Proposed Mechanisms of Photobiomodulation (PBM) Mediated via the Stimulation of Mitochondrial Activity in Peripheral Nerve Injuries

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Evidence shows that nerve injury triggers mitochondrial dysfunction during axonal degeneration. Mitochondria play a pivotal role in axonal regeneration. Therefore, normalizing mitochondrial energy metabolism may represent an elective therapeutic strategy contributing to nerve recovery after damage. Photobiomodulation (PBM) induces a photobiological effect by stimulating mitochondrial activity. An increasing body of evidence demonstrates that PBM improves ATP generation and modulates many of the secondary mediators [reactive oxygen species (ROS), nitric oxide (NO), cyclic adenosine monophosphate (cAMP), and calcium ions (Ca^{2+})], which in turn activate multiple pathways involved in axonal regeneration.

Key words

Axon regeneration; Mitochondria; Photobiomodulation; Peripheral nervous system

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INTRODUCTION

Mitochondria are dynamic organelles playing a pivotal role in energy generation, signal transmission, and calcium homeostasis essential for neurons due to their high energy consumption.¹ Most axonal mitochondria are stationary and exhibit a linearly interspersed distribution in stationary state.² Axonal regeneration in the peripheral nervous system (PNS) initiates a vigorous regenerative response via permissive Schwann cell environment and results in the formation of a new growth cone. During axonal regeneration, mitochondria are transported to the proximal segment of injured axons, which require large energy for regeneration.^{3,4} This process consumes a large amount of energy and molecules, and therefore altered mitochondrial behavior may represent one of the key intrinsic mechanisms for peripheral nerve regeneration.

Photobiomodulation (PBM) entails absorption of non-ionizing optical radiation in the visible and near-infrared spectral range by endogenous chromophores to elicit photo-physical and photo-chemical events at various biological scales.^{5,6} Mitochondria contain chromophores for the absorption of photons during PBM. In this review, we summarize the behavior of mitochondria and elucidate their role in axonal degeneration following peripheral nerve injury. We also describe the therapeutic mechanism of PBM based on these effects.

MITOCHONDRIAL BEHAVIOR FOLLOWING PERIPHERAL NERVE INJURY

In contrast to the central nervous system, the peripheral nerve system exhibits a high regenerative capacity. Injury to the peripheral nerve triggers Wallerian degeneration of the distal axon to create a microenvironment conducive for axonal regrowth and reinnervation, while the proximal axons regenerate growth cones that drive axon elongation.⁷

Axonal degeneration is intimately associated with mitochondrial dysfunction, including decreased adenosine triphosphate (ATP) synthesis, increased generation of reactive oxygen species (ROS), disequilibrium of mitochondrial fission and fusion, impaired axonal mitochondrial transport, and aberrant mitophagy.⁸⁻¹² Under normal physiological conditions in neurons, the principal role of mitochondria is ATP production via oxidative phosphorylation using the respiratory machinery, composed of four respiratory complexes and the F1FO ATP synthase complexes.¹³ The energy needs of the nervous system are enormous, primarily to restore the ionic balance after the

generation and transmission of nerve impulses through the activity of the Na⁺/K⁺ ATPase, an ATP-dependent pump.¹⁴ Several studies reported that nerve injuries increase the oxygen consumption without increasing ATP production.¹⁵ This ATP dissipation phenomenon may depend on mitochondrial uncoupling (any pathway that enables proton re-entry into the matrix independent of ATP production) or F-ATP synthase uncoupling (any condition that inhibits the coupling between the F1 catalytic activities and the proton translocation by FO).^{16,17} Thus, the reduced levels of ATP following nerve injury can reduce the Na⁺/K⁺ ATPase activity, and interfere with restoration of the ionic equilibrium by neurons. Mitochondria also play a role in the production and detoxification of ROS.¹⁸⁻²⁰ Mitochondrial dysfunction leads to increased ROS either by the organelle itself or indirectly by the endoplasmic reticulum (ER).^{20,21} This oxidative stress is exacerbated by the inflammation associated with neuronal damage, creating a vicious circle.²² Oxidative stress damages the inner mitochondrial membrane housing oxidative phosphorylation (OXPHOS) machinery,²³ which in turn reduces aerobic ATP production, and thereby induces a metabolic switch to anaerobic glycolysis to restore the intracellular levels of ATP.^{15,24} High ROS levels trigger a vicious circle of ROS-stimulated glucose uptake and glucose-stimulated ROS production.²⁴ Since mitochondria play a pivotal role, together with the ER, in the maintenance of cytosolic Ca²⁺ levels,^{25,26} the altered mitochondrial metabolism leads to cytosolic Ca²⁺ imbalance.

Several studies reported that multiple proteins are inhibited or activated in response to injury during axonal degeneration. Active degeneration requires Sterile alpha and TIR motif containing 1 (SARM1) and mitogen-activated protein kinase (MAPK) including dual leucine zipper kinase (DLK), while the nicotinamide mononucleotide adenylyl transferase (NMNAT) attenuates Wallerian degeneration. NMNAT, a key enzyme mediating nicotinamide adenine dinucleotide (NAD⁺) synthesis, is well known for its neuroprotective function mediated via modification of mitochondrial function.²⁷⁻³⁰ The activity of endogenous NMNAT is greatly inhibited by defective mitochondrial structure and function, which decreases mitochondrial transport, and ROS accumulation following axonal injury.^{27,31-33} Together with increased intra-axonal Ca²⁺ levels, the rapid decrease in NAD-biosynthetic enzyme NMNAT activates SARM1, which triggers Wallerian degeneration.³⁴⁻³⁸ SARM1 triggers NAD⁺ depletion and activates mitogen activated protein kinase (MAPK) signaling.^{39,40} The DLK (or MAP3K), an axonal integrity sensor, interacts with NMNAT and activated SARM1.^{36,37,41,42} SARM1-

MAPK pathway disrupts axonal energy homeostasis by reducing ATP production before physical breakdown of damaged axons.³⁶ Decreased NAD⁺ synthesis reduces energy generation and ATP levels, causing defects in Na⁺/Ca²⁺ exchangers and Ca²⁺ channels, and the loss of mitochondrial membrane potential (MMP).^{39,43} Thus collectively, these proteins damage axonal integrity.

Mitochondria are essential for axon regeneration. Increased mitochondrial density effectively promotes axonal regeneration.^{1,44} Increasing mitochondrial density at the proximal segment of injured axons is achieved, mainly by increasing mitochondrial transport and mitochondrial fission. *In vivo* studies indicate that enhanced mitochondrial transport and early mitochondrial fission after axon damage accelerates axonal regeneration.^{1,45,46} Mitochondria not only supply the structural components of cells during axonal transport, but also provide appropriate levels of ATP to the growth cone of regenerating axons.^{47,48} In an *in vitro* study of sciatic nerve injury, the axon cyclin-dependent kinase 5 (CDK5) levels were increased after nerve injury and translocated into the mitochondrial membrane of regenerating axons.⁴⁹ Mitochondrial CDK5 phosphorylates mitochondrial signal transducer and activator of transcription 3 (STAT3), thereby increasing mitochondrial membrane potential. By interacting with electron transport chain proteins, STAT3 regulates ROS production and cytochrome c release, and contributes to ATP energy supply for axonal regeneration.⁵⁰

Therefore, approaches to stimulate mitochondrial activity may provide an effective therapeutic strategy to enhance axonal regeneration in the injured peripheral nerve.

PBM STIMULATES MITOCHONDRIAL ACTIVITY

Mitochondria in the injured axon play a pivotal role in axonal degeneration and regeneration. Increased mitochondrial transport facilitates the replacement of damaged mitochondria by healthy ones to provide adequate ATP energy for axonal regeneration. PBM exerts a photobiological effect via stimulation of cytochrome c oxidase (CCO) located in the cytochrome of the mitochondrial respiratory chain complex IV. It has been hypothesized that PBM enhances the activity of CCO and subsequently improves the generation of ATP.⁵¹ Photo-dissociation of nitric oxide (NO) from CCO leads to the gain of an electron from each of the four cytochrome C molecules by CCO, which then transfers four protons to a single oxygen to form two molecules of water. This process contributes to the formation of the proton gradient, which drives the

activity of ATP synthase. CCO activation by PBM enhances the synthesis of ATP and consequent modulation of ROS production, NO release and Ca²⁺ homeostasis.⁵²⁻⁵⁴

Extracellular ATP induces Ca²⁺ influx by binding to P2X receptors, which are membrane ion channels selectively permeable to Na⁺, K⁺ and Ca²⁺. Binding of the ATP to P2Y receptors, which are G-protein-coupled receptors, triggers the release of Ca²⁺ from the ER via inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) pathway.⁵⁵ Thus, the increased ATP synthesis due to CCO stimulation by PBM induces Ca²⁺ influx together with the ER. Also, PBM increases the level of cyclic adenosine monophosphate (cAMP) synthesized from ATP by adenylate cyclase.^{56,57}

PBM is known to activate multiple pathways such as MAPK/extracellular signal-regulated kinase (ERK) pathway, or phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway,^{58,59} in various molecular networks in the cellular system. Ca²⁺ influx and increase in intracellular Ca²⁺ activate MAPK/ERK or PI3K/AKT via calmodulin.⁶⁰ The second messenger cAMP activates MAPK/ERK pathways⁶¹ and ROS signaling leads to the activation of PI3K/AKT pathway.⁶² ERK/MAPK and PI3K/AKT signal channels are known to regulate cell survival, growth, and proliferation, and possibly play an important role in regeneration after nerve injury.⁶³⁻⁶⁵ Genetic elevation of Ca²⁺ or cAMP accelerates the formation of a growth cone from the injured axon, facilitates apparent fusion of axonal fragments, and promotes branching to postsynaptic targets.⁶⁶ Thus, PBM stimulates mitochondrial activity, and subsequently promotes regeneration of peripheral nerve after injury. For example, studies reported that PBM promotes axonal regeneration of crushed facial nerves by up-regulating the PI3K/AKT signaling pathways,⁵⁹ and restores Na, K-ATPase disrupted in response to ouabain via MAPK/ERK pathway.⁶⁷ These findings suggest that PBM directly or indirectly supports injured nerve recovery via mitochondrial bioenergetics. Nevertheless, further studies are still needed to elucidate the mechanism of PBM in axonal degeneration and regeneration by stimulating mitochondrial activity.

DISCUSSION

Understanding the mechanisms regulating axonal degeneration and regeneration is crucial for developing treatments for nerve injury. Mitochondrial dysfunction in the injured axon plays a pivotal role in initiation of axonal degeneration and inhibition of axonal regeneration.⁸⁻¹² Thus, the present knowledge of mitochondrial dysfunction

tion following peripheral nerve injury may facilitate therapeutic interventions to aid axonal regeneration. Despite the elusive underlying mechanism, mitochondrial dysfunction not only causes ATP production and oxidative stress but also activates multiple proteins that damage axonal integrity.²⁷⁻³² In contrast, enhancing mitochondrial function is an important intrinsic mechanism of axonal regeneration.^{1,44-46} Accumulating evidence demonstrates that axonal regeneration requires adequate energy production and mitochondrial transport to the growth cone of regenerating axons. Therefore, treatment strategies that directly target mitochondria will enable axonal regeneration by mitigating local ROS production or restoring Ca^{2+} homeostasis.

In the last decade, PBM has been introduced as a non-invasive treatment to enhance the recovery from peripheral nerve injury based on the leading hypothesis of the mechanism that the photons dissociate inhibitory NO from the CCO, resulting in increased electron transport, MMP and ATP production. Stimulation of mitochondrial activity activates numerous signaling pathways via ROS, cAMP, NO and Ca^{2+} , leading to the activation of MAPK/ERK or PI3K/AKT pathways.^{46,52,53,63} These signaling pathways lead to axonal regeneration. Despite the effectiveness of the PBM mechanism in mitochondria, several molecules and substrates participate in the mitochondrial dynamics to facilitate axonal regeneration. Further studies are needed to fill the gap between axonal regeneration and mechanisms underlying PBM. Further, the switch to human studies is not easy, due to the complexity of different wavelengths with unpredictable depth of penetration to the injured nerve through tissues of different type and thickness.

CONFLICT OF INTEREST

Ji Eun Choi is an editorial board member of the journal but was not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

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