

## Joint effort proposed to explore medical relevance of Maillard reaction

Plans are advancing to set up a £4-5 million (US\$6.2-7.8 million) project that could take research into Alzheimer's disease and other neurodegenerative disorders in a new direction. The project would test the hypothesis that the Maillard reaction, a basic spontaneous chemical reaction between sugars and proteins that was first described in 1912, is in some way involved in the pathology of certain neurodegenerative diseases such as Alzheimer's, Parkinson's and Creutzfeldt-Jakob disease.

The UK Office of Science and Technology is now considering whether to back the initiative, which would involve a consortium of researchers from academic institutions and industry. If support is forthcoming, the project will begin later this year.

Diseases under study are characterized by the formation of insoluble protein deposits or amyloid plaques that accumulate in the brain. Although it has been known for some time that these modified proteins are derived from normal cellular proteins, the mechanism of their formation is unclear. It is now proposed that in the body the Maillard reaction between sugars and protein to form glycated protein might account for the modification of normal cellular protein into amyloid plaques.

The project would be set up under the auspices of the government's LINK research programme. (LINK is a mechanism by which government sponsors research on a 50:50 cost-sharing basis with industry. It was established to promote technology development and transfer from academic institutions to industry.)

The consortium would set out to determine the potential pathophysiological relevance of the Maillard reaction, in the hope that this will lead to new forms of therapy based on inhibitors that act on the reaction pathway. The project would likely concentrate on four main areas: namely, the relationship between nutrition and the Maillard reaction, the role of the reaction in metabolic regulation, and in oxidative stress, and the possible toxic effects of the end products of the reaction.

The hypothesis that the Maillard reaction may have a role in the pathology of certain neurodegenerative diseases was put forward by Camilo Colaco, head of the Quadrant Research Foundation in Cambridge, England, an independent research

company funded by the biosciences company Quadrant Holdings. Since then, there has also been evidence that glycation may be involved in the development of Alzheimer-type pathology.

Last September, Colaco organized a meeting in Cambridge, sponsored by the Ciba Foundation and chaired by Aaron Klug, then director of the Medical Research Council Laboratory of Molecular Biology in Cambridge, in part to discuss the significance of the Maillard reaction in human disease but also to gauge the level of interest in this area. The meeting brought together academic researchers, as well as government officials from the Department of Health and the Ministry of Agriculture, Fisheries and Food. There was also considerable interest from industry: Novo Nordisk, Wellcome, SmithKline Beecham,

Glaxo, Unilever, Rhône-Poulenc Rorer and Zeneca all sent representatives.

The meeting highlighted the fact that most of the information on the Maillard reaction so far has come from the food industry where its importance in the production of colour and flavour in cooked foods, and in the spoilage of foods in storage, is widely recognized. Its possible physiological relevance was first hinted by Anthony Cerami and colleagues who, in 1977, identified a product of the Maillard reaction in a minor haemoglobin variant in diabetes. Since then, glycated proteins have been implicated in the pathogenesis of late diabetic complications, including atherosclerosis.

The US company Alteon of Northvale, New Jersey, is presently carrying out clinical trials to determine the efficacy of a Maillard reaction inhibitor that is intended to prevent diabetic complications.

It is also thought that the Maillard reaction may have a role in ageing. For example, the pharmaceutical company Glaxo is undertaking research in this area, as are groups at Columbia University in New York, Case Western Reserve University in Cleveland, Ohio, and the Picower Institute for Medical Research in New York State.

The possibility of a link between the Maillard reaction and neurodegenerative diseases occurred to Colaco as a result of research being undertaken at Quadrant Holdings, which has patents on the use of the sugar trehalose in the preservation of pharmaceuticals, foodstuffs and blood. (Trehalose is the sugar that is substituted for water molecules when organisms such as rotifers or desert plants go into suspended animation during periods of drought.) During experiments to compare the stabilizing ability of trehalose with other sugars, Quadrant researchers noted reducing sugars produced a brown coloration during storage of dried biomolecules. Further research showed that this coloration was a result of the preserving sugar reacting with the protein being preserved, and undergoing the Maillard reaction.

NUALA MORAN  
London

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**The Maillard reaction, first described by Louis-Camille Maillard in 1912, is actually a cascade of chemical reactions. The first step is a spontaneous carbonyl-amine condensation between reducing sugars and proteins to form a Schiff's base. This step, which requires very little activation energy, is reversible in the presence of water. There follows a complex cascade of dehydration, condensation, fragmentation, oxidation and cyclization reactions ultimately leading to the production of brown pigments, and both fragmentation and cross-linking of the proteins involved.** (Courtesy of Charles R. Harrington and Camilo A. L. S. Colaco. Reprinted with permission from *Nature* 370, 247; 1994, Macmillan Magazines Ltd.)

Colaco, C. A. L. S. & Harrington, C. R. *NeuroReports* 5, 859-861 (1994).  
Vitek, M. P. et al. *Proc. natn. Acad. Sci. U.S.A.* 91, 4766-4770 (1994); Smith, M. A. et al. *Proc. natn. Acad. Sci. U.S.A.* 91, 5710-5714 (1994).  
Harrington, C. R. & Colaco, C. A. L. S. *Nature* 370, 247-248 (1994).