Are mitochondria the key to reduce the age-dependent decline in axon growth after spinal injury?

Theresa C. Sutherland, Cédric G. Geoffroy

Mitochondria are essential for the maintenance of normal cellular function and energy production, which are critical for axonal growth and regeneration. In aging neurons, mitochondrial dysfunction is exacerbated, resulting in decreased axon growth and regeneration potential. This decline can be attributed to several factors, including increased reactive oxygen species (ROS) production, altered Ca2+ homeostasis, and disrupted mitochondrial dynamics. These alterations can be exacerbated by age-related decline in mitochondrial activity and bioenergetics, which limits the ability of neurons to efficiently produce energy to support axonal growth and regeneration.

In young neurons, mitochondria are essential for promoting axonal growth and regeneration, as they provide the necessary energy and bioenergetic support required for axonal transport. However, in aging neurons, mitochondrial dysfunction leads to decreased bioenergetics, altered Ca2+ homeostasis, and oxidative stress, all of which contribute to the age-related decline in axon growth potential.

The increased oxidative stress observed in the aging environment can worsen injury outcomes, as it can worsen axon growth and also contribute to increases in oxidative stress. The increased oxidative stress observed in the aging environment is also seen, more subtly in the normal aging CNS, once again leading to an additive effect when age and injury meet.

Axonal trafficking is essential for growth, shutting necessary supplies to the extending axon, including organelles, cytoskeletal proteins, and other necessary components. Mitochondria are essential for the energy requirements of neurons, and especially projecting motor neurons with extremely long axons, presents unique challenges for energy homeostasis and distribution. Mitochondrial bioenergetics is particularly in demand at the growth cones of axons and in synapses, requiring efficient mitochondrial trafficking and axonal transport to these areas (Sheng, 2017). Axonal growth has been seen to decline with age (Figure 1A). In aged peripheral nervous system, the reduced speed of axon growth has been correlated with a diminished rate of axonal transport. There is an age-related decline in mitochondrial transport, both in the peripheral nervous system, the reduced speed of axon growth in aging neurons. One of these factors is mitochondria dysfunction. The mitochondrial theory of aging suggests that the main mechanism involves mitochondrial dysfunction and oxidative stress, which can play a critical role in regulating age-related decline in axon growth potential.

The very active oxygen metabolism and high lipid content of the CNS leaves it particularly vulnerable to oxidative stress and subsequent subcellular damages, such as mitochondrial dysfunction (Jia et al., 2012). The effects of oxidative stress and neuronal excitotoxicity after injury are wide reaching and seen in a range of cells, especially the supporting glia. Increased ROS has been associated with pro-inflammatory microglia and reactive astrocytes involved in the detrimental progression of the SCI lesion (Sutherland and Geoffroy, 2020). The increased oxidative stress and SCI, is coupled with a decrease in antioxidant capacity with aging to create a greater vulnerability to oxidative stress and damage in aged individuals (Geoffroy, 2020). To date there have been several clinical and pre-clinical trials of different anti-oxidant therapies for SCI (Rabchevsky et al., 2020), however, the potential for these has received little attention. Observations from our own research suggest that mitochondria in both aging cortical neurons and astrocytes, in dissociated conditions, exhibit an increased stress and dysfunctional state. This is likely to impair the ability of these mitochondria to efficiently produce the necessary energy and also contribute to increases in oxidative stress. The increased oxidative stress observed in the injury environment is also seen, more subtly in the normal aging CNS, once again leading to an additive effect when age and injury meet.
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axon growth
cortical neurons pharmacologically enhancing mitochondrial Our pilot experiments indeed demonstrate that strategy to improve neuroprotection after SCI, mitochondria may result in decreased transport of essential molecules into the matrix and impaired protein turn-over. (D) Calcium buffering and the mitochondrial permeability transition pore (mPTP) with increased ROS and an oxidative stress state the mPTP in aged mitochondria is more active and shows prolonged opening, effecting calcium buffering ability and contributing to mitochondrial membrane depolarization. All of these elements are detrimental to neuronal health and may contribute to the age-dependent decline in axon growth potential. ADP: Adenosine diphosphate; ATP: adenosine triphosphate; C: cytoplasm; CI-CV: OXPHOS complex 1–5; Δφ: membrane potential; IM: inner membrane; IMS: inter-membrane space; M: mitochondrial matrix; mPTP: mitochondrial permeability transition pore; OM: outer membrane; ROS: reactive oxygen species; TIM: translocate inner membrane; TOM: translocase outer membrane.

permeability transition pore, Ca\(^{2+}\) signaling and transmembrane channels, as well as antioxidant strategies (Mccwne et al., 2011; Rabchevsky et al., 2020). ‘MitoCeuticals’ may be an effective strategy to improve neuroprotection after SCI, as well as potentially promote axon growth. Our pilot experiments indeed demonstrate that pharmacologically enhancing mitochondrial biogenesis increases neurite outgrowth of adult cortical neurons in vitro. To our knowledge, enhancing mitochondrial biogenesis to stimulate axon growth in vivo in a more chronic injury phase and in older animals has not been attempted to date.

An interesting idea in recent years is the transplantation of mitochondria as a therapeutic agent. There is evidence that transplantation of autologous mitochondria, either directly or systemically, is beneficial in a variety of models such as neurodegeneration and cardiac ischemia. The transplantation of mitochondria in SCI is based on the emerging idea that mitochondria released from cells after CNS injury may transfer between cells to assist in oxidative phosphorylation. It is postulated that transplanted mitochondria supplement endogenous antioxidant systems allowing for increased Ca\(^{2+}\) buffering and greater energy production (Rabchevsky et al., 2020). One particularly interesting proposition arising from this may be to transplant mitochondria from young mice into aging mice to promote mitochondrial bioenergetics and improve axon growth. These therapeutic strategies may be promising but have yet to be explored in SCI in an aging paradigm.

It is clear that mitochondria play important role in normal aging, in both axon regeneration and sprouting, and in the progression of SCI. We contend that alterations in mitochondrial functioning and bioenergetics with age is detrimental to axon growth potential, and will compound the mitochondrial disfunctions occurring after a SCI. Conversely, this also makes them an interesting target for potential therapeutic manipulation to improve SCI outcomes, regardless of the age of the patient. The promotion of mitochondrial function may be a key element to promote axon growth in injured neurons, regardless of age or time post injury, a contention that we will be assessing in the context of SCI. However, to effectively harness mitochondria as a therapeutic target in the wider SCI population we must more fully understand what impact both age and injury has on mitochondrial function, and how this will correlate to axon growth.

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Amit Mitochondria in aging neurons show decline from their young counterparts in a range of functional areas. (A) Antioxidant homeostasis: aged mitochondria produce excessive reactive oxygen species and show decreased antioxidant capability, leading to oxidative stress. (B) Bioenergetics: aged mitochondria exhibit decreased ability to efficiently and effectively meet the high energy demand of the cell especially in the growing axon. (C) Transmembrane transport: decreased expression and/or function of transmembrane transport channels in aged mitochondria may result in decreased transport of essential molecules into the matrix and impaired protein turn-over. (D) Calcium buffering and the mitochondrial permeability transition pore (mPTP) with increased ROS and an oxidative stress state the mPTP in aged mitochondria is more active and shows prolonged opening, effecting calcium buffering ability and contributing to mitochondrial membrane depolarization. All of these elements are detrimental to neuronal health and may contribute to the age-dependent decline in axon growth potential. ADP: Adenosine diphosphate; ATP: adenosine triphosphate; C: cytoplasm; CI-CV: OXPHOS complex 1–5; Δφ: membrane potential; IM: inner membrane; IMS: inter-membrane space; M: mitochondrial matrix; mPTP: mitochondrial permeability transition pore; OM: outer membrane; ROS: reactive oxygen species; TIM: translocate inner membrane; TOM: translocase outer membrane.

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Theresa C. Sutherland, Cédric G. Geoffroy Department of Neuroscience and Experimental Therapeutics, Texas A&M Health Science Center, Bryan, TX, USA.

*Correspondence to: Cédric G. Geoffroy, PhD, geoffroy@tamu.edu.

https://orcid.org/0000-0002-7671-147X (Cédric G. Geoffroy) https://orcid.org/0000-0002-2919-1504 (Theresa C. Sutherland)

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