

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.

Recent research showed that APP and peptides derived from its proteolytic cleavage are involved in cholesterol and ganglioside metabolism. Our hypothesis is that APP is involved in energy flux between the body and the brain. During ageing or in case of pathology such as insulin resistance, glucose availability can be reduced in the brain leading to a compensatory increase in the expression of APP. This compensatory increase could be the starting point of disruption of metabolic and neurotransmitter homeostasis leading to cognitive deficit.

The aim of this project 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. This would provide new evidences in the pathological process of Alzheimer's disease and diabetes.

Experiments were carried out on the hippocampus of transgenic mice B6.129S7 having 2 (+/+, WT), 1 (+/-, HT) or 0 (-/-, KO) allele of the APP gene allowing the study of three levels of APP expression. This model has the advantage of excluding the possible role of beta-amyloid aggregates because the endogenous murine form of the beta-amyloid peptide does not aggregate into oligomers and fibers. The expression of APP gene and protein was evaluated by genotyping and Western-Blotting respectively.

The correlation between APP expression level and metabolic activity in the hippocampus was evaluated by ¹H-NMR spectroscopy and has allowed to discriminate each genotype on the basis of their metabolic profile. We observed a decrease in the level of glucose in the hippocampus of KO mice compared to WT mice. Creatine and phosphocreatine were also reduced in APP KO mice compared to HT and WT whereas the level of GABA increases in the hippocampus of KO mice. The interesting thing is that heterozygote mice (HT) present an intermediate level of each of these metabolites.

The physiological impact of the interaction between APP and glucose was studied by extracellular electrophysiological recordings of cell excitability and synaptic activity in acute hippocampal slices. Slices were incubated with three different concentrations of glucose in the aCSF to assess their sensitivity to hypoglycaemia (10mM, normoglycemia; 5mM, mild hypoglycaemia; 2.5mM, severe hypoglycaemia). Preliminary results showed that the reduction of glucose level from 10mM to 5mM induced a large decrease of the synaptic response in WT mice (50 % of reduction) while the decrease in synaptic activity was much less important in KO mice (30% of reduction). Here again heterozygote mice presented an intermediate phenotype (40% of reduction). The sensitivity to moderate hypoglycaemia seems to be correlated with the level of expression of APP in the hippocampus.

Moreover a higher decrease in glucose supply (2.5mM) further reduced the synaptic response, indicating that a more pronounced glucose hypometabolism has more deleterious consequences on neural viability. Finally ageing also seems to have an effect on the hippocampus. Indeed, 6 month-old mice showed a decrease in synaptic activity and excitability compared to 6 week-old mice.

As we observed a modification of the expression of GABA, we studied the effect of disinhibition on electrical activity by adding picrotoxin (PTX) to the aCSF. In the normoglycemic condition the intensity of the epileptiform activity was higher in KO mice than in the other two groups. When the glucose was reduced to 2.5mM, we observed an extinction of the fEPSP in most of the WT slices compared to the KO slices, where epileptiform activity was still high. Once again HT mice presented an intermediate phenotype.

These preliminary results still need to be completed to better understand the mechanisms responsible of the establishment of Alzheimer's disease in order to stop them before the onset of clinical symptoms.