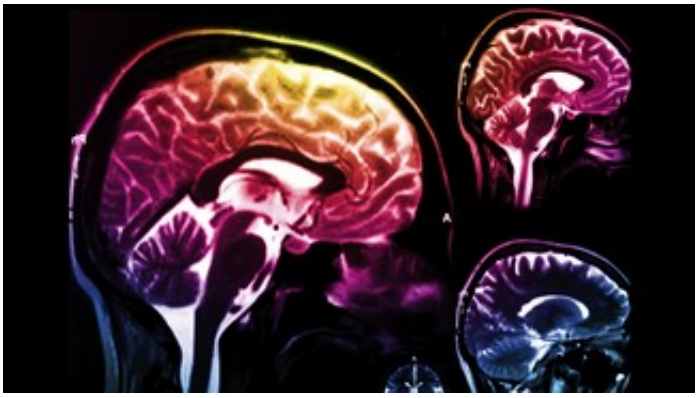
A new tool for understanding Parkinson's disease

April 2 2015, by Nik Papageorgiou



EPFL scientists have developed a new method that can accurately simulate the chemical modification of the protein behind Parkinson's disease. The technique, has opened a new way of understanding Parkinson's, and can be expanded to other proteins and diseases as well.

Parkinson's disease is characterized by the aggregation of the protein alpha-synuclein in brain cells that control movement, giving rise to the disease's symptoms. Evidence suggests that alpha-synuclein begins to aggregate when it undergoes a chemical process where nitrogen groups are attached to four of its amino acids. This process, called nitration, has been impossible to study on alpha-synuclein in the lab. Scientists at École Polytechnique Fédérale de Lausanne (EPFL) have developed the

first-ever method where alpha-synuclein can be nitrated to simulate the nitration patterns seen in Parkinson's disease. The method, which can be expanded to investigate the effect of nitration in other proteins, is published in the *Journal of the American Chemical Society* and opens new possibilities for understanding the role of this nitration in health and disease.

The exact causes of Parkinson's disease, which affects around ten million people worldwide, are still unclear. But one place to look is the protein alpha-synuclein, which begins to clump together inside brain cells to form long fibrils, which then evolve into aggregates that eventually destroy the cell. This has been linked to a several chemical modifications of alpha-synuclein, one of which is nitration, where nitrogen groups attach to its tyrosine amino acids.

However, nitration of alpha-synuclein has proven hard to study in the lab. The problem is that current nitrating methods generate non-homogeneous mixtures of α-synucleins that are nitrated at different amino acid sites. As a result, the proteins have different properties to natural alpha-synuclein, and cannot be used effectively to mimic and study what happens in Parkinson's disease.

A new approach to dissecting nitration

Hilal Lashuel's team at EPFL has now developed the first technique to produces homogeneous α-synucleins, where one or more of its tyrosines can be properly nitrated. The scientists used a sophisticated protein synthesis technique to make fragments of alpha-synuclein where nitrated tyrosines could be incorporated and therefore nitrated independently from each other. Because of this, it was also possible to control the exact number or combinations of nitrated tyrosines, which offers a powerful tool to study this process.

The fragments were then recombined to produce the entire alpha-synuclein with correctly nitrated tyrosines. Normally, this recombining involves a desulfurization step that can ruin the attached nitrogen groups by adding electrons to them (this is known as "reduction"). But lead author Ritwik Burai conceived of a way to bypass the problem by modifying the desulfurization process.

The new method produced a completely homogenously nitrated or tailored mixture of nitrated alpha-synuclein. When tested in in vitro, the modified proteins lost their ability to interact properly with vesicles, such as those found in cells. Further tests also showed that site-specific nitration changed alpha-synuclein's structure, which directly influences the protein's tendency to form the aggregates seen in Parkinson's disease.

Tools that shape the future

Hilal Lashuel's team has been working on chemical modifications of alpha-synuclein and other proteins for over five years. This method is the latest achievement in this line, overcoming the last barrier, nitration. "These advances allow us now to reconstruct, in vitro, a-synuclein species with the same chemical properties as those isolated from diseased human brains," says Hilal Lashuel. Since the normal functions of alpha-synuclein are still a mystery, being able to reconstruct its chemical properties as they exist in the human brain may also open new avenues for understanding its biological role, and how it can become impaired in disease.

The new method is not limited to alpha-synuclein, but can be used across different proteins and different types of chemical modifications, which often underlie a multitude of diseases. Just in the context of Parkinson's disease, Lashuel anticipates that the chemical tools his group has developed will have an tremendous impact: "These advances will facilitate the development of antibodies and imaging agents for the

detection and quantification of different a-synuclein species and aggregates along the progression of Parkinson's disease, which could lead to novel approaches for its diagnosis and treatment."

More information: "Elucidating the role of site-specific nitration of α-synuclein in the pathogenesis of Parkinson's disease via protein semisynthesis and mutagenesis." *JACS* 13 March 2015. DOI: 10.1021/ja5131726

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