

**Title:** WISTAR AUDIOGENIC RAT (WAR): A NEW AND NON-CONVENTIONAL  
MODEL FOR THE STUDY OF SPORADIC ALZHEIMER'S DISEASE  
HYPOTHESIZED AS TYPE 3 DIABETES

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## **ABSTRACT**

### **Introduction**

Alzheimer's disease (AD) is the most frequent cause of dementia. Due to significant alterations in the insulin signaling pathway observed in post-mortem brain samples from patients with this type of dementia, AD has been considered by many authors as type 3 diabetes. Previous studies from our group have identified memory impairment, abnormal tau hyperphosphorylation, and metabolic abnormalities in the Wistar Audiogenic Rat (WAR) strain, a genetic model of epilepsy.

### **Objective**

To investigate the WAR strain as an alternative model for the study of the sporadic late-onset form of AD related to central insulin resistance.

## Methods

We selected 49 male adult and aged animals (n=28 Wistars and 21 WARs). The animals were subjected to the Morris Water Maze (MWM) test. After the MWM, the rats were euthanized and their ventral (VH) and dorsal (DH) hippocampi were dissected and stored for Thioflavin T fluorescent assay and Western blot analysis in order to measure the levels of A $\beta$ , tau, pTau (S396), insulin receptor (IR), alpha and beta phosphorylated glycogen synthase kinase 3 (pGSK-3 $\alpha/\beta$  Ser21/9). The results were confirmed by immunohistochemical analysis. We also added an additional group (7 animals) to quantify the number of positive cells for phospho-insulin receptor substrate-1 (pIRS-1 S312) through immunohistochemistry. All protocols were approved by CEUA (protocol n° 167/2016).

## Results

Both adult and aged WARs showed longer latency (p<0.001) and distance travelled (p<0.001) to find the escape platform in the MWM test. Aged WARs present worse performance than adult WARs in the tests (p<0.01). Both strains presented progressive increase in amyloid-beta levels (p<0.0001), but they did not differ from each other. The adult WARs presented lower IR expression in the VH (p<0.05), higher pGSK-3 $\alpha/\beta$  (S21/9) expression in the DH (p<0.05), and higher number of positive cells for pIRS-1 (S312) in the hippocampus (p<0.01). The aged WARs presented higher pTau (S396) expression in both VH and DH (p<0.01), lower IR expression in the VH (p<0.05), higher pGSK-3 $\alpha/\beta$  (S21/9) expression in both VH and DH (p<0.05).

## Conclusions

Although the WAR strain does not present the classic AD pathology observed in transgenic mice, our findings suggest the coexistence of an AD-like phenotype and central insulin resistance in addition to the initially selected epilepsy phenotype. Further studies are needed for a better understanding of the epilepsy-Alzheimer's-diabetes connection.

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