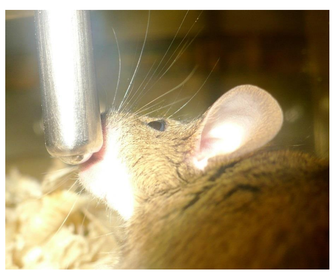
Effect of resveratrol in a transgenic animal model of Alzheimer´s disease



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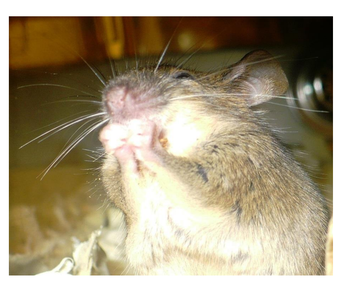
Introduction:



Alzheimer's disease (AD) is a degenerative brain disease characterized by the presence of two neuropathological hallmarks: amyloid plaques and neurofibrillary tangles. Both are involved in the process leading to progressive neurodegeneration and neuronal death. Beta-amyloid depositions are mainly located in the frontal and parieto-temporal cortex.

Fig 1: Triumph™ PET/SPECT/CT Scanner (TriFoil Imaging)

Resveratrol is a liposoluble polyphenol present in grapes and other nutrients. Many in vitro studies have indicated that
it has an antioxidant effect preventing the formation of toxic beta-amyloid oligomers. Binding to amyloid fibrils have been also described.

Pittsburgh Compound B labeled with ^{11}C (PIB) is a PET tracer that binds to fibrillary beta-amyloid and is used clinically in the diagnosis of AD as well as in other amyloidosis.

The Uruguayan Centre of Molecular Imaging (CUDIM) is dedicated to develop research, training and applications in health sciences, where diagnosis and biomedical research activities are promoted. Clinical examinations for patients primarily in the fields of oncology and neurology are performed.

Methods:

The aim of this study is to evaluate the effect of resveratrol on amyloid depositions in a transgenic (Tgs) mouse model of AD (B6; 129-*Psen1*^{tm1Mpm} Tg(APPSwe,tauP301L)1Lfa/Mmjax). Translation of the over expressed transgenes to be restricted to the central nervous system, notably in Alzheimer's disease-relevant areas including the hippocampus and cerebral cortex. The initial characterization of this mouse line indicated a progressive increase in amyloid beta peptide deposition, with intracellular immunoreactivity being detected in some brain regions as early as 3-4 months. Synaptic transmission and long-term potentiation are demonstrably impaired in mice 6 months of age. Between 12-15 months aggregates of conformationally altered and hyperphosphorylated tau are detected in the hippocampus. This mutant mouse exhibits plaque and tangle pathology associated with synaptic dysfunction, traits similar to those observed in Alzheimer's disease patients. (Provider Description: The Jackson Laboratory)

Two groups of Tgs females mice (n=4) were used, weight (19–28)gr one under treatment with resveratrol and another as sham control. The treatment started when the mice were 10 weeks old with an oral administration (in water) of (1.5-2.0) mg/day of resveratrol.

PET/CT studies with PIB were performed using a preclinical PET/SPECT/CT camera (Triumph™) (Fig 1) at 3, 6 and 9 months old for all the groups. PIB was injected i.v. immediately before starting dynamic acquisitions during 1hour (Injected Activity:13.11±2.93MBq; Specific activity: 119.72 ± 45.52 GBq/µmol) PIB uptake was analysed in different brain regions and normalized to a specially defined cerebellar cortex VOI. The image analysis and quantification was done using PMOD software.

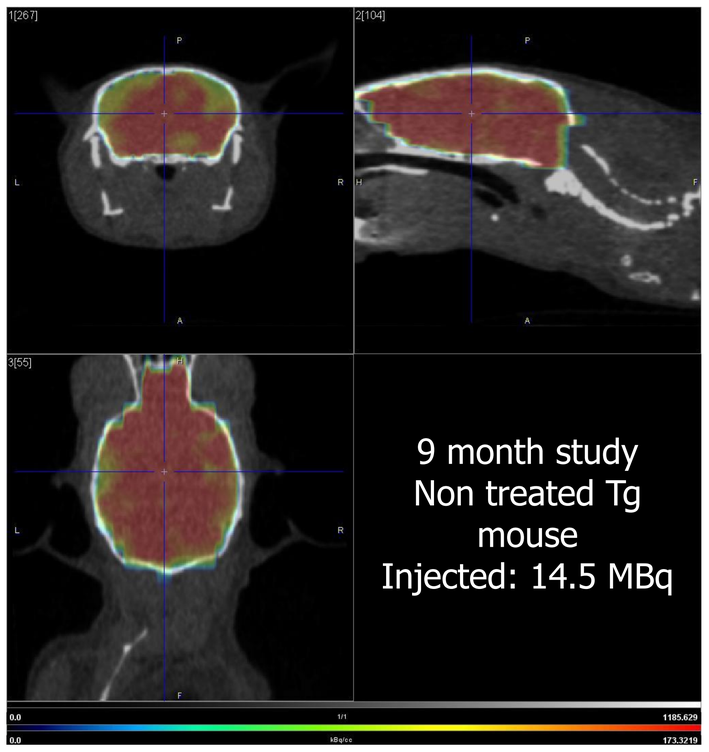


Fig 2: Tg Sham 9m

Results and discussion:

In the treated six-month-old Tgs mice a significant difference in PIB uptake in the hippocampus, cerebral cortex and midbrain was observed compared with the sham group. After nine months, the significant difference was observed even in the hypothalamus and the amygdala. No significant difference was found between treated Tgs and Tgs Sham 3m (normal control), in any of the above referred brain regions. (Tabla 1, Fig 2 y 3)

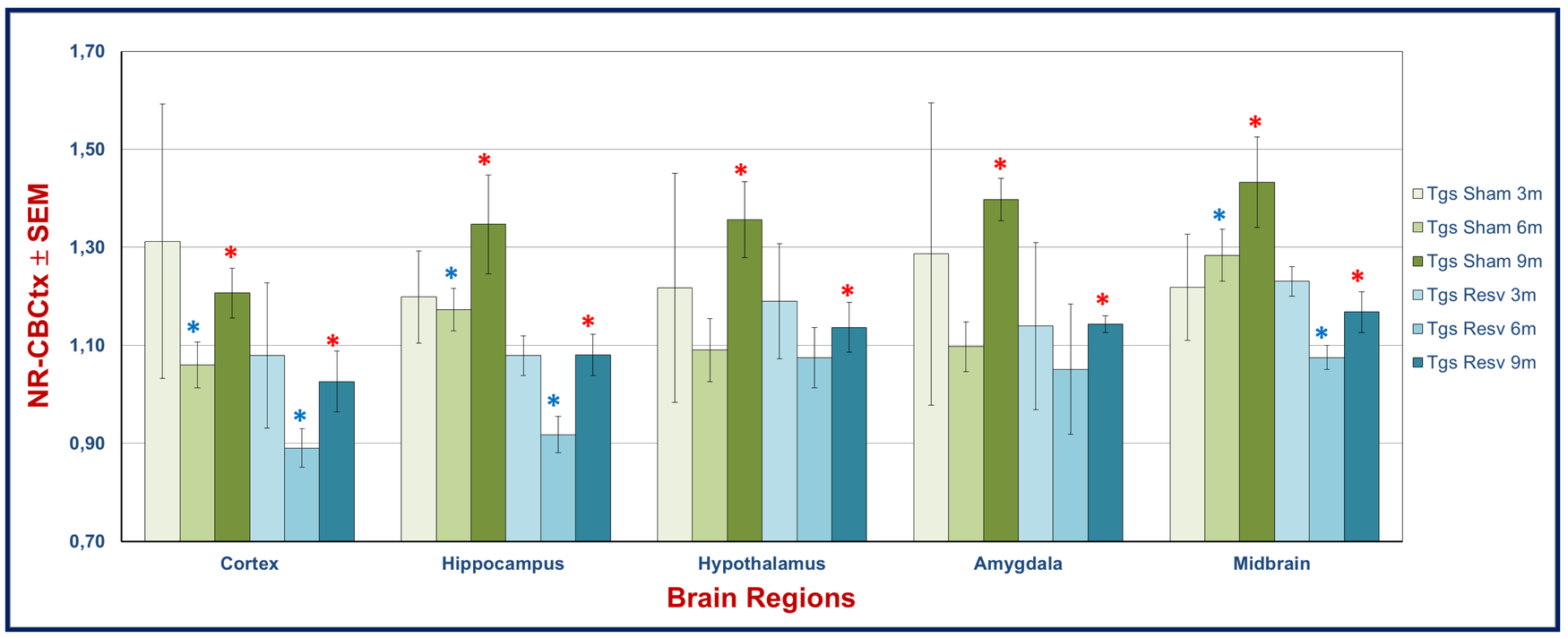


Table 1: NR-CBCtx Tgs, Sham and Resveratrol (3, 6, and 9 months) **p>0,05 ANOVA

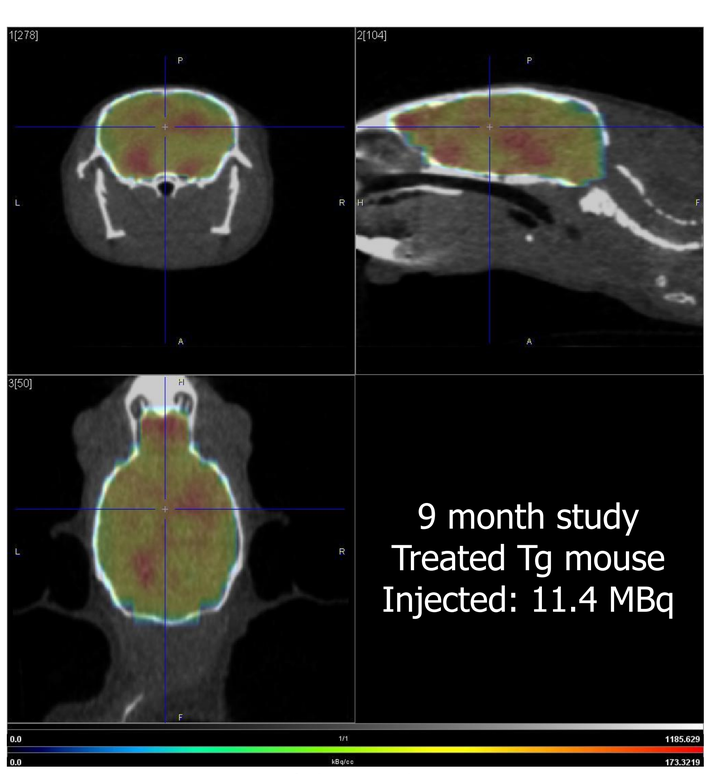


Fig 3: Tg Resv 9m

Conclusions:

These preliminary results support our hypothesis that resveratrol could bind to amyloid; blocking PIB and/or delaying amyloid depositions in Tg mice. These findings must be confirmed by anatomopathology and behavioural studies, which are in process