

Workshop Updates

The Hereditary Disease Foundation and The Lou Ruvo Brain Institute
Common Threads Workshop II:
Calcium in Neurodegeneration
February 5-6, 2008
Las Vegas, Nevada
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Age-related neurodegenerative disorders, such as Huntington's (HD), Parkinson's (PD), and Alzheimer's (AD) diseases, are major causes of morbidity and mortality worldwide. Despite having very different symptoms and pathologies, these different diseases also have much in common. All are characterized by the accumulation of protein aggregates in the brain, for example. What do the similarities and differences reveal about the underlying pathology that drives these neurodegenerative disorders, and how might that knowledge help scientists develop new preventions and therapies? To help answer those questions, the Hereditary Disease Foundation and Keep Memory Alive, the foundation that supports the Lou Ruvo Brain Institute in Las Vegas, Nevada, sponsored their second "Common Threads" workshop in February. The workshop was devoted to the calcium hypothesis, which suggests that imbalance in the level of calcium in certain neurons in the brain is a major trigger for neurodegeneration.

The workshop was chaired by Carl Johnson, Executive Director for Science of the Hereditary Disease Foundation, and Zaven Khachaturian, CEO of the Lou Ruvo Brain Institute. The participants from North America and Europe comprised experts in the field of calcium and neurodegenerative disease.

Calcium is essential for life and is found in all cells in the body. But having too much calcium can be detrimental. This is particularly true in neurons, or nerve cells, which depend on calcium as a "signaling" molecule. Neurons in the brain are embedded with proteins that act as calcium channels. When these

proteins are activated, they allow calcium to rush into the cells. This influx of calcium kick-starts a variety of calcium-dependent processes inside the neuron. These processes are essential for the cell to respond to its environment and are the basis for a variety of highly evolved functions such as control of movement and learning and memory.

But calcium can also be bad for neurons. Nerve cells die if they are over-stimulated and allow an entry of too much calcium. This is because there are also detrimental signaling pathways in the cell that are driven by calcium. Some of these processes trigger cell death.

Calcium equilibrium is a challenge for every cell since calcium is found in a variety of different pools. Cells have to manage calcium coming into the cell from outside, calcium inside the cell in the cytoplasm, and also calcium in a variety of intracellular organelles, such as the nucleus, the mitochondria that provide the cell with energy, and a compartment called the endoplasmic reticulum, which is a site of protein synthesis and maturation. Calcium imbalance in any of these compartments may be toxic to cells and eventually cause them to die. This is the basis for the calcium hypothesis of neurodegenerative diseases, which posits that an imbalance in calcium in certain specific cells of the brain is a major contributor to disease pathology.

Participants discussed some of the latest evidence linking calcium to Parkinson's, Huntington's and Alzheimer's diseases. One of the most puzzling aspects to these different disorders is that disease pathology is found in specific subset of neurons, despite the presence of the mutated proteins in many different cells of the brain. The scientists tried to reconcile this specificity with the ubiquitous nature of calcium biology.

Participants also discussed the latest evidence linking Parkinson's disease to a specific type of calcium channel protein. This channel component, called Cav1.3, is found in exactly the

same neurons that are damaged in PD. In experimental models of the disease, blocking or removing this calcium channel protects the neurons from a variety of toxins that have been linked to sporadic PD in humans and cause PD-like symptoms in mice. There was discussion as to why this channel might make these neurons vulnerable to disease and the potential of using a specific calcium channel blocker as a new form of PD therapeutic.

Indications that calcium is important in HD and AD pathology are not as well-grounded, but the participants looked at a multitude of evidence that links calcium imbalance with both diseases. In HD patients, for example, there are a greater number of calcium channels on the surface of striatal neurons. There is also evidence that the mutated huntingtin protein interferes with the calcium homeostasis by altering release of calcium from intracellular pools. In AD, too, proteins that are intimately associated with disease pathology can alter calcium dynamics. Mutant presenilin, a protein that is implicated in both inherited and sporadic AD, may itself act as a calcium channel, promoting release of calcium from the endoplasmic reticulum. Amyloid-beta, a small toxic protein that is a major pathological hallmark of AD may disrupt calcium in a similar fashion. There is evidence that amyloid-beta forms an assembly that inserts into the cell membrane creating a pore that allows calcium to enter the cell.

The participants concluded that there is now a growing consensus that calcium imbalance contributes to neurodegeneration and that there is a pressing need to further investigate the calcium hypothesis. ■

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