Researchers find new clues about protein linked to Parkinson's disease

June 17 2011

Researchers at the Keck School of Medicine of the University of Southern California (USC) have uncovered structural clues about the protein linked to Parkinson's disease (PD), which ultimately could lead to finding a cure for the degenerative neurological disorder.

The alpha-synuclein (α-synuclein) protein is commonly found in the healthy human brain even though its function is not clear. The protein has been the subject of substantial Parkinson's research, however, because it is a major component in the protein clumps found in PD cases.

Unlike most proteins, which are typically rigid and occur in one definitive form, the alpha-synuclein protein can fold and change its structure. Researchers Tobias S. Ulmer, Ph.D. and Sowmya Bekshe Lokappa, Ph.D. at the Keck School-affiliated Zilkha Neurogenetic Institute have determined that the energy difference between two particular alpha-synuclein structures is less than previously speculated.

Their study, to be published in the June 17 issue of The *Journal of Biological Chemistry*, is the first to quantify that energy difference, 1.2±0.4 kcal/mol.

"We're trying to understand the mechanisms of protein folding and misfolding," said Ulmer, the study's principal investigator and an assistant professor in the Department of Biochemistry and Molecular Biology at the Zilkha Neurogenetic Institute. "Then we can say why

something is going wrong, which is essential to treating neurodegenerative disorders like Parkinson's."

If proteins misfold, they are repaired or they break down. However, when alpha-synuclein misfolds it aggregates and becomes toxic to surrounding nerve cells, Ulmer said. Understanding its folding and finding what causes aberrant folding is therefore key to determining the root cause of the disorder, he added.

To put the discovery into perspective, Ulmer compared the energy that researchers thought was needed to change the protein's structure to hurricane-force winds and the actual energy required to a light summer breeze. The experiments were conducted in 2010, measuring the energy of elongated and broken helix forms of alpha-synuclein through circular dichroism spectroscopy, fluorescence spectroscopy and isothermal titration calorimetry.

"There may be a continuous interconversion between folded alpha-synuclein structural states that might contribute to its pathological misfolding," said Lokappa, a post-doctoral research associate at the Center for Craniofacial Molecular Biology at USC and the study's co-author. "But we need to have even better insight into the mechanisms of protein folding and misfolding to explain what's going wrong in the brain."

The paper is the sixth in a series of studies that Ulmer has published on alpha-synuclein.

Parkinson's is a neurological disorder that has no cure or determined cause. It is a slow-progressing degenerative disease that most commonly affects motor function. According to the National Parkinson Foundation, the disorder is the second-most common neurodegenerative disease after Alzheimer's, affecting 1 million people in the United States and some 4

million worldwide.

More information: www.jbc.org/content/286/24/21450.full

Provided by University of Southern California