Methylglyoxal and AGEs: culprits for cognitive decline in Alzheimer's disease.

Theme: Life Sciences and Technology

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Scientific background and general objective
Aging is the major risk factor for Alzheimer’s disease (AD). One of the hallmarks of aging is an increase of the very reactive dicarbonyl methylglyoxal (MGO) and the formation of advanced glycation end products (AGEs) [1]. MGO is the main precursor in the formation of AGEs. The primary chemical toxicity of MGO and AGEs are both linked unequivocally to the primary pathologies of AD, namely, amyloid plaques and neurofibrillary tangles [2]. Interestingly, we recently found that plasma AGEs are associated with cognitive decline [3] and depression [4]. Increasing evidence indicates that the brain vasculature tightly controls cognition. Considering that AGEs and the receptor of AGEs (RAGE), which is primarily activated by MGO-AGEs, markedly affect vascular function, we hypothesize that MGO-promotes cognitive decline in AD by affecting the physiology of the brain vasculature.

Specific aims
1. To determine MGO and AGEs in CSF and brain tissue of AD patients.
2. To explore the MGO-AGE/RAGE axis on cognition and brain vasculature in animal model of AD.

Rationale & methods
The focus will be on aim 1. Cognitive decline is associated with vascular dysfunction in AD. We first will determine MGO and specific AGEs in CSFs of AD patients with UPLC-MSMS. For this, we use well-defined CSF samples from 20 control, 60 mild cognitive impairment and 60 AD cases, from whom 1–2 year follow up data are available. The fill in of the specific work plan of aim 2 is depending on the availability of the amount of bench fee. We intend to explore a causal relationship between MGO-AGE/RAGE-signaling and cognitive decline in a mice model of AD. To study the impact of MGO, AD mice with or without overexpression of glyoxalase 1 are used. Glyoxalase 1 enhances the detoxification of MGO. Finally, we will assess if MGO-AGE/RAGE-signaling affects mouse brain endothelial, meningeal, and choroid plexus cells from WT and GLO-1 transgenic. We determine endothelial injury, NO bioavailability, and the expression of cognition-related mediators.

Expected results
This project will lead to putative new markers for early screening of AD and to an increased understanding of the role of MGO and AGEs in AD. In particular, it will help deepen the scientific knowledge of the role of AGEs on brain vascular function. This understanding will in turn contribute to the development of novel, improved strategies for the prevention and treatment of AD.

Literature: