sciforum
IECBS 2022 The 3rd International Electronic Conference on Brain Sciences
01–15 OCTOBER 2022 | ONLINE
Neuropsychology
Sciforum – 063418
brain sciences MDPI

Obesity, impaired glucose metabolism and hepatic histopathological damage in 3xTg-AD mice at different stages of disease compared to mice with normal aging

UAB Universitat Autònoma de Barcelona

Clara Pérez-Gozalbo 1 and Lydia Giménez-Llort 1,2

1. Institut de Neurociències and 2. Dept Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

INTRODUCTION

- Obesity significantly increases the risk for cognitive impairment and leads to brain insulin resistance because of the disruption of homeostatic mechanisms. Some studies show that weight-loss reversal of insulin resistance improves cognitive performance and neuropsychiatric function and that adherence to Mediterranean diets reduces the metabolic risk for AD [1] .
- The most common form of diabetes, T2DM, is characterized by insulin resistance and is considered a metabolic disorder closely tied to overweight or obesity. Ongoing research has demonstrated that the diabetes epidemic results from a complex interaction between genetic and epigenetic predispositions and societal factors that, in combination, determine behavioral and environmental risks [2].
- Studies have linked peripheral insulin resistance, visceral obesity, and metabolic syndrome to brain atrophy, cognitive impairment, and impaired executive function [3]. Overall, the findings in humans and experimental models suggest that peripheral/systemic insulin resistance disease states serve as cofactors in the pathogenesis and progression of neurodegeneration [4].
- NASH, first described by Ludwig et al. in 1980 [5], is a form of non-alcoholic fatty liver disease (NAFLD) characterized by fat accumulation in the liver, inflammation, and hepatocellular lesion [6]. Steatohepatitis increases endoplasmic reticulum stress, oxidative damage, mitochondrial dysfunction, and lipid peroxidation, which drive hepatic insulin resistance, dysregulating lipid metabolism and promoting the production of toxic lipids [1]. Toxic lipids generated in the liver can cause degeneration [4]. NAFLD with T2DM and visceral obesity are associated with brain atrophy and cognitive impairment.
- The crosstalk between obesity, diabetes, steatohepatitis, and dementia creates a controversial scenario also when studied using animal models.

AIMS

In the present work, this crosstalk was investigated in male and female 3xTg-AD mice for Alzheimer's disease (AD) [7] at different ages/stages and compared to sex- and age-matched counterparts with normal aging.

METHODS and RESULTS

The relevance of the genetic background and classical intrinsic factors (AD genotype and sex) were determined using a retrospective analysis of population data and an experimental design. Age/stage of disease was considered a source of stochastic and non-stochastic factors. Data from two different colonies of 3xTg-AD mice with distinct genetic backgrounds were analyzed to verify the functional interplay between the studied factors. Data from asymptomatic (2m)/prodromal (4m) to early (6m)/advanced (12,15 and 18m) stages of the disease were screened.

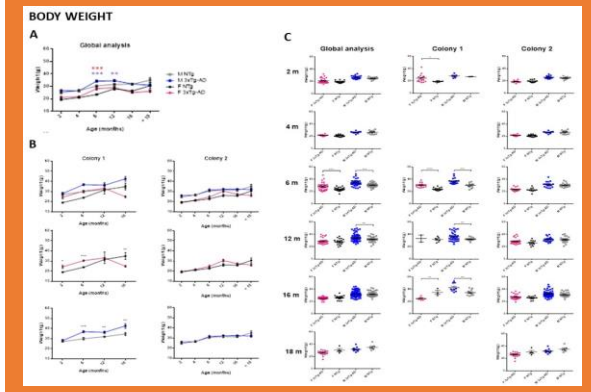

Fig1. Body Weight A. Global analysis. Mean weight in male and female NTg and 3xTg-AD mice. B. Mean weight in the two colonies 1 and 2. C. Scatter plot for individual data. In all cases, at different ages in males (blue) and females (red). *$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Then, all factors' relationships were studied in an experimental design using a same set of male animals. The population data unveiled that the genetic background and sex effects were confirmed with regards to the variable body weight, with changes during the disease development and progress. Besides, sexual dimorphism was found as an important factor in glucose metabolism.

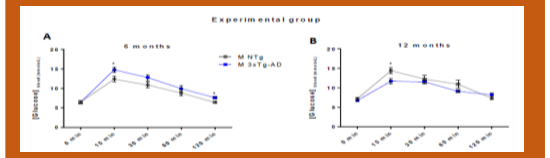

Fig2. Intraperitoneal glucose tolerance test A. IPGTT (mmols/L) after 15, 30, 60 and 120 min of glucose injection at 6- (A) and 12-(B) months of age. Student's t-test, *$p < 0.05$.

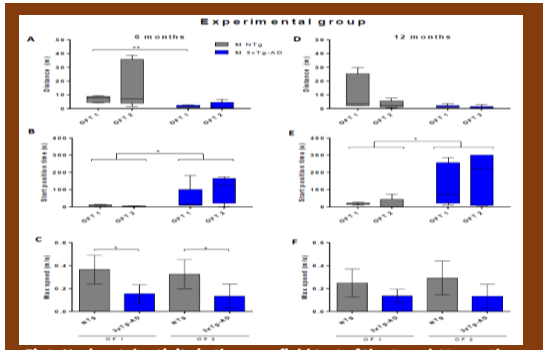

Fig3. Horizontal activity in the open field test of the 6- and 12-month-old Experimental group animals. Min to max values of the distance (A & E), start position time (B & E) and max speed during the test (C & F). Two-way ANOVA analysis for B & E; student t' test for A, D, C & F.

Statistically significant differences in glucose tolerance and behavioral assessment (exploration, anxiety, and cognition in a two-days open-field paradigm) were found when all the factors were analyzed.

CONCLUSIONS

The existing crosstalk between obesity, diabetes, steatohepatitis and AD development is not elucidated nowadays, so the use of a widely used model such as the 3xTg-AD mice may enable the contributing factors as genetic background, sex, age and genotype to be defined.
Specifically, we found that males showed more weight problems starting at 6 months of age depending on the genetic background and genotype but females revealed an impaired glucose metabolism much sooner depending on the same factors. In the experimental group, there is not difference in weight nor weight loss after OF but the difference becomes clear in the glucose tolerance test, when the 6-month-old 3xTg-AD group reveals a similar impairment than the 12-month-old NTg group because of the normal aging. Furthermore, the anxiety-like profile present at both age groups correlates data with AD development. Therefore, the 3xTg-AD mouse models human sex differences in the progression and expression of the disease and elucidates a distinct functional interplay of the weight, glucose tolerance and behavior/pathology among the age. Moreover, interaction effects among genetic background, age, sex, and genotype should always be taken into consideration when assessing the outcome of those interventions.
In summary, the present study shows that all the studied factors should always be considered when assessing the outcome of the research interventions in the field because they have a distinct functional interplay through the process of normal and AD-pathological aging and from a gender perspective.

REFERENCES

1. De la Monte SM (2014) Endocrinol Metab Clin North Am 43:245–267.
2. Culberson JW (2017) Progress in Molecular Biology and Translational Science (Vol 146, pp. 1-11). Elsevier B.V.
3. Baglietto-Vargas D, Shi J, Yaeger DM, Ager R, LaFerla FM (2016) Neurosci Biobehav Rev 64:272–287
4. De la Monte SM, Tong M (2014) Biochem Pharmacol 188:548–559.
5. Ludwig J, Viggiano TR, McGill DB, Oh BJ (1980) Mayo Clin Proc 55:434—438
6. Adams 2019 Adams LA (2019) Hepatol Int 13:389–397
7. Oddo et al. (2003) Neuron 39:409–421.