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Unraveling the mysteries of the mitochondria in Huntington's disease – and getting fast, clear, and useful results from research studies

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At Risk for Huntington's Disease

HD is a genetically caused brain disorder that causes uncontrollable bodily movements and robs people's ability to walk, talk, eat, and think. The final result is a slow, ugly death. Children of parents with HD have a 50-50 chance of inheriting the disease. There is no cure or treatment.

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TUESDAY, JUNE 30, 2015

Unraveling the mysteries of the mitochondria in Huntington's disease – and getting fast, clear, and useful results from research studies

In the collaborative quest for Huntington's disease treatments, deepening affected families' understanding of the key scientific challenges is vital. It can demystify the process of research, inspire involvement in investigative studies and clinical trials, and ultimately bolster the chances of defeating this horrible malady.

Noting the global nature of HD research, last month I highlighted key work on the West Coast of the United States. Andrew F. Leuchter, M.D., and Michael Levine, Ph.D., plan to measure brain energy waves to decipher the signals emitting from HD-affected individuals. Their work could ultimately lead to new drugs (click here to read more).

On the East Coast, at the Magnetic Resonance Research Center (MRRC) of the Yale School of Medicine, Doug Rothman, Ph.D., and his collaborators will conduct two unique studies that seek to unravel long-standing mysteries about Huntington's and the mitochondria, the complex powerhouses of most of our cells.

"All the brain cells depend on them very heavily," Dr. Rothman said during an interview at the MRRC on April 12.

Mitochondria came onto the evolutionary path about a billion years ago, he noted. They use oxygen to burn fuels (such as glucose, or common sugar) to provide energy for brain cells. In focusing on the mitochondria, Dr. Rothman's studies aim to shed light on the serious energy deficits caused in HD and to provide tools for improving clinical trials.

As the Huntington's community ramps up to a growing number of those trials, the paramount work of these scientists can help insure clear and useful results.

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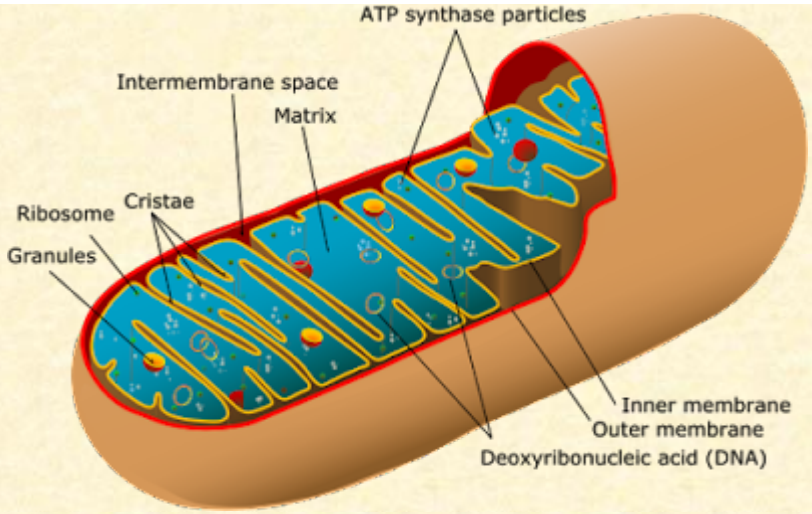


A mitochondrian (Wikipedia diagram by Mariana Ruiz Villarreal)

Novel and unique *human* studies

In people carrying the HD genetic abnormality, why do so many brain cells become damaged and eventually die, leading to HD symptoms? For decades, scientists researching this question mainly in animals and cell cultures have found much evidence implicating the mitochondria in the cells' problems. However, they still don't know exactly what the problem is.

Using the latest brain-scan technology, Dr. Rothman's studies will involve *human* participants. They will focus on the mitochondria and the decline in cellular energy production, one of the main characteristics of HD.

"Anything that impairs the energy supply will severely impact brain function and will eventually impact cellular health," Dr. Rothman said, adding that researchers suspect that mitochondrial dysfunction plays a part in many other neurological disorders.

Doug Rothman, Ph.D. (photo by Gene Veritas)

The first study seeks to identify a mitochondria-linked biomarker (a sign of disease or a disease mechanism) that could lead to a faster, more efficient way of testing potential HD remedies. The second aims to answer a major question: are less active mitochondria a cause or an effect of the disease?

"There's lots of preclinical studies that suggest mitochondrial alterations," Dr. Rothman said, referring to animal studies. "What's nice is that the MR [magnetic resonance] technology allows this aspect of mitochondrial function to be measured non-invasively in vivo."

These studies are "novel" and "unique" because they will involve "patients who have the gene," he added. "Before it would have to be done on a preclinical model. There was no way to directly study humans until the development of the MR technology."

Described below, the specific types of MR scans in Dr. Rothman's studies will be used on HD-affected individuals for the first time, he said.

Pioneering the technology

Dr. Rothman helped pioneer this technology. It is recognizable to most people in the form of the MRI scanners that became common in medical diagnostics worldwide over the past two decades.

In working toward his Ph.D. at Yale, received in 1987, Dr. Rothman specialized in a technique known as NMR, nuclear magnetic resonance. When used in humans NMR is now referred to as MRS, magnetic resonance spectroscopy. He and other specialists have applied MRS to the study of disease. In 1989 he was appointed to the Yale Medical School faculty, and in 1995 he became the director of the Magnetic Resonance Research Center.

As researchers refine these techniques, they have become ever more capable of picking up the resonance – literally a radio frequency – of the chemicals that make up living organisms, including humans.

In both MRS and the more familiar MRI, radio pulses are given to subjects inside huge magnets. The radio pulses excite (stimulate) chemicals in the body while a person lies in the machine, analogous to a bell being struck. Each compound then resonates (again analogous to a bell) at a characteristic radio frequency. By measuring the radio signal from the different resonating chemicals the chemical composition of different brain regions can be determined.

Dr. Rothman stressed that the technology is safe. "You're not exposed to any radiation at all – literally just radio frequency," he said of the scanners, which detect the radio frequencies coming out of the body.

"You literally could set up an FM radio and pick these up," he continued. "Really, the system's main difference from a standard radio is just the sensitivity and stability, because we're talking about very small differences of frequency, as opposed to say a megahertz, as you have in FM radio."

The scanner sends the readings to a computer for analysis.

Understanding brain metabolism

Using MRS, Dr. Rothman and his colleagues at the MRRC contributed to breakthroughs in understanding the biochemistry of type 2 diabetes. He also helped make important discoveries about the biochemistry of the liver and muscles.

At the same time, he and others discovered ways to measure levels of chemicals in the brain. Those chemicals included metabolites, which provide energy, and neurotransmitters, which are involved in signaling between brain cells.

For the first time in human brain scans, Dr. Rothman and his colleagues detected key chemicals such as ethanol and glucose. They also saw the major neurotransmitters glutamate and GABA (gamma aminobutyric acid), substances mentioned frequently in the world of HD research.

This group of scientists made other important advances in the understanding of brain metabolism. Of particular potential importance for HD, they discovered the energy cost for supporting brain glutamate and GABA neurotransmitter activity, providing a direct link between mitochondrial health and brain function.

As a result of their discoveries, Dr. Rothman and a group of colleagues saw how levels of glutamate and GABA are altered in depression, epilepsy, and other psychiatric disorders, and how drugs can impact those levels.

Dysfunction seen in animals

Several years ago, Dr. Rothman added Huntington's disease to his focus. Funded by CHDI Foundation, Inc., the multi-million-dollar nonprofit virtual biotech dedicated to finding HD treatments, Dr. Rothman and his lab staff conducted research on mitochondria and brain cell metabolism in two types of transgenic HD mice.

Using MRS scans, in both groups of mice the team found a decline in metabolism in three key regions of the brain (cortex, thalamus, and striatum). They also discovered a reduction in brain cell glutamate and GABA signaling activity.

"The changes were much more profound as the models reached the late premanifest or manifest stage," Dr. Rothman said during a presentation of the research in February at the CHDI-sponsored 10th Annual HD Therapeutics Conference.

These findings suggested that mitochondrial dysfunction plays a role in HD. This and his upcoming studies are part of a larger group of biomarker studies necessitated by the advent of clinical trials.

You can watch Dr. Rothman's presentation in the video below.

Evidence for Mitochondrial Dysfunction in Mouse Models of Huntington's Disease?

from Gene Veritas

42:16

Evidence for Mitochondrial Dysfunction in Mouse Models of Huntington's Disease? from Gene Veritas on Vimeo.

High-powered brain scans

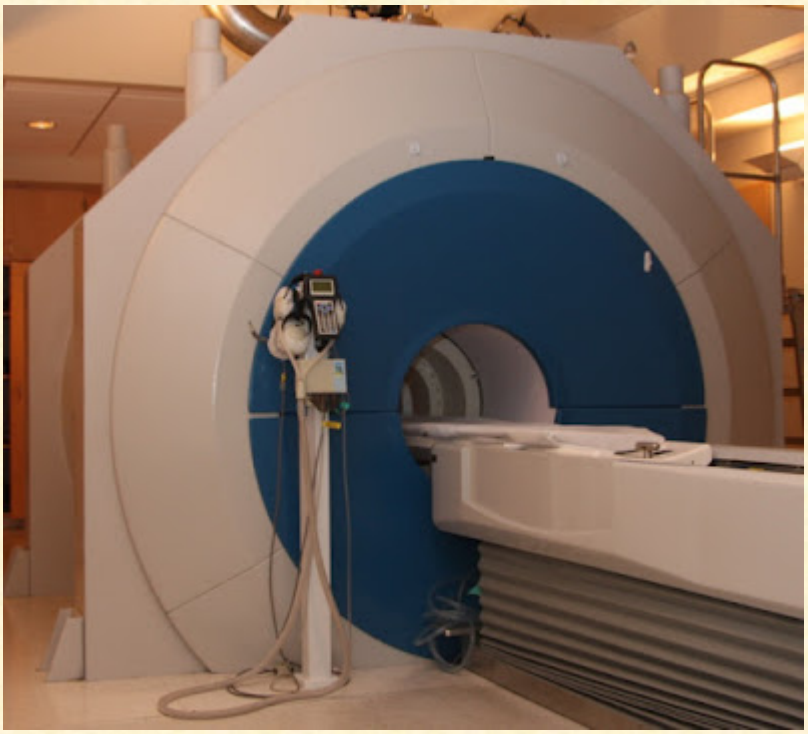
With CHDI support, Dr. Rothman hopes to carry out the human studies in the second half of this year.

Each study will require about 40 volunteers: 20 early-stage HD-affected individuals and 20 gene-negative volunteers to act as a comparison group. Each study will involve a brain scan and take two or three days, including travel time. The study will cover the cost of travel, food, and lodging. Volunteers can take part in both studies, if they wish.

In the first study participants will undergo a so-called proton scan lasting 60-90 minutes. The Rothman team will use Yale's 7 Tesla scanner. The number of Teslas corresponds to the power of the magnet, with higher Tesla giving greater sensitivity (the ringing discussed above has a higher amplitude and frequency).

"Seven Tesla is about the highest magnetic field that can be used for human studies," said Dr. Rothman. "Your molecules move around and jitter and release a radio signal that interferes with the measurement, and so we need as about as high a sensitivity as possible. Interestingly, within a chemical, the protons all have different frequencies. So you can actually identify a chemical based on the pattern of resonance frequencies."

At this level, the scientists can measure more types of metabolites and with greater sensitivity, allowing them to distinguish between glutamate and another neurotransmitter, glutamine. Both are involved in a cycle involving GABA, brain cell signaling, and metabolism. The research team aims to determine whether glutamine or glutamate is most altered by the disease.



Yale's 7 Tesla scanner (photo by Gene Veritas)

Optimizing treatments

The researchers will focus primarily on glutamine, because it is the most sensitive chemical marker in the brain, but it's not easily measured in humans at 3 Tesla or lower (scanners with less sensitivity), Dr. Rothman explained.

The more sensitive the biomarker, the better the chance of measuring the effects of the disease and potential treatments, he added.

This biological fine-tuning raises the possibility of studying the disease and testing therapies in small groups, perhaps even single subjects – a far more efficient, inexpensive, and faster way to treatments than the traditional, larger studies involving dozens or scores of individuals.

"The hope is that it would be possible to get immediate feedback before any behavioral-motor changes and use that to optimize individual subjects' therapy," Dr. Rothman elaborated.

Tracing the journey of sugar

In the second study Dr. Rothman will use ^{13}C (carbon-13) MRS, the same technique used in the HD-mouse mitochondria project (discussed above) and in human scans for a variety of conditions. Carbon-13 is a natural, stable isotope that makes up about 1.1 percent of all the carbon on earth. Researchers use it to label substances so they can be tracked through the body.

Participants will lie in a 4 Tesla scanner for about two hours. They will be continuously injected with ^{13}C-labeled glucose through a catheter in one arm. From a catheter in the other arm small blood samples will be taken to read levels of ^{13}C and glucose. Glucose is used because it is the main fuel that the mitochondria burn to provide the brain with energy.

Lab assistants will monitor participants' glucose levels to make sure they remain stable. Afterwards, the participants will receive orange juice and lunch in a standard recovery room, where assistants will make sure that their glucose levels have returned to normal.

As Dr. Rothman explained, the ^{13}C MRS technique will allow his team to watch the glucose go through the various stages of the energy cycle in the brain. This metabolic process includes the transformation of glucose into lactate, then into glutamate by way of what is known as the TCA (tricarboxylic acid) cycle in mitochondria. The rate of flow of glucose into the mitochondria is proportional to the amount of energy the mitochondria produce.

"We can also measure the flow from glutamate to glutamine, which gives us the rate of glutamate neurotransmission, a direct measure of brain function," he added.

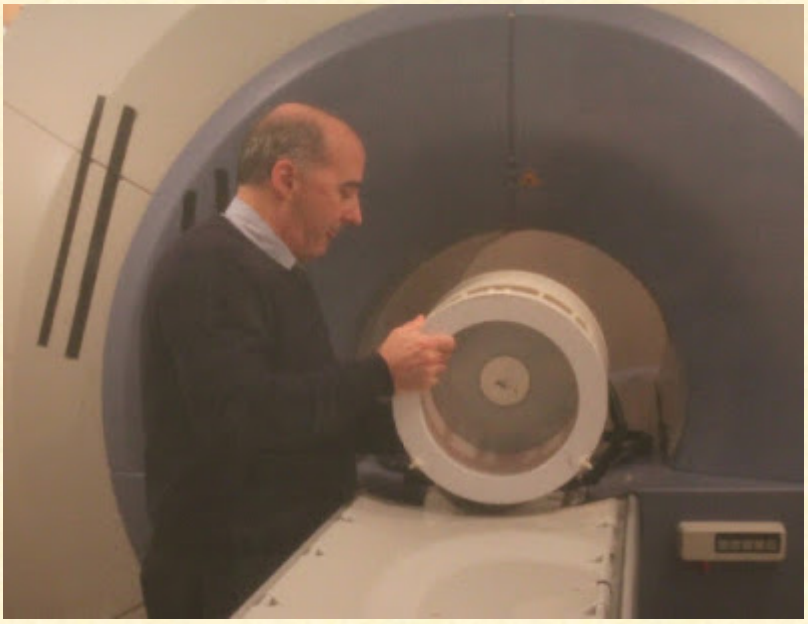
As a result, the team can measure the rate of energy production in individual brain cells, as well as the rate of brain signaling (neurotransmission).

Dr. Rothman summarized: "We have a measure of both the energetics of the neuron – how much energy is the mitochondria making – and a measure of the function of the neuron – how much it's signaling, how much glutamate it's releasing through the flow into glutamine."

The team will attempt to answer two questions: whether energy production decreases in early-stage HD individuals, and, if so, whether the drop results from impairments in the mitochondria.

Based on animal studies and previous human studies using other techniques, Dr. Rothman and his team believe they will find diminished energy production in the mitochondria.

"But that doesn't, by itself, tell us that the mitochondria are causing it," he said. "It could be many other things."



Dr. Rothman making an adjustment on Yale's 4 Tesla scanner (above) and standing the in recovery room where ^{13}C study volunteers will have glucose readings monitored afterwards (below) (photos by Gene Veritas)

Verifying the impairment

The ^{13}C experiment will examine the *rate* of energy production of the mitochondria. To further tease out the questions about the role of the mitochondria in HD, Dr. Rothman and his team want to measure the *demand* on the mitochondria for energy production.

To do so, they will run a second experiment during the ^{13}C scans. Using phosphorous magnetic resonance spectroscopy, they will analyze the level of other compounds used for brain cell energy. Specifically, they will measure the synthesis of ATP (adenosine triphosphate) from ADP (adenosine diphosphate) (click here to learn about this process). The breakdown of ATP back into ADP by the mitochondria releases energy to fuel cellular processes, he said.

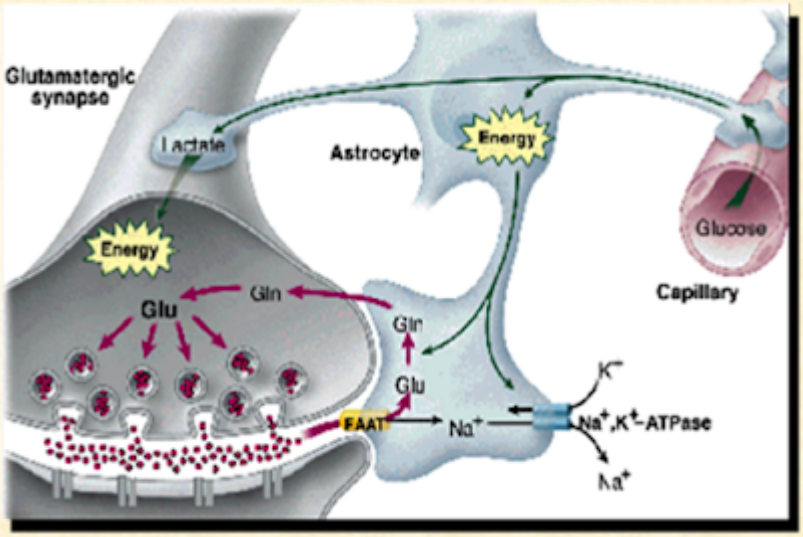
"In the muscle it fuels contraction," Dr. Rothman said. "In the brain it fuels neurotransmission. If the mitochondria have a defect or have a low

number or activity, they have to be driven harder for the same amount of energy production."

For this measurement to occur, the participants must have their brains stimulated. "So both people with HD and control subjects will be given visual scenes in the magnet that will force the visual cortex we're measuring to be active," Dr. Rothman explained.

If the HD subjects have a mitochondrial impairment, the team will be able to determine whether the mitochondria "are being forced to work harder, because their capacity is less," he said.

In combination with the ^{13}C MRS readings, this experiment will help the scientists conclude whether "the problem is at the mitochondria," Dr. Rothman said. This knowledge will help in the design of potential remedies and the clinical trials to test them.



The ^{13}C study will measure energetics and signaling, as shown in this rendition of the glutamatergic synapse (image courtesy of Dr. Rothman)

Gratitude for the scientists' work

Dr. Rothman said he expects the proton study to take about 18 months and the ^{13}C study about 24 months. Once the studies commence, a call for volunteers will go out from the MRRC. If recruitment goes well, the studies may finish sooner, he said.

Upon the completion of the proton study, CHDI will evaluate the feasibility of glutamine as a treatment biomarker in comparison with glutamate and other MRS biomarkers under study, he added. Later Dr. Rothman's team will file a report on the studies with CHDI, and they aim to submit their work to a scientific journal.

The engagement of Dr. Rothman and Yale Medical School in HD science exemplifies the seriousness of CHDI and HD researchers in the quest for treatments.

With the goal of unraveling the mysteries of the mitochondria, Dr. Rothman's experiments can potentially complete key parts of the HD treatment puzzle. The search for effective biomarkers and increased knowledge about the role of the mitochondria can speed the movement of discoveries from scientific bench to patient's bedside.

As a Yale graduate and carrier of the HD genetic defect, I was especially thrilled to interview Dr. Rothman. My alma mater may very well be

helping to save me and thousands of others from the ravages of HD.

I am grateful each day for the commitment of Dr. Rothman and scientists around the globe to defeat HD.

Gene Veritas (aka Kenneth P. Serbin) at Yale University in New Haven, CT, April 2015 (photo by Gene Veritas)

Posted by Gene Veritas at 3:04 PM

Labels: brain , CHDI , clinical trials , Doug Rothman , energy , glucose , Huntington's disease , magnetic resonance spectroscopy , metabolite , mitochondria , MRI , neurotransmitter , researcher , treatments , volunteers , Yale

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