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Press information

A New Therapeutic Target for Treating Spinocerebellar Ataxias?

Spinocerebellar ataxias are neurodegenerative genetic diseases of the cerebellum and brain stem that lead to numerous motor disorders. The most well-known of these ataxias is SCA3, which is also called Machado-Joseph disease. In her research published on June 14 in *Acta Neuropathologica*, Nathalie Cartier-Lacave, Inserm researcher at the Brain and Spine Institute, discovered with her team the crucial role of an enzyme that can improve symptoms of this disease in mice.

Certain neurodegenerative diseases are caused by a mutation that leads to the production of malformed proteins in possession of excess amino acids (polyglutamine expansion). This occurs with Huntington's disease and some forms of spinocerebellar ataxia.

In this study, a team from the Brain and Spine Institute (Inserm/Sorbonne Université/APHP) led by Nathalie Cartier-Lacave looked at another group of diseases that presents this polyglutamine-expanded protein production – spinocerebellar ataxias – and more specifically SCA3. In this disease which affects 1-2 in every 100,000 people, the ataxin 3 protein mutates and aggregates in neurons, leading to their death and the subsequent onset of motor disorders. The researchers were able to show that supplying a key enzyme of brain cholesterol metabolism, CYP46A1, to the regions affected by the disease improves symptoms. A strategy that could also be effective in the other ataxias linked to polyglutamine expansion.

The researchers began by studying the cholesterol metabolism in mice with SCA3, revealing an imbalance in this metabolism and decreased levels of the enzyme CYP46A1.
These initial findings led the researchers to test whether or not restoring the expression of this enzyme in SCA3 mice could be beneficial. They performed a single injection of a gene therapy vector carrying gene *CYP46A1* into the cerebellum of SCA3 mice, revealing reduced degeneration of the Purkinje neurons of the cerebellum, an improvement in the motor disorders, and decreased ataxin 3 aggregates when compared with untreated mice with the disease. "*These findings show that CYP46A1 is an important therapeutic target for restoring this metabolism, decreasing*

toxic mutated protein aggregates and thereby improving the symptoms of the disease",
explains Inserm Research Director Cartier-Lacave.

To further elucidate the phenomenon, the researchers revealed that the pathway used to evacuate the malformed or mutated proteins – the autophagy pathway – is disrupted in SCA3 mice. This led them to conclude that ataxin 3 proteins aggregate as a result of dysfunction of this pathway. However, if normal CYP46A1 levels are reinstated, autophagy is restored, and the disease symptoms attenuated.

Interestingly, the researchers also observed improved evacuation of the ataxin 2 aggregates during overexpression of the enzyme, leading to hopes for treatment, with one product having the potential to be effective in multiple severe and rare diseases.
A European program (Erare) coordinated by Inserm at the Brain and Spine Institute (N. Cartier, A. Durr) is in progress to confirm these results on other models of ataxia and to evaluate the feasibility and tolerance of a potential therapeutic application in patients with these severe genetic diseases.

Sources

Restoring brain cholesterol turnover improves autophagy and has therapeutic potential in mouse models of spinocerebellar ataxias

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