



MITOCHONDRIAL TOXICITY

WHAT ARE MITOCHONDRIA?

Mitochondria (my-toe-con'-dree-a) are small "organs" in our cells. They are the cell's power plant. They use oxygen, fat and sugar to produce adenosine triphosphate (ATP). This process is called "cellular respiration." When the cell needs energy, it breaks down molecules of ATP to release the stored energy.

The more energy the cell needs, the more mitochondria it contains. One cell can have anywhere from a few mitochondria up to thousands. The highest numbers are found in nerve, muscle, and liver cells.

Some scientists believe that mitochondria are the key to aging. As we grow older, our mitochondria collect more and more mutations. Our cells have a way to check for mistakes (mutations) when they multiply, but mitochondria don't.

WHAT IS MITOCHONDRIAL TOXICITY?

Mitochondrial toxicity (MT) is damage that decreases the number of mitochondria. If there are too few mitochondria in a cell, it might stop working properly. It's not clear how much loss of mitochondria can occur before there is loss of cell function.

WHAT ARE THE SIGNS OF MT?

One of the most common signs of MT is muscle weakness (myopathy). If muscle cells can't get enough energy through cellular respiration, they have to get energy without oxygen. This "anaerobic" energy production creates lactic acid as a waste product.

Lactic acid can cause sore muscles. For example, the soreness people feel

after running a marathon is caused by a buildup of lactic acid.

Some people with MT have very high levels of lactic acid in their blood. This rare condition is called lactic acidosis. There is a blood test for lactic acid levels, but experts disagree on how to interpret the results. Physical exertion before the blood test – including climbing stairs or walking quickly – can increase lactic acid levels and throw off the test results.

It's difficult to know if you have MT. However, you can look for the following signs of lactic acidosis:

- Nausea
- Vomiting
- Severe fatigue
- Recent weight loss
- Rapid, deep breathing
- Cramps, muscle aches and numbness or tingling
- Muscle weakness that rapidly gets worse

Lactic acidosis can be fatal. See your health care provider immediately if you have these symptoms.

MT may also cause nerve damage (peripheral neuropathy, see Fact Sheet 555). It has been linked to kidney damage and hearing loss. Some researchers believe it might also contribute to fat redistribution (lipodystrophy, see Fact Sheet 553) in people taking antiretroviral medications (ARVs).

HOW DO ARVs CAUSE MT?

Mitochondria have an enzyme that helps them multiply. This enzyme is called polymerase gamma, or "pol gamma." It is very similar to HIV's reverse transcriptase enzyme. Unfortunately, this means that the drugs we use to inhibit reverse transcriptase can also inhibit pol gamma. When this happens, fewer new mitochondria are produced.

The nucleoside analog reverse transcriptase inhibitors (AZT, 3TC, ddI, d4T, and abacavir) all inhibit pol gamma to some degree. MT is more likely to occur the longer you take these drugs.

Different medications build up in different parts of the body. This could explain how MT caused by different drugs can lead to side effects in different parts of the body.

We know that MT can cause muscle weakness in people taking AZT. It is probably the cause of "fatty liver" (hepatic steatosis) and high levels of lactic acid that can be caused by all of the nukes. Unfortunately, there is very little research on how much mitochondrial damage each ARV causes to different parts of the body. We also don't know which combinations of drugs cause the most MT.

Researchers know how to measure the number of mitochondria in different cells, compared to normal. However, they don't know many mitochondria a cell can lose before there are problems.

WHAT'S NEXT?

Unfortunately, there is very little research on MT caused by nukes. Laboratory and animal studies show that MT can cause nerve damage. But there are no human studies.

Over the next few years, researchers will study MT. They will work on tests to identify it. They will also study the link between MT and various side effects. Some researchers believe that certain vitamins and minerals can help mitochondria overcome the effects of ARVs.

In the meantime, people with HIV need to know the symptoms of lactic acidosis, a rare side effect that can be fatal.

