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Sex-dependent hepatomegaly and increased hepatic oxidative stress in old male and female 3xTg-AD mice as compared to mice with physiological aging

INc Institut de Neurociències

Juan Fraile-Ramos 1,2 , Lydia Giménez-Llort 1,2

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

UAB Universitat Autònoma de Barcelona

INTRODUCTION

- Among the neurodegenerative diseases, Alzheimer's disease (AD) stands out as the cause of the most prevalent form of dementia and its main risk factor is age. Most symptoms are not apparent for years until the progress of the disease debuts at a certain age. Therefore, clinical and basic biological research of AD is not just focused on its neuropathological hallmarks but also the search of biomarkers of its incipient stages or those that can be useful for disease monitoring [1].
- Thus, in addition to well-known hallmarks such as β-amyloid plaques and hyper-phosphorylated tau protein, research now reveals that AD generation and progression is not only dependent on these neuropathological alterations but oxidative stress and inflammation play an important role [2-4]. In this sense, the derangement of these physiological processes in AD may be regulated by peripheral organs [5]
- Until now, most research has focused on the brain, but this new perspective raises questions about the involvement of other organs, such as the liver, main organ regulating metabolism and involved in supporting the immune system [5,6].
- REFERENCES:

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AIMS

In the present work, we studied the impact of AD-genotype and sex effects on liver dysfunction in 16-month-old males and females 3xTg-AD mice [7], an age mimicking neuro-pathological advanced stages of disease [8], and as compared to age- and sex-matched C57bl/6J non-transgenic mice with normal physiological aging.

METHODS

For this purpose, livers from male and female (C57BL/6) mice and 3xTg-AD mice were extracted, weighed and processed.
The anti-oxidant capacity was studied from the evaluation of the levels of total glutathione (GSH), as well as the enzymatic activity of glutathione peroxidase (GPx) and reductase (GR) from the homogenization of the liver.

Results are expressed as mean ± SEM. GraphPad Prism 8. The size of nests was analyzed with RM repeated-measures ANOVA with genotype and sex as between factors, day as within factor. One-way analysis of variance (ANOVA) followed by Bonferroni's post-hoc test; additional T-test were also used. Statistical significance: p<0.05.

RESULTS

1. Liver index

The results of physical damage observed in the weight correspond to a loss of liver weight in the case of 3xTg-AD female mice.
The mass index showed a trend of hepatic damage exhibited as hepatomegaly in 3xTg-AD mice, being significative in the males (Fig 1, G, genotype and S, sex factors, both *p<0.05).

2. Hepatic tissue oxidative stress, measured through antioxidant enzymes glutathione reductase (Gr) and glutathione peroxidase (Gpx), and antioxidant compound glutathione (GSH), was found altered in 3xTg-AD mice and differed according to sex.

GSH was observed to tend to be lower in females.
Gr and Gpx showed opposite alterations according to genotype, while Gr increase its levels in transgenic mice, the opposite happens in Gpx and levels tend to decrease (Fig 2, G, genotype and S, sex factors, *p<0.05, **p<0.01).

3. Correlation analysis

Furthermore, the meaningful correlations analysis between the enzymes themselves and the hepatic index also showed S, sex and G, genotype differences (Fig 3). Some of the correlations become more significant while others move from positive to negative correlation and vice versa.

1. Liver index

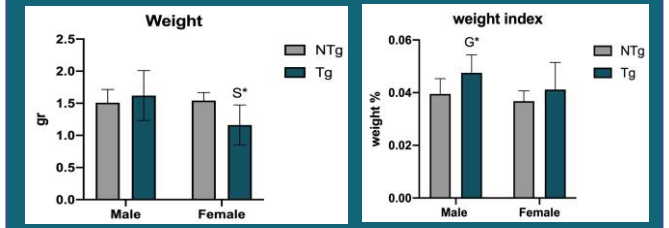

Figure 1. Liver weight and liver index.
N= 6-10 MEAN ± SD, G* p< 0.05, S* p<0.05.

2. Hepatic oxidative stress

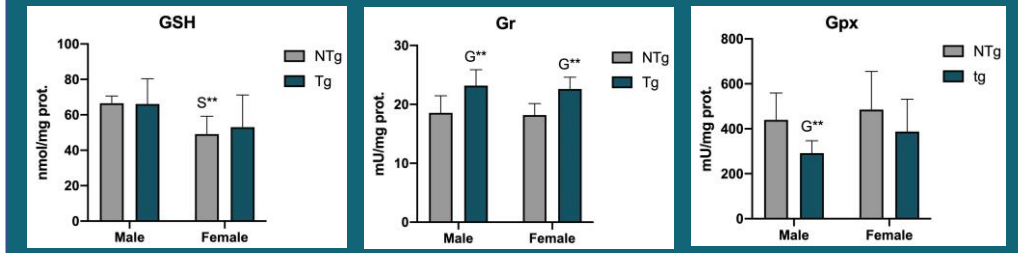

Figure 2. Levels of total GSH and enzymatic activity of Gr and Gpx.
N= 6-10
MEAN ± SD,
G** p< 0.01,
S** p<0.01.

3. Correlation analysis

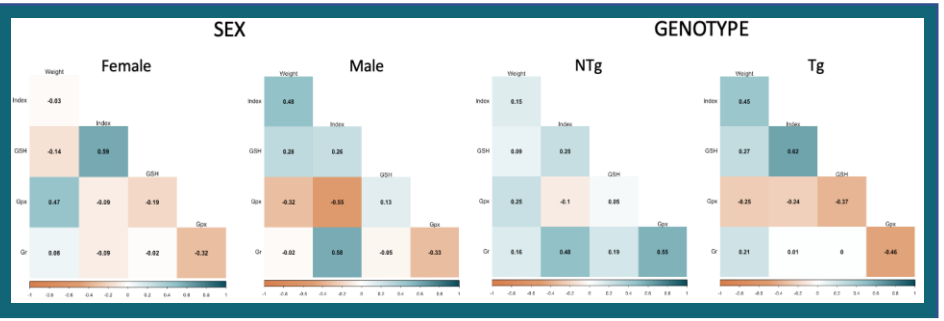

Figure 3. Correlation plot representing the positive and negative relation between variables

N = 12-20
Pearson correlation test, significance p<0.05.

CONCLUSIONS

The liver status was affected in the 3xTg-AD mice, and it was in a sex-dependent differential manner and could be favoring its progression.
Further ongoing research would determine if these alterations correlated with a worse prognosis of the disease.