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Press release

Modulation of brain cholesterol: a new line of research in Alzheimer's disease treatment?

We have known for some years that Alzheimer's disease is characterised by two types of lesions, amyloid plaques and degenerated tau protein. Cholesterol plays an important role in the physiopathology of this disease. Two French research teams (Inserm/CEA/University of Lille/University of Paris-Sud[1]) have just shown, in a rodent model, that overexpressing an enzyme that can eliminate excess cholesterol from the brain may have a beneficial action on the tau component of the disease, and completely correct it. This is the first time that a direct relationship has been shown between the tau component of Alzheimer's disease and cholesterol. This work is published in the 10 September 2015 issue of *Human Molecular Genetics*.

Excess brain cholesterol cannot freely cross the blood-brain barrier; to be eliminated it must be converted into 24-hydroxycholesterol (24-OHC) by the enzyme CYP46A1 (cholesterol-24-hydroxylase). At Inserm Unit 1169, Nathalie, Cartier, coordinator of this work, and Patrick Aubourg, director of the unit, proposed the hypothesis that increasing the efflux of cholesterol from the brain by overexpressing CYP46A1 might have a beneficial effect on the elements of Alzheimer pathology.

The first step in this work made it possible to show that injecting a viral vector, AAV-CYP46A1, effectively corrects a mouse model of amyloid pathology of the disease, the APP23 mouse. CYP46A1 thus appears to be a therapeutic target for Alzheimer's disease.

Conversely, *in vivo* inhibition of CYP46A1 in the mice, using antisense RNA molecules delivered by an AAV vector administered to the hippocampus, induces an increase in the production of Aß peptides, abnormal tau protein, neuronal death and hippocampal atrophy, leading to memory problems. Together these elements

[1] Teams led by David Blum and Luc Buée (Jean-Pierre Aubert Research Center, Inserm Unit 1172/University of Lille/CHRU) and by Nathalie Cartier, Inserm Research Director (Inserm Unit 1169, "Gene Therapy, Genetics and Epigenetics in Child Neurology, Endocrinology and Development," University of Paris-Sud, CEA, Paris), based at MIRCen (Molecular Imaging Research Center), Preclinical Research Facility, French Alternative Energies and Atomic Energy Commission (CEA) Centre, Fontenay-aux Roses

reproduce a phenotype mimicking Alzheimer's disease.

These results demonstrate the key role of cholesterol in the disease, and confirm the relevance of CYP46A1 as a potential therapeutic target (work published in *Brain* on 3 July 2015).

Taken together, this work now enables the research team coordinated by Nathalie Cartier, Inserm Research Director, to propose a gene therapy approach for Alzheimer's disease: intracerebral administration of a vector, AAV-CYP46A1, in patients with early and severe forms (1% of patients, familial forms) for whom there is no available treatment.

"To achieve this objective, we are carrying out all the preclinical steps of development and validation of the tools (vector, neurosurgical protocol, elements of monitoring) for demonstrating the efficacy and tolerance of the strategy, in order to submit an application for authorisation of a clinical trial," explains Nathalie Cartier.

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Sources

CYP46A1 inhibition, brain cholesterol accumulation and neurodegeneration pave the way for Alzheimer's disease

F Djelti, J Braudeau, E Hudry, M Dhenain, J Varin, I Bièche, C Marquer, F Chali, S Ayciriex, N Auzeil, S Alves, D Langui, MC Potier, O Laprevote, M Vidaud, C Duyckaerts, R Miles, P Aubourg and N Cartier

Brain, 3 July 2015

Cholesterol 24-hydroxylase defect is implicated in memory impairments associated with Alzheimer-like tau pathology

Marie-Anne Burlot, Jerome Braudeau, Kristin Michaelsen-Preusse, Brigitte Potier, Sophie Ayciriex, Jennifer Varin, Benoit Gautier, Fathia Djelti, Mickael Audrain, Luce Dauphinot, Francisco-Jose Fernandez-Gomez, Raphaelle Caillierez, Olivier Laprevote, Ivan Bi.che, Nicolas Auzeil, Marie-Claude Potier, Patrick Dutar, Martin Korte, Luc Buée, David Blum and Nathalie Cartier

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