Summary - Drug Toxicity & Mitochondria
Dr. James Dykens

Individual Reactions

There is concern today that there are some toxic reactions to drugs by certain individuals that others do not have. An individual, for example, may metabolize a drug differently than someone else, and this causes what is know as an idiosyncratic response. Dr. Dykens (and others) began to wonder, however, if there were some other reason besides metabolism which causes these reactions. He and his colleagues looked at drugs as they were just being developed, and studied organ toxicity in rats, and sure enough, mitochondria were being adversely affected. By doing this, they were able to stop development of those drugs which show such toxicity, but this is just a small number of developing drugs.

Mitochondrial Toxicity & Drug Trials

Consideration of mitochondrial toxicity is an important factor in all drug trials, but is only at the very beginning stages. Mitochondria can fail in many different ways and sometimes it is the buildup of the drug over time that causes the damage. Today's standard methods of drug testing cannot demonstrate such damage. There are 44 drugs which have been withdrawn from the market since 1960 which demonstrate idiosyncratic mitochondrial dysfunction (See Slide). There are also another 384 drugs which are listed by the FDA as Black Box Warnings, where toxicity to mitochondria is higher than expected. These are drugs to be avoided if someone has mitochondrial disease. It is important to note that the target organ for po (taken by mouth medications) is the liver because it is exposed to a higher concentration of drug than other organs and can often result in elevated liver enzymes.

The importance of this small organelle, the mitochondria, cannot be stressed enough. When mitochondria are damaged or destroyed, the whole cell will quickly show damage. Drug toxicity may target not just protein in the electron transport chain but also membrane integrity; mitochondria are highly sensitive organelles. As an example of how important mitochondria are to a person, the amount of ATP turnover by a person at rest/day can be calculated: about 148 lbs for a resting female and about 193 lbs for a resting male.

Drugs with Mitochondrial Liabilities

Until recently it has been difficult to extrapolate the mitochondrial liability of drugs. Persons with mitochondrial disease also may have a lower threshold for certain drugs, so weighing the risks and benefits of taking medications becomes problematic for all involved. Mitochondria also might be affected if exposed to some drugs for long periods of time - this is especially true of antibiotics and antivirals. Antibiotics should be used for the shortest period of time needed to kill the offending organism so as to expose the mitochondria for the least amount of time. It is known that the HIV antiviral drugs do in fact damage mitochondria and can induce mitochondrial disease symptoms. It should not be surprising to scientists and physicians that drugs which have known organ toxicity (for example, those that are known to have as a side effect potential liver damage), will also damage mitochondria. Drug toxicity can also take place at any

number of places along the electron transport chain (see Slides) and the effects may be small or large, but there will be a cost to mitochondrial function. Idiosyncratic drug toxicity will also be affected by age, genetics, function of organ history, and other factors.

Current Research

Evidence is accumulating rapidly about the importance of mitochondrial dysfunction in drug development and how to screen for dysfunction. There are several new assays which can monitor oxygen consumption and decreased ATP production so that we can learn how these drugs effect the mitochondria. These assays allow us to find dysfunctions early in the process of drug development and, thereby, stop development of such drugs. Several of the newer drugs used to treat Diabetes have been tested in this way and certain ones have been found to be damaging to mitochondrial function while others are safer. This method has also been used with the statin drugs which also may have mitochondrial liability but with varying degrees of potency. Use of these drugs means that physicians and patients must weigh the risks versus the benefits to determine which ones to use. Other newer methods allow us to focus on the ph of the media the cells are grown in which helps monitor drug potency; other methods allow us to identify where the mitochondrial dysfunction occurs in the transport chain. Much still needs to be done.

History

One of the reasons that mitochondrial dysfunction has never been looked at as part of basic drug development for toxicity is due to the Crabtree & Warburg Effect. Since 1929 cell cultures have used a glucose media that is approximately 5X that of a normal human cell. This was done because of the speed of the reaction. However, this speeded up reaction allowed the mitochondria not to have to function at all in the production of ATP, so no dysfunction is ever discovered. A newer method can now be used which will help researchers see evidence of mitochondrial dysfunction. It is important that ALL drug testing use this method and/or be aware of the chances for mitochondrial drug toxicity.

Up until recently the models to test for idiosyncratic drug toxicity did not look at mitochondrial dysfunction. We were able to look at off target uses that yielded organ dysfunction, but now we can (and must) look at actual mitochondrial dysfunction and actually evaluate the threshold at which cell death occurs. It is important to find this mitochondrial liability early on in drug testing so that other alternative drugs can be pursued.

Where do we go from here?

Many older drugs which are currently in use were never tested for mitochondrial liability, so much of our studies may have to be retrospective. We may also need to look at other environmental liabilities which would make certain drugs more toxic in mitochondrial disease. Advocacy and raising awareness in the entire medical community of mitochondrial disease is imperative. The drugs listed on slides presented with this talk may be shared with pharmacists and/ or primary care physicians. Patients and doctors must weigh the risks and benefits of using drugs which are known to cause mitochondrial dysfunction. Any time a new drug is prescribed for a mitochondrial patient,

they should look the drug up on *Pubmed* on the Web - typing in the drugs generic name and "mitochondrial dysfunction" to see if anything is known about liability/toxicity. Many drugs have not been tested yet, but this is a start.

In closing...

It is Dr. Dyken's mission to get the FDA to test all drugs for mitochondrial dysfunction. But until this happens, patients must advocate for themselves. Antibiotic use should be for the shortest period needed to kill the "bug" so that the cells are exposed for only a limited period of time; once the antibiotic is gone from the patient's system, mitochondrial replication will return (it is suppressed or inhibited as part of the antibiotic's actions). Not much is known about anesthesia, but we know that these agents effect the cell membrane and that they are cleared by the body fairly rapidly; hopefully they will be studied in the future. No work has been done yet either on vaccines; we use things like Tamaflu on mitochondrial patients and honestly do not know whether there is any effect on the mitochondria. Only time will tell. There is much work still to be done, but Dr. Dykens and his colleagues have begun the process of testing all drugs for mitochondrial toxicity.