Overexpression of uncoupling proteins in cultured DRG neurons significantly decreases both basal and hyperglycemia induced reactive oxygen species formation and prevents glucose-induced neuronal death. Oxidative stress in the mitochondria critically aters energy regulation and survival through three mechanisms. First, physiological levels of nitric oxide (NO) reversibly compete with molecular oxygen for binding to cytochrome C oxidase, producing reversible inhibition and acting as a regulatory switch for electron transfer, in contrast, in the presence of superoxide anion, NO is converted to peroxynitrite (ONOO-) which competes with molecular oxygen for irreversible binding to cytochrome C oxidase. Thus, peroxynitrite affects mitochondrial function and inhibits ATP synthesis. Second, mitochondrial oxidative stress through excess superoxide anion and peroxynitrite production inhibits the import of essential proteins to the mitochondria that are in turn degraded in the cytosol. Thirdly, oxidative damage of existing inner membrane proteins induces membrane permeability transition, a permeabilization of the mitochondrial inner membrane that precedes cytochrome c release and apoptosis. The inner membrane permeabilization caused by membrane permeability transition results in loss of matrix components, impairment of mitochondrial functionality, and substantial swelling of the organelle, with consequent outer membrane rupture and cytochrome c release. Mitochondria in the DRG are especially vulnerable, because in the hyperglycaemia neuron they are the origin of production of reactive oxygen species, which can damage their DNA membranes, deregulation of fission and fusion proteins that control mitochondrial shape and number can impair cell functions and might leads to degeneration and neuronal injury may be the greatest contributor to DN.

Because glucose enters neurons via facilitated concentration dependent transport, neurons are more susceptible to glucose flux and subsequent increased oxidative stress.