, lipid and blood pressure indexes, diabetes duration, and height. Diabetic neuropathy affects all peripheral nerves including pain fibers, motor neurons and the autonomic nervous system. With the exception of tight glucose control, there are no specific treatments for diabetic neuropathy, and current therapeutical strategies are rather aimed at reducing pain and other symptoms (Options for pain control include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), antiepileptic drugs (AEDs), etc.)

Pathology Model

Primary cultures of DRG neurons, harvested from normal Sprague Dawley rats, will be cultured in presence of high concentration of glucose (e.g. 60mM) in order to recreate diabetic condition in vitro.

Increasing evidence indicates that one of the major causes of diabetic peripheral neuropathy is an over-production of reactive oxygen species which leads to oxidative stress, mitochondrial dysfunction, neuronal damage and finally apoptosis.

Neurons isolated from dorsal root ganglia (DRG) of mammals such as rodents and hamsters rendered diabetic by treatment with drugs such as streptozotocin and alloxan have been used for study of diabetic neuropathy.. Primary culture of DRG neurons from normal untreated rodents are now the preferred in vitro model given they mimic events occurring in vivo and permit detailed molecular analysis. Furthermore the use of primary cultures of DRG neurons has been adopted to obtain conspicuous data relative to changes in morphology such as reduction in neurite extension, changes in the activity of enzymes involved in the tricarboxylic acid cycle, electron transport chain, antioxidant systems and molecular events involved in mitochondrial dysfunction leading to apoptosis. DRG primary cultures are also convenient systems to trace the time kinetics of the molecular events occurring during cell death, due to oxidative stress. Most of these events have been shown to peak between 1-3 h after treatment with glucose due to sudden increase in ROS and associated stress. These observations concur with in vivo studies.

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Readouts

The following assays will be performed:

- Cytoskeletal disruption
- Morphological Analysis- structural test in high content automated microscopy
- Functional analysis - functional test on neuronal network electrophysiological activity (MEA system**)**