Sirtuin Inhibition Achieves Neuroprotection by Decreasing Sterol Biosynthesis

In January, we reported that a SIRT1 inhibitor has gone into Phase I clinical trials in for Huntington's Disease in Europe. A new report has identified SIRT2 inhibition as another potential therapeutic strategy. Collaborators from the University of California at Irvine, Massachusetts General Institute for Neurodegenerative Disease, the Brain Mind Institute in Switzerland and other labs have shown that SIRT2 inhibition is helpful in invertebrate and striatal neuron models of Huntington's Disease.

The new study is ground breaking for two reasons. First, it is the first study to confirm the neuroprotective effects of reducing sterol biosynthesis in transgenic models of HD. Sterol biosynthesis is the production of cholesterol and cholesterol esters. Second, this is the first study to show that SIRT2 has a role in cellular metabolism.

Sirtuins are protein deacetylase enzymes. The name sirtuin comes from the Silent Information Regulator gene 2 (Sir2), a gene which is associated with longevity in yeast and invertebrates. There are seven sirtuins in mammals. SIRT1 is the most studied. SIRT2 is known to play a role in cell division but its role in neurons (which do not divide) has been unknown.

Since previous research has shown that SIRT2 inhibition has neuroprotective effects in models of Parkinson's disease, the researchers decided to explore whether it would be neuroprotective in HD models as well. They tested two newly discovered SIRT2 inhibitors, AGK2 and AK-1, in drosophila (fruitfly) and a c. elegans (flatworm) models of HD both of which express N-terminal Htt fragments (N-ter Htt) from human HD exon1. Both inhibitors were administered in the drosophila's food and both reduced neurodegeneration as measured by the number of surviving neurophotoreceptors. Both also reduced cytoxicity in the c. elegans model as measured by improvement in a defective response to a light touch on the tail.

To learn about the mechanism by which these disease modifying effects were found, the researchers then tested the inhibitors in a striatal cell model of HD. Both inhibitors reduced HD toxicity. To make sure that SIRT2 was indeed the target, they overexpressed SIRT2 at the same time and achieved no neuroprotective effects. In addition, they found that the expression of a dominant negative, deacetylase-deficient SIRT2 mutant that diminishes cellular SIRT2 activity also improves toxicity in a similar way to the inhibitors.

They also checked to see that SIRT2 was not abnormally elevated in HD. They found no differences between two HD models of mice and normal mice in SIRT2 expression.

Because SIRT2 is a histone deacetylase, they hypothesized that it might affect nuclear gene transcription. The mutant HD protein is known to dysregulate gene transcription and this is thought to be a major pathology in the disease. Since primary neurons with the exon one of the HD gene reproduce this pathology, they are a good model for testing the hypothesis. They found that genes regulating sterol biosynthesis were significantly

downregulated by either the use of a SIRT2 inhibitor or with the SIRT2 mutant that has reduced SIRT2 activity.

They found that the levels of cellular sterols were increased in the HD striatal cells as compared to controls. Both of the SIRT2 inhibitors and the mutant SIRT2 were each able to reduce the levels.

Most of the genes that were downregulated by the inhibitors of the SIRT2 mutant are controlled by the same transcription factor, the sterol response element binding protein 2, SREBP-2. SREPB-2 does its work by relocating from the endoplasmic reticulum to the cell nucleus. Inhibiting SIRT2 led to a reduction of SREBP-2 in the nucleus. This shows that SIRT2 exerts its affect by regulating the nuclear trafficking of SREBP-2.

Previous research by Coalition scientist Elena Cattaneo and colleagues has shown that the HD protein dysregulates cholesterol homestasis and that sterols are decreased in various HD models of the disease. Unpublished research by Valenza and Leoni (as cited in the review article referenced below), shows that levels are normal early on and decrease over time and are negatively correlated with CAG counts (the higher the count, the greater the decrease).

It has not been clear whether the reduction of cholesterol is a pathology or a compensatory mechanism, possibly to protect against excitotoxicity. Cattaneo and colleagues cite an earlier study showing that reduced biosynthesis is neuroprotective against NMDA-induced excitotoxicity.

It is important to learn more because cholesterol is extremely important for brain function. Cholesterol does not cross the blood brain barrier so the brain must produce all that is needed. The brain has a high need for cholesterol; it has ten times as much as any other organ in the body. Cholesterol is needed for insulating myelin and regulating its structure. It is involved in membrane trafficking, signal transduction, and synaptogenesis.

Even small disturbances in cholesterol homestasis can cause disease so how is it that reduced cholesterol could be neuroprotective? The authors state that “Our working hypothesis is that a plurality of sterol-pathway-related mitigatory effects exists and that the balance of these activities and specific nutrient conditions determines the net outcome.”

More work is needed to determine the molecular pathways by which SIRT2 inhibition affects sterol biosynthesis and achieves neuroprotection and whether other mechanisms might be involved as well. They also found that the number of protein aggregates were decreased. However, their shape and size were unaffected unlike with the alpha-synuclein inclusions in a Parkinson’s model in an earlier study. It is also possible that that transport of BDNF may be improved. SIRT2 inhibition and sterol biosynthesis appear to be potentially profitable areas for further research.

References:

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- *Marsha L. Miller, Ph.D., June 29, 2010*