Washington University Medical School Researchers Develop a New Caspase Six Inhibitor

Ever since Coalition for the Cure researcher Dr. Michael Hayden and colleagues reported that caspase six resistant mice with the HD gene do not develop Huntington's Disease, a number of researchers have been working on developing a safe, effective, and narrowly targeted caspase six inhibitor. A team of researchers at Washington University Medical School have developed new caspase six inhibitors which represents a major advance over the existing ones.

The word caspase comes from cysteine-aspartic-acid-proteases. Caspases are enzymes which are used in apoptosis, programmed cell death. There are various caspases that initiate the process, that cleave proteins and that actually 'execute' the cell. Apoptosis is a necessary process in development and also in destroying tumors. Unfortunately, apoptosis is also implicated in neurodegenerative disorders. Apoptosis is triggered by cellular stress, especially mitochondrial stress, and this is known to occur with Huntington's and the various other neurodegenerative disorders. Caspase six cleaves the HD protein into toxic fragments which enter the nucleus of neurons and interfere with gene transcription.

In the Hayden study, HD mice were also engineered to be resistant to caspase six cleavage and they did not experience neurodegeneration. This strategy was used rather than testing them with a caspase six inhibitor since the existing ones were based on peptides and did not cross the blood brain barrier. Dr. Robert Mach and his colleagues were able to develop a series of analogues of a small molecule which overcame that obstacle.

They started with istatin derivative with michael acceptors which are known to inhibit caspases 3, 6, and 7. Using the techniques of medicinal chemistry, they were able to make a series of chemical changes and produce a series of analogues with increased potency and selectivity for caspase six inhibition.

Dr. Mach and colleagues consider the new caspase six inhibitor analogues to be first generation drugs. They are now doing molecular modeling studies that will provide insight so that they can make additional chemical changes that will improve the drug even more. When further optimization produces a second-generation drug, it will be tested in mouse models for HD and Alzheimer's.

Caspase six has also been implicated in Alzheimer's Disease and this research was funded by AD research grants. The broader utility of a potential treatment increases both the incentive and the amount of available funding for drug development.

References

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- *Marsha L. Miller, Ph.D., May 8, 2009*