Relationship linking glucose metabolism to Amyloid Protein Precursor expression and processing

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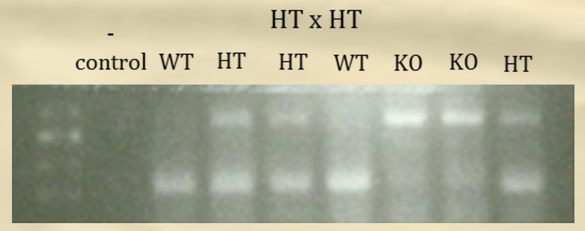
Introduction

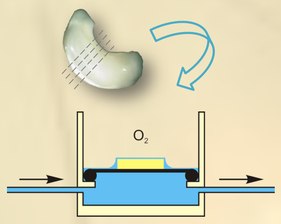
Nowadays, there is evidence that brain glucose metabolism and Alzheimer's disease (AD) are linked. Patients suffering from type II diabetes present a higher risk to develop AD while in Alzheimer's disease patients the brain glucose metabolism is reduced, leading to a general hypometabolism. This abnormal glucose metabolism can already be observed in genetically predisposed people before the expression of any clinical sign. It is therefore very important to better understand the link between brain utilization of glucose and AD. On the other hand, while beta-amyloid aggregates are one of the principal hallmarks of the disease, all strategies targeting these aggregates have failed until now to prove their efficacy. Targeting the amyloid precursor protein (APP) itself and its role in brain metabolism could bring some new insights and lead to novel therapeutic strategies.

Aim

The aim is to better understand the link between the expression and the processing of APP and brain glucose metabolism and its impact on neuronal activity and synaptic connections.

Experimental design





[Glucose] in the aCSF	Condition
10mM	Control
5mM	Mild GD
2.5mM	Severe GD

APP knockout mice

Genotypes obtained from APP heterozygous (HT, +/-) mice breeding. Primers target the APP WT allele (+) or the KO allele (-).

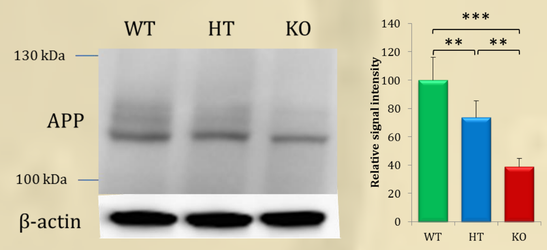
Glucose deprivation in acute hippocampal slices

The hippocampus is isolated from the brain and cut into 400µm thick slices. Slices are incubated in oxygenated aCSF at 32°C. aCSF glucose concentration is modulated to have 3 different conditions: control, mild and severe glucose deprivation (GD).

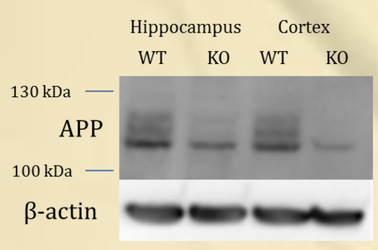
Preliminary results

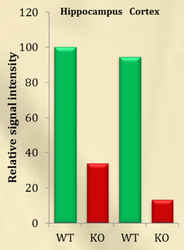
Western-Blotting

Hippocampus



Cortex

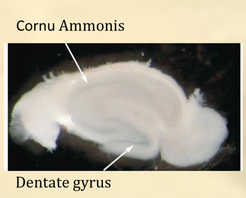


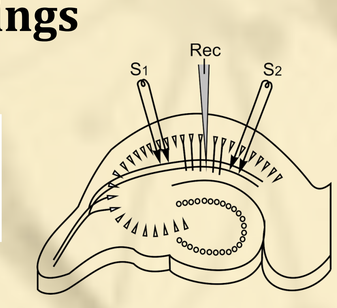


Relative APP signal detection in WT, HT and KO mice in the hippocampus (n=3) and in the cortex (n=1).

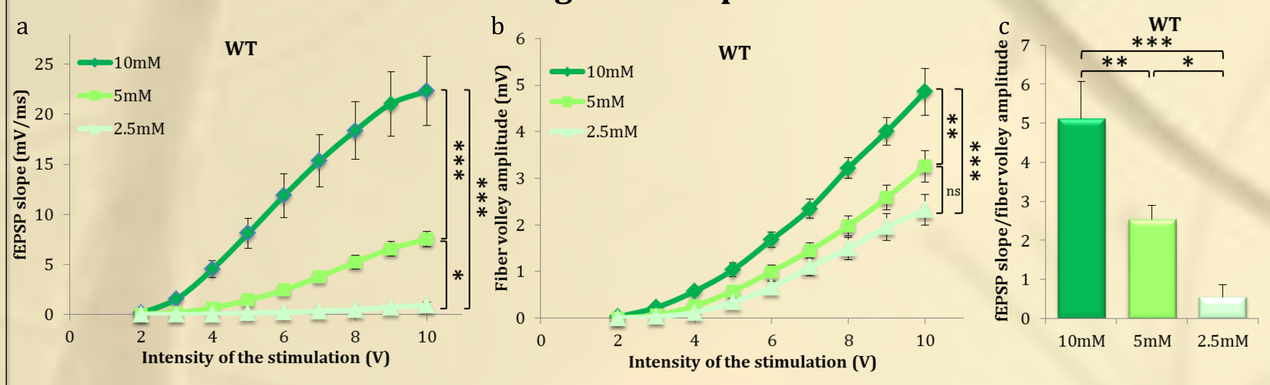
Electrophysiological recordings

Activity of the CA1 neuronal network is tested by stimulating the Schaffer collaterals and recording the fiber volley and the fEPSP in the *stratum radiatum* of hippocampal slices.

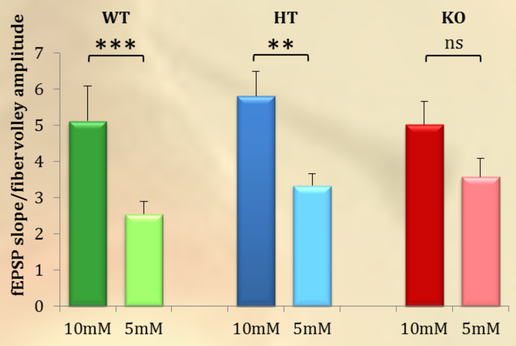




Effect of glucose deprivation

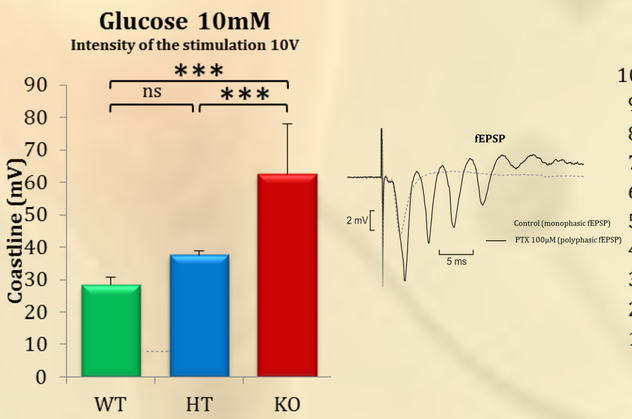


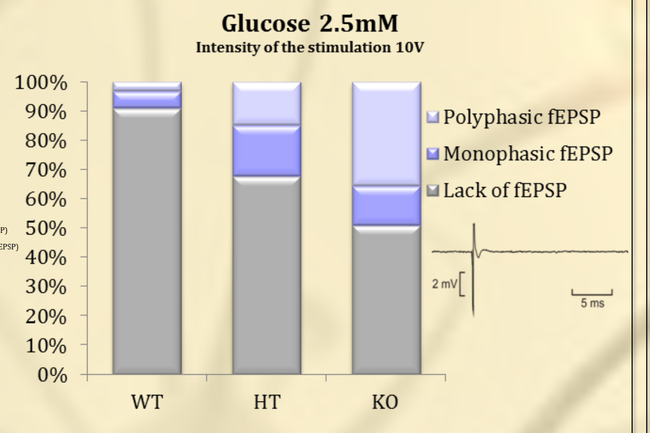
Glucose deprivation reduces synaptic transmission and excitability in CA1 area of hippocampal slices in a concentration dependant way. fEPSP slope (a) and fiber volley amplitude (b) are measured in response to increasing stimulation intensity (2V-10V). (c) Ratio between fEPSP slope and fiber volley amplitude at 10 mV (10mM: n=10, 5mM : n=10, 2.5mM: n=8).



The sensitivity to moderate glucose deprivation seems to be correlated with the level of expression of APP in the hippocampus (WT 10mM: n=10, WT 5mM: n=10, HT 10mM: n=15, HT 5mM: n=18, KO 10mM: n=10, KO 5mM: n=10).

Effect of GABA antagonist, picrotoxin (PTX)

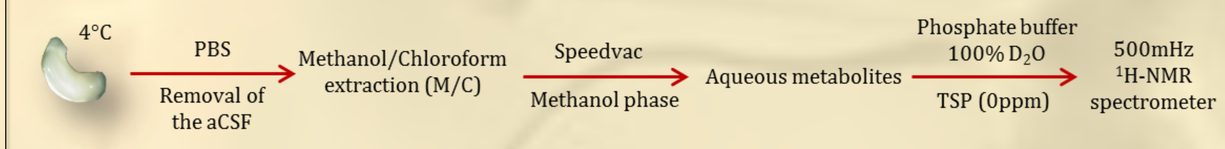


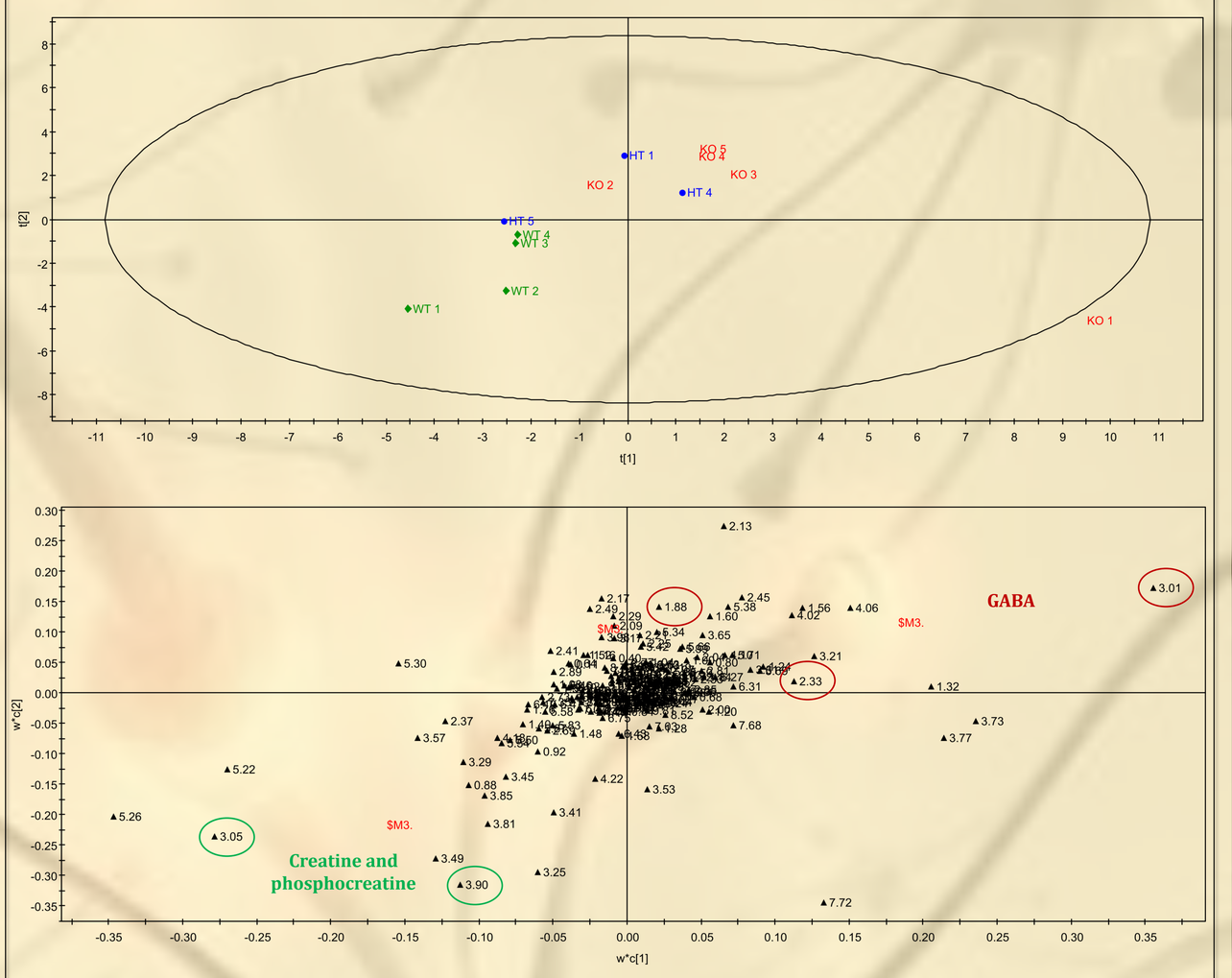


Increased intensity of the epileptiform activity in KO mice in control condition (WT: n=8, HT: n=15, KO: n=16).

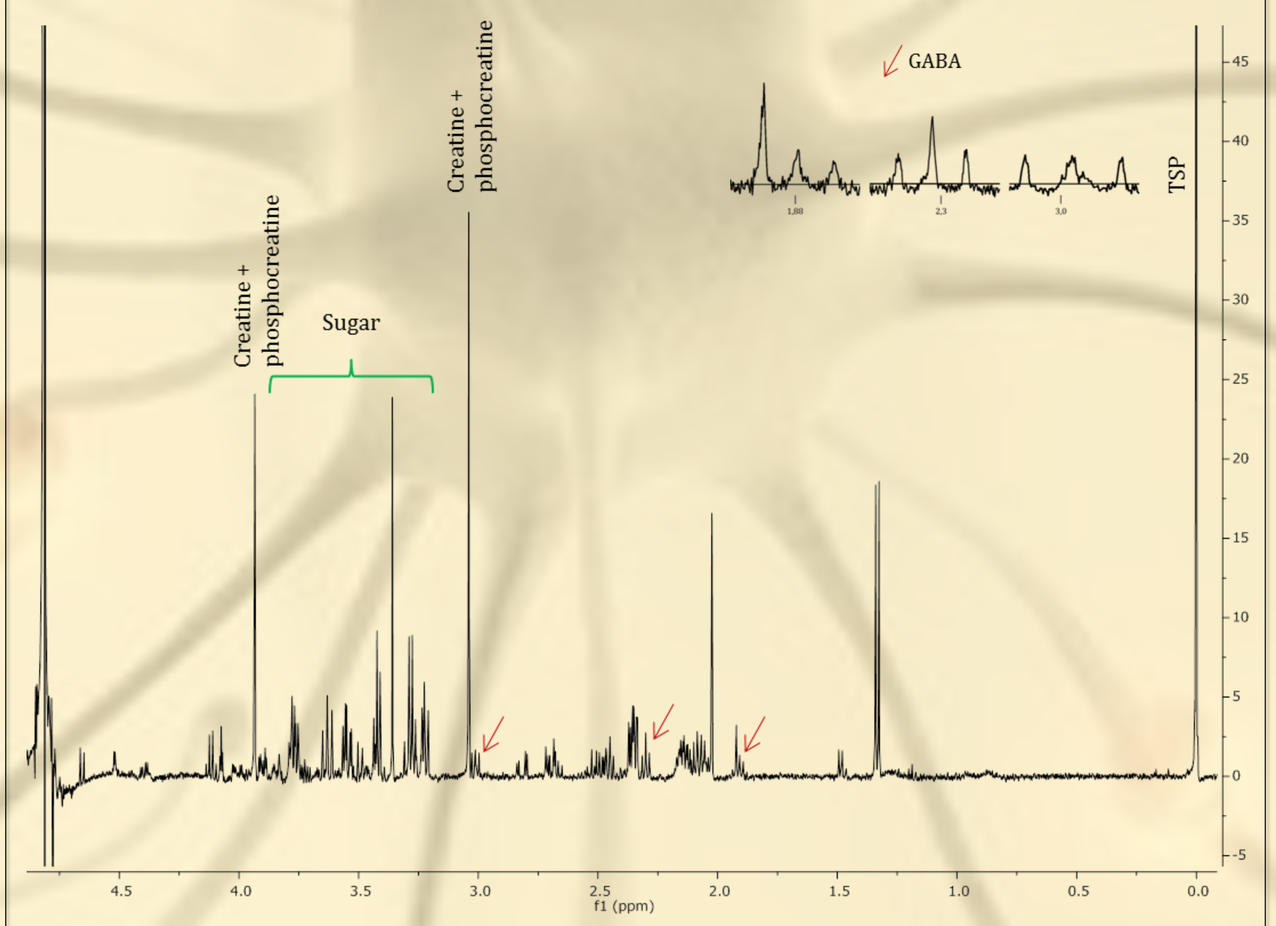
Increase in the occurrence of polyphasic fEPSP in KO mice in severe glucose deprivation (number of I-O to have 100%: WT: n=37, HT: n=52, KO: n=51).

Metabonomics (^{1}H-NMR spectroscopy)





Mice expressing different levels of APP can be discriminated on the basis of their metabolic profile at the level of the hippocampus. Principal component analysis (score plot and loading plot, PC1 and PC2) of the ^{1}H-NMR spectra of WT (n=4), HT (n=3) and KO (n=5) hippocampi. The score plot indicates the separation between the genotypes and the loading plot indicates the discriminant metabolites.



Knockout mice present an increase in GABA expression and a decrease in glucose and creatine/phosphocreatine in the hippocampus. Representative ^{1}H-NMR spectrum of a KO extracted hippocampus. HT mice present an intermediate phenotype for each of the discriminant metabolites.