A ketogenic approach in a new mouse model of early Alzheimer's disease: characterisation of diets and the APP^{NL-G-F}/MAPT model in males and females

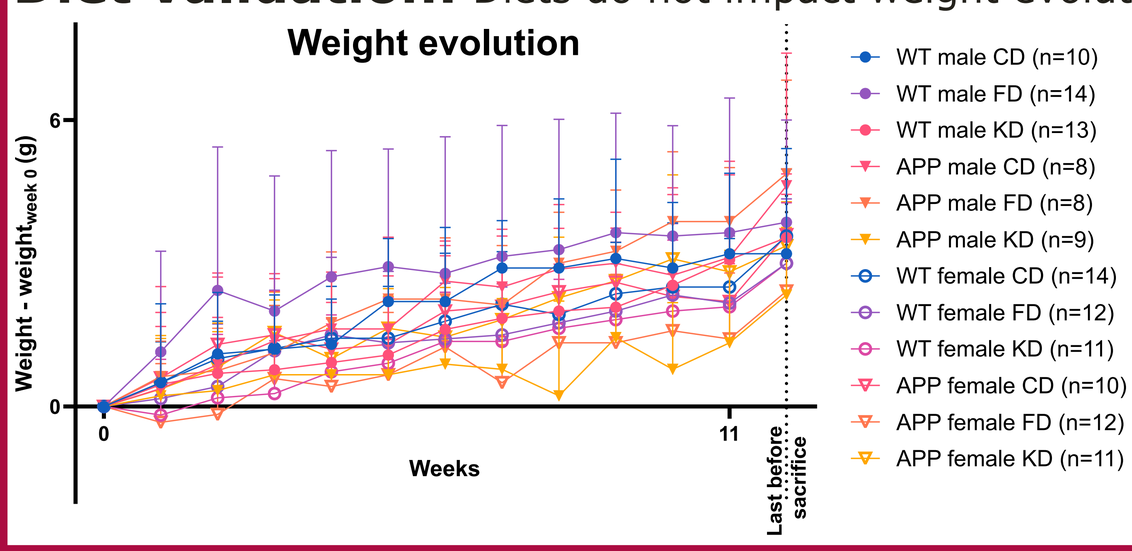
Antonin Morancé[1], Agnès Villers[1], Aurore Colomar[1,2], Laurence Ris[1]

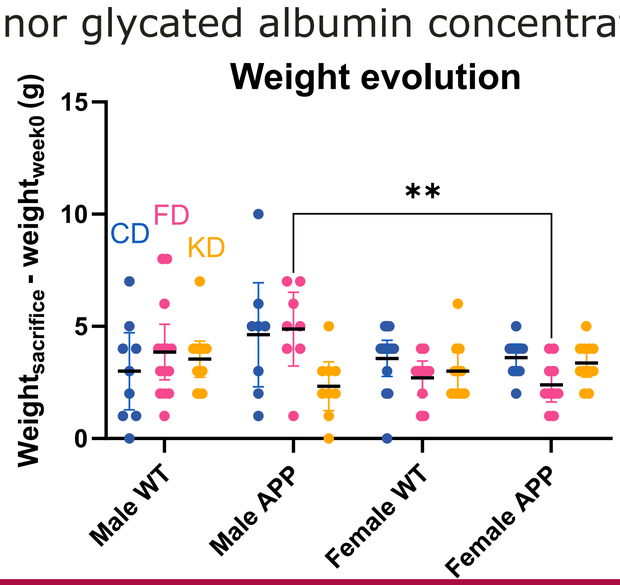
Introduction

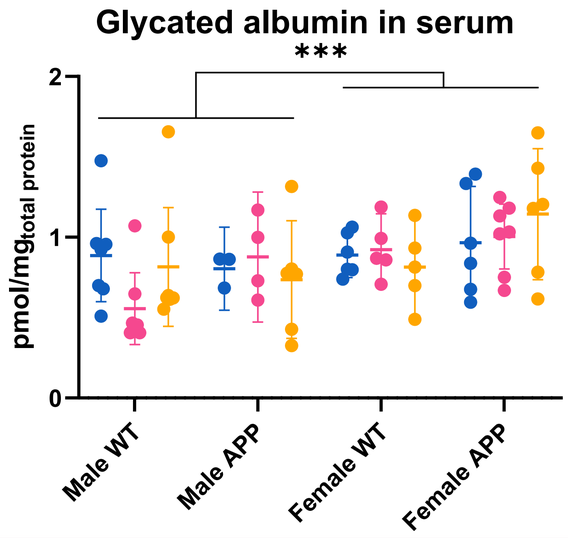
- Glucose hypometabolism is one of the earliest hallmarks of Alzheimer's disease (AD) (Mosconi *et al.*, 2008)
- The metabolism of ketone bodies is not affected in the brain of AD patients (Croteau *et al.*, 2018)
- Fructose can decrease brain metabolism and so the modern diet could impact the development of AD (Johnson *et al.*, 2023)
- Women are the most affected by the disease therefore sexual metabolic features are important to consider
- The ketogenic diet has beneficial effects but a bad adherence and we still do not understand all the mechanisms involved (role of PPAR-α for example)

Objective: In this first part we will characterize the new APP^{NL-G-F}/MAPT model and its brain metabolism as well as analyze the effect of a fructose-rich diet (FD) and a ketogenic diet (KD) in both males and females compared to a control diet (CD)
The **goal** is to determine a ketogenic approach specific for AD patients
Hypothesis: We expect the model to show signs of early AD pathology at 6 months
The ketogenic diet will prevent/delay the development of AD pathology in contrast to the fructose diet, which will worsen the pathology. Female and male mice will show different reactions to the diets and to the model mutations

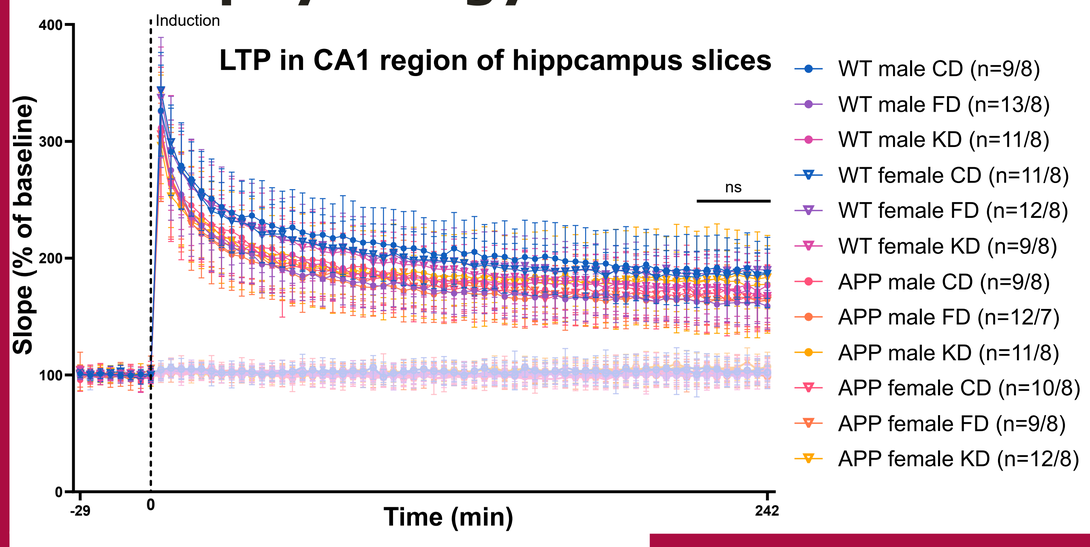
Diet validation: Diets do not impact weight evolution nor glycated albumin concentration

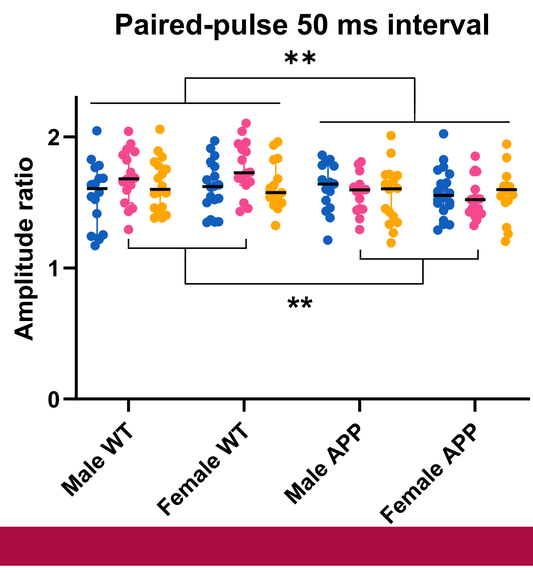


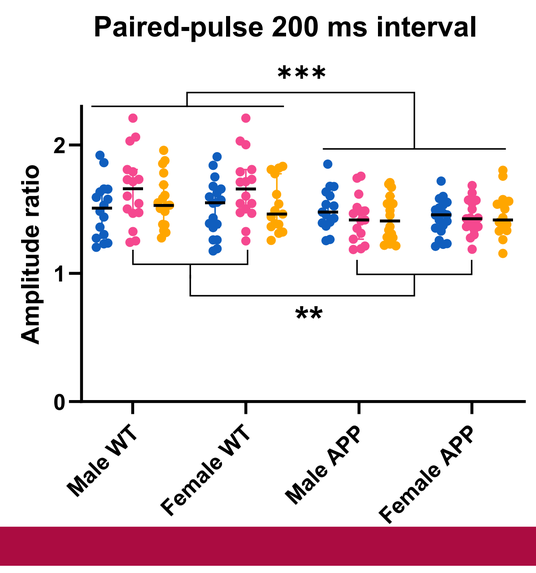


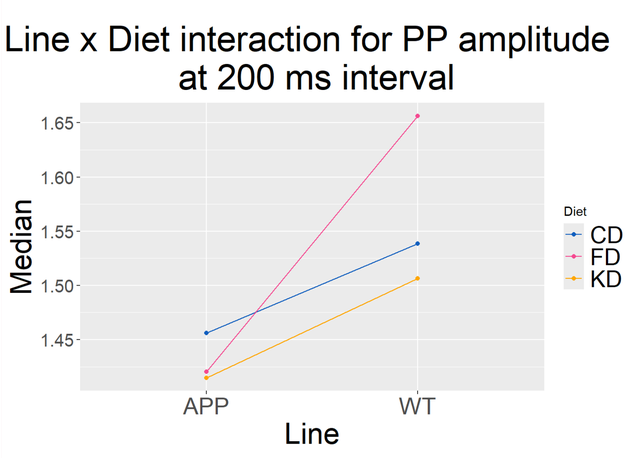


Electrophysiology: The strain did not affect LTP, but reduced paired-pulse facilitation with FD boosting the effect

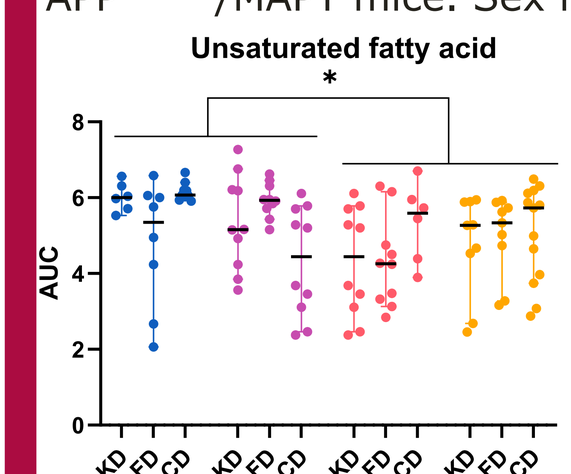


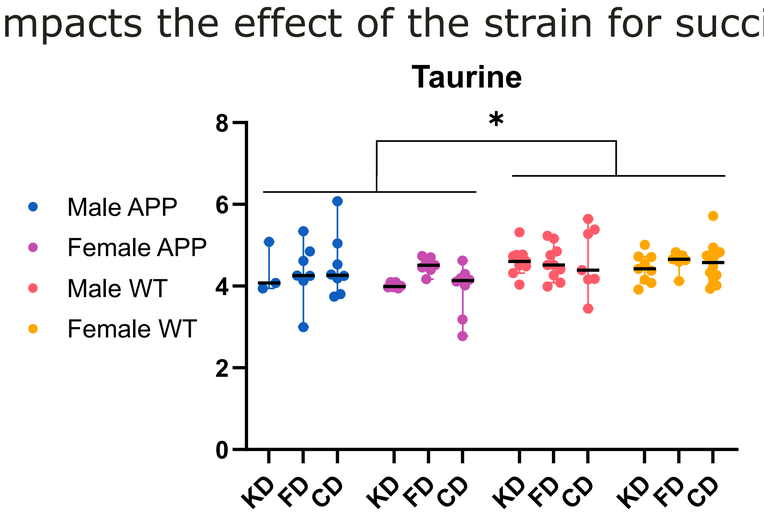


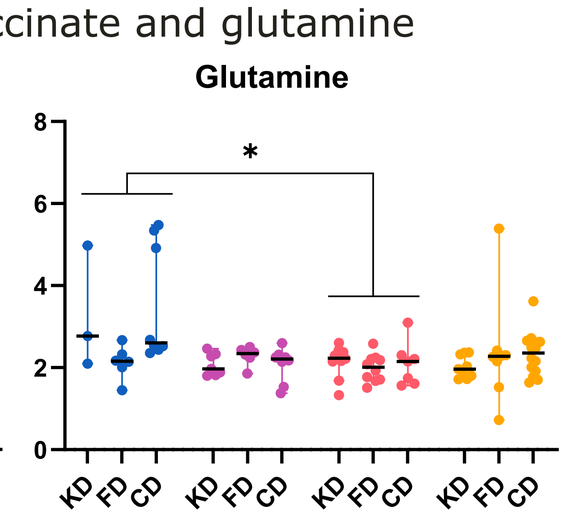


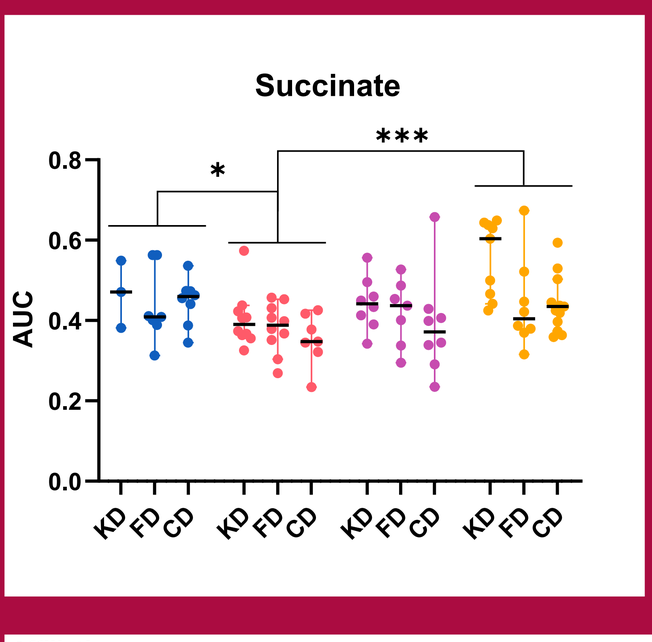


^{1}H-NMR: Taurine and unsaturated fatty acids levels are affected in the cortex of APP^{NL-G-F}/MAPT mice. Sex impacts the effect of the strain for succinate and glutamine









Conclusion

- At 6 months of age, the strain does not show deficits on LTP but short-term plasticity is altered, probably due to modification in synaptic Calcium homeostasis
- APP^{NL-G-F}/MAPT mice show little effect on cortex metabolism with an increase in UFA and a decrease in taurine, which is a common marker of AD
- Sex interacts with the effect of the strain, males showing more senstivity to metabolic changes of the APP^{NL-G-F}/MAPT strain while diets barely affected metabolism in the cortex
- KD failed to resolve deficits in APP^{NL-G-F}/MAPT mice. On the contrary, FD seems to amplify the effect of the strain on cognition

Perspectives: Aβ and inflammation investigation at 6 months as well as continuing the characterization of the model and the diets at later stages.
Completion of the data with behaviour, mass spectrometry and immunofluorescence

Affiliations:
1. Department of Neuroscience, Research Institute for Health Sciences and Technology, University of Mons, Mons, Belgium
2. Cognitive Psychology and Neuropsychology Department, University of Mons, Belgium

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