

# RAGE and mitochondrial degeneration in diabetes

<https://neurodegenerationresearch.eu/survey/rage-and-mitochondrial-degeneration-in-diabetes/>

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### Country

USA

## Title of project or programme

RAGE and mitochondrial degeneration in diabetes

## Source of funding information

NIH (NIA)

## Total sum awarded (Euro)

€ 1,348,494.50

## Start date of award

01/08/2015

## Total duration of award in years

3

## The project/programme is most relevant to:

Alzheimer's disease & other dementias

## Keywords

receptor for advanced glycation endproducts, Mitochondria, Advanced Glycosylation End Products, Diabetes Mellitus, Dynamin

## Research Abstract

? DESCRIPTION (provided by applicant): Mitochondrial dysfunction and synaptic damage are early features of Alzheimer's disease (AD)-6- 10 and diabetes-affected brains. Diabetes

negatively affects the brain, increasing the risk of depression and dementia. In neurons, mitochondria at synapses are vital for maintenance of synaptic function and transmission through normal mitochondrial dynamics, proper distribution and trafficking, energy metabolism, and synaptic calcium modulation. Imbalance of mitochondria dynamics contributes to oxidative stress- and hyperglycemia-induced alterations in mitochondrial morphology and function. The underlying molecular and cellular mechanisms are poorly understood. RAGE (Receptor for Advanced Glycation Endproducts, AGEs) is a multiligand receptor of the immunoglobulin superfamily. RAGE functions as a signal transducing cell surface acceptor site for AGEs, S100/calgranuline, or amyloid-beta peptide (A $\beta$ ). Interaction of RAGE and its ligands increases oxidative stress, inflammation, A $\beta$  accumulation, and impairs synaptic function and learning memory. However, the impact of RAGE on mitochondrial and synaptic function in diabetes mellitus (DM) remains unknown. It is unclear whether RAGE is important mediator for AGE- and diabetes-induced mitochondrial and synaptic stress; whether and how RAGE-dependent signal transduction contributes to alterations in mitochondrial and synaptic structure and function in DM. In our preliminary studies, we have revealed a number of novel findings related to the regulation of mitochondria by RAGE. First, genetic depletion of neuronal RAGE alleviates AGE-induced synaptic dysfunction. Blockade of RAGE signaling rescued high glucose-induced mitochondrial alterations. Second, genetic depletion of global RAGE rescued abnormal mitochondrial morphology/function and synaptic injury in diabetes mouse brains as well as induction of proinflammatory mediators. Finally, RAGE exhibited biochemical interaction with DLP1 (dynamin-like protein 1), suggesting that DLP1 serves as a novel substrate to mediate the effect of RAGE on mitochondrial distribution. Further, inhibition of excessive mitochondrial fission or RAGE attenuated DM-induced induction of proinflammatory cytokines and chemokine. These findings lead us to hypothesize that in diabetes, chronic and sustained accumulation of AGEs and proinflammatory RAGE ligands, and upregulation of RAGE, perturbs mitochondrial structure and function, and oxidative stress, leading to synaptic mitochondrial dysfunction and synaptic injury in DM. This proposal will address the fundamental questions of whether RAGE is a key player in diabetes-induced mitochondrial and synaptic injury and whether blockade of RAGE restores mitochondrial and neuronal function.

### **Lay Summary**

**PUBLIC HEALTH RELEVANCE:** The goal of this proposal is to gain new insight into the role of RAGE in diabetes-induced mitochondrial and synaptic injury and possible cross talk of molecular and cellular mechanisms between diabetes and Alzheimer's disease. Our findings will provide further substantial support for targeting RAGE as a key therapeutic strategy in diabetes in particular for prevention and treatment of mitochondrial and synaptic degeneration at the early stage of disease.

### **Further information available at:**

#### **Types:**

Investments > €500k

#### **Member States:**

United States of America

#### **Diseases:**

Alzheimer's disease & other dementias

#### **Years:**

2016

**Database Categories:**

N/A

**Database Tags:**

N/A