NASCIC
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ADVOCACY COURSE

Module 6 – Neuroprotection

Mitochondrial Therapies

Mitochondria are tiny, complex organelles, or mini-organs, found inside almost all our cells. Their primary function is to produce the cell's major source of energy, a molecule called "ATP."

Free radicals are a byproduct of ATP synthesis. Therefore, healthy mitochondria must engage in a balancing act that maximizes the synthesis of ATP while limiting radical production to just the right amount.

After an SCI, mitochondria that are damaged or dysfunctional produce an excessive amount of free radicals and release other substances that cause additional damage to neurons and other cells. To develop ways to repair or replace damaged mitochondria, researchers first had to determine how healthy mitochondria work, as well as how they become damaged following an SCI.

These researchers have shown that the physical structure of mitochondria helps them balance ATP synthesis and free radical production by separating positively and negatively charged molecules in compartments contained within two membranes: a smooth, round outer membrane, and a wrinkled inner membrane.

The region in between the two membranes, called the "intermembrane space," stores high amounts of positively charged hydrogen ions. The space inside the inner membrane, called the "matrix," stores high amounts of negatively charged molecules.

When the balance between positive and negative charges is properly maintained, hydrogen passes through the inner membrane to creates a sufficient amount of ATP without producing too many radicals.

After an SCI, the amounts of positive and negative charges stored in the mitochondrial compartments are disrupted, which activates coping mechanisms that help mitochondria restore balance, but also can damage mitochondria further if they are over-activated. Theses coping mechanisms may be targets for neuroprotection therapies.

One of the coping mechanisms is called "uncoupling proteins." Uncoupling proteins work to relieve the build-up of too much charge in the intermembrane space. In mitochondria that are damaged or dysfunctional, too much charge accumulates in the intermembrane space, which results in uncreased production of free radicals.

Uncoupling proteins create pores in the mitochondria's inner membrane that allow hydrogen ions to pass through without producing ATP. Allowing hydrogen ions to pass through the membrane in this way reduces the charge in the intermembrane space and avoids producing additional radicals. But it also means the hydrogen is no longer available to produce ATP, which can compromise the cell in other ways, especially after an injury, when cells need even more energy than usual for the healing process.

Another coping mechanism is called the mitochondrial permeability transition pore, or mPTP for short. Following an SCI, excess calcium is shuttled into the mitochondrial matrix to keep the calcium from over-activating processes that damage cells and tissues.

Because calcium has two positive charges, and the matrix is where mitochondria store negative charge, the entry of calcium upsets the required balance between the positive charge in the intermembrane space and the negative charge in the matrix. This is called "depolarization."

Depolarization causes mPTPs to open, creating a pore that allows contents of the mitochondria to exit and contents of the cell to enter until the balance of charges is restored. But if mPTPs are open for a sustained period, then water entering the mitochondria causes them to swell and rupture, generating both oxygen radicals and proteins that break down other proteins and lead to cell death.

This understanding of how mitochondria respond to injury and compensate for damage has led to several research questions that are being studied to protect neurons and other cells from secondary damage after an SCI:

- Can blocking the formation of mPTPs prevent mitochondria from bursting and releasing damaging calcium stores and radicals?
- Can we increase the body's natural production of uncoupling proteins to reduce free radical production without affecting ATP production, or develop drug candidates that mimic the function of uncoupling proteins?
- Can we safely stimulate the clearance of dysfunctional mitochondria to prevent them from causing further damage?
- Can we stimulate the body to produce new mitochondria to supply the amounts of ATP necessary to support healing and damage repair?
- Or, can we transplant healthy mitochondria from undamaged tissue into the injured area?