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2009 : July 2009 - Fast Moving Fronts : Dora M. Kovacs

FAST MOVING FRONTS - 2009

July 2009



Dora M. Kovacs talks with *ScienceWatch.com* and answers a few questions about this month's Fast Moving Front in the field of Neuroscience & Behavior.

**Article: Alzheimer's disease: the cholesterol connection**

Authors: Puglielli, L;Tanzi, RE;Kovacs, DM

Journal: NAT NEUROSCI, 6 (4): 345-351 APR 2003

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SW: Why do you think your paper is highly cited?

Our article addresses the connection between two important health issues, cholesterol and Alzheimer's disease (AD). Given that drugs currently on the market can reduce blood cholesterol levels, the question is whether these same drugs can also alleviate symptoms of AD. Therefore, interest in this connection is high from researchers around the world.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

This review paper outlines our current understanding of the role of cellular cholesterol in AD. Cellular cholesterol levels and distribution do not always correlate with blood cholesterol. However, the toxic molecule in AD called amyloid- β ($A\beta$) peptide is generated from cells, necessitating studies on cellular cholesterol. We have also summarized potential therapeutic strategies based on modulating cholesterol in patients affected by the disease. We have placed particular effort on fairly representing all aspects of this connection, including cellular, animal, and clinical studies.

SW: Would you summarize the significance of your paper in layman's terms?

Genetic and epidemiological data support a role for altered cholesterol metabolism in the pathogenesis of AD. In particular, studies of both animal and cellular models of AD show that cholesterol within single cells (intracellular) regulates the generation of the toxic $A\beta$ peptide. In animal models, hypercholesterolemia induced by high-cholesterol diets increased deposition of $A\beta$ in brains of rabbits and transgenic mouse models of AD. Pharmacological agents such as statins and ACAT inhibitors, which induce changes in cellular levels and distribution of cholesterol, have repeatedly been shown to modulate $A\beta$ production.

Statins reduce $A\beta$ production in cells and in most animal models of AD.

Mechanistically, statins not only reduce cholesterol, but also affect other metabolic pathways. Unfortunately, so far statins have failed to consistently improve

symptoms of AD in clinical trials.

Our own interest lies in another promising cholesterol pathway, mediated by acyl-coenzyme A: cholesterol acyltransferase (ACAT). ACAT inhibition has long been studied as a potential antiatherosclerotic strategy, resulting in both reduced intestinal cholesterol absorption and foam cell formation. We have first presented genetic, metabolic, and pharmacological evidence that ACAT inhibition dramatically reduces A β generation. Later, we confirmed this in animal models of AD.

Therefore, the significance of studying the role of cholesterol in AD is three-fold. First, statins and/or ACAT inhibitors represent potential strategies for the prevention and/or treatment of the disease. Second, mechanistic studies will lead to the understanding of novel pathways for the regulation of A β generation. Third, these novel pathways may in turn lead to novel therapeutic strategies for reducing A β production in AD patients.

"Therapies already developed for atherosclerosis and cardiovascular disease are being considered for Alzheimer's disease."

SW: How did you become involved in this research and were any particular problems encountered along the way?

More than 10 years ago, we had noticed that a particular cell line lacking ACAT failed to generate the toxic A β peptide. We confirmed this by inhibiting ACAT in different ways in cell-based models of AD and in primary neurons. We showed that two existing ACAT inhibitors also inhibited A β production by up to 50%. Excited by these results, we examined the effect of ACAT inhibitors in transgenic mouse models of AD. In particular, in one model we found that two months of treatment with an ACAT inhibitor decreased brain amyloid plaque load by 88-99% and insoluble A β levels by 83-96%.

These results are highly encouraging for the potential use of ACAT inhibitors in AD patients. However, ACAT inhibitors are currently not marketed for the prevention of high blood cholesterol or atherosclerosis. More research is needed to develop safe and effective inhibitors for human use.

SW: Where do you see your research leading in the future?

Therapies already developed for atherosclerosis and cardiovascular disease are being considered for AD. Clinical trials with statins are ongoing. As the mechanism of action of ACAT inhibitors is not well-characterized, more studies are needed to determine how exactly ACAT inhibition reduces generation of the toxic A β peptide.

More recently, we've studied an ACAT inhibitor which has previously been tested in clinical trials for prevention of atherosclerosis. As expected, this inhibitor also improved AD-like pathology in the brains of transgenic mice. Most importantly, it was also effective in an older animal group where the mice had already developed significant pathology before the treatment. This experiment was similar to treating AD patients, as in this case the mice have recovered from already existing amyloid pathology. Our studies using older animals offer the strongest hope that ACAT inhibition may be considered for the treatment and prevention of AD.

SW: Do you foresee any social or political implications for your research?

Our finding that ACAT inhibition reduces A β generation *in vitro* and *in vivo* suggests that ACAT inhibitors, currently under development for the treatment of cardiovascular disease, may also be effective in the treatment of amyloid pathology in AD patients. We hope that our findings will encourage the development of new ACAT inhibitors and clinical trials with these new compounds against AD.

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