

## The bile acid TUDCA improves glucose homeostasis through increase of insulin levels in mice with Alzheimer's disease

Lucas Zangerolamo\*, Jean Franciesco Vettorazzi, Carina Solon, Gabriela Moreira Soares, Raquel Crespo Enchn, Everardo Magalhães Carneiro, Licio Augusto Velloso, Antonio Carlos Boschero, Helena C. L. Barbosa-Sampaio

### Abstract

Alzheimer's disease (AD) and Type 2 Diabetes Mellitus (T2DM) are two of the most prevalent disorders in the elderly population. Studies suggest that people with T2DM have higher risk of developing AD. Likewise, AD brains presents Insulin resistance resulting in low capacity of glucose uptake. There is a growing evidence that insulin resistance and downstream abnormalities in the insulin signaling pathway are present in the AD brain and contribute to the development of cognitive dysfunction. Here we reported that C57BL/6 mice submitted to intracerebroventricular injection of streptozotocin, model of AD, and treated during 10 days with the bile acid TUDCA presented reduced accumulation of A $\beta$  oligomer in the hippocampus and higher insulin secretion and glucose tolerance, besides improvement in memory test, suggesting that TUDCA treatment interferes with glucose-insulin homeostasis in brain and consequently attenuates AD.

### Key words:

TUDCA, glucose homeostasis, Alzheimer

### Introduction

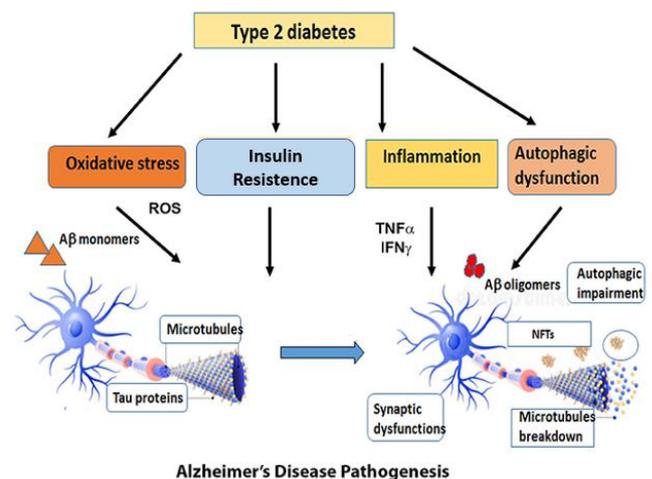
Alzheimer's is a neurodegenerative disease, hallmarked by the accumulation and extracellular deposition of amyloid- $\beta$  protein, intraneural hyperphosphorylated TAU and inflammation in the hippocampus and frontal cortex of the brain, resulting in the process of neuronal death, leading to memory deficits and progressive cognitive decline. Metabolic disorders characteristic of Type 2 Diabetes, such as glucose intolerance and insulin resistance, have been found in mice with Alzheimer, suggesting an intimate relationship between Diabetes and Alzheimer.<sup>2</sup> Tauroursodeoxycholic acid (TUDCA) is an endogenous bile acid with potent neuroprotective properties in several experimental models of AD. Furthermore, TUDCA regulates glucose metabolism by improving insulin secretion, signaling and degradation. The treatment with the bile acid TUDCA in animal models of Alzheimer's reduces the accumulation of amyloid- $\beta$ . Furthermore, mice with Alzheimer's have reduced brain levels of TUDCA. The aims of our study were to investigate the effects of bile acid TUDCA on glucose homeostasis in Alzheimer's disease mice model.

### Results and Discussion

C57BL/6 mice were submitted to intracerebroventricular injection of streptozotocin (Stz) for induction of Alzheimer's disease. AD was confirmed by increased amyloid oligomer in hippocampus, assessed by Western Blotting and reduced discrimination index in novel object recognition test (NORT), a memory test, in Stz mice. The treatment with the bile acid TUDCA (300 mg/Kg) reduced A $\beta$  deposition and increases NORT index, compared to Stz. Moreover, TUDCA treatment improved glucose tolerance, fasted and fed glycemia. In order to evaluate insulin levels, we measured insulin in serum of mice in fasted (16h) and after 30 minutes of glucose gavage. Mice treated with TUDCA presented higher levels of insulin in serum after glucose gavage, compared to Stz

mice, what could explain, at least in part, the improvement in glucose tolerance.

**Image 1.** Overview of the diverse mechanisms by which Type 2 Diabetes can cause AD pathogenesis.<sup>1</sup>



### Conclusions

Our results show that the bile acid TUDCA improves glucose homeostasis in a model of Alzheimer disease, probably through increased insulin secretion, and, thus, attenuating glucose disorders observed by Alzheimer's disease in Stz mice.

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<sup>1</sup> Chatterjee S and Mudher A. Alzheimer's Disease and Type 2 Diabetes: A Critical Assessment of the Shared Pathological Traits. *Front. Neurosci.* 2018; 12:383.

<sup>2</sup> Gaurav Bedse, Fabio Di Domenico, Gaetano Serviddio, Tommaso Cassano. Aberrant insulin signaling in Alzheimer's disease: current knowledge. *Front Neurosci.* 2015; 9: 204.