Metabolic response to a neuroinflammatory challenge in a model of Alzheimer's disease

Henryk Faas[1], Maria Yanez Lopez[1], Samira Parhizkar[2], Stacey Knapp[2], Dorothee Auer[1], and Marie Christine Pardon[2]

[1]*Clinical Neurosciences, University of Nottingham, Nottingham, Nottingham, United Kingdom,* [2]*Life Sciences, University of Nottingham, Nottingham, Nottingham, United Kingdom*

TARGET AUDIENCE

Researchers interested in the metabolic response - assessed noninvasively by MRS - to neuroinflammation involved in neurodegenerative disorders, in particular Alzheimer's disease (AD).

PURPOSE

Neuroinflammation is the response to pathological insult in the CNS, where glial react by accumulating and transforming from resting to an activated state. In MR spectroscopy, molecular markers such as myoinositol (Ins) are biomarkers of glial activation, yet it is not clear how myoinositol relates to neuroinflammation. We therefore use an established neuroinflammatory challenge, lipopolysaccharide (LPS) and follow metabolite levels non-invasively by MRS.

METHODS

To assess the differential metabolic response to a neuroinflammatory challenge in an AD mouse model (n=5, APPSwe-PS1dE9, 5 - 11 months old) vs. age-matched WT controls (n=5), we monitored brain metabolites with MR spectroscopy in a voxel (2x2x2 mm) placed in the hippocampus and thalamus, before and after i.v. administration of lipopolysacharide (LPS, 100 µg/kg). We acquired MR spectroscopy data on a Bruker 7T preclinical system (PRESS, TE/TR = 3/2500 ms, NA = 512, acquisition time = 21 min). To establish baseline prior to LPS injection we acquired two spectra which were averaged as baseline. To track the metabolic response to LPS, a spectrum was acquired every hour for 4 h after LPS administration. Temperature and anesthesia levels were controlled to keep a breathing rate of 90-120 /min. MRS data were analysed using LC model (Cranmer-Rao bounds < 20%) and InVivoStat, a statistical software based on R. Animals were sacrificed immediately after the scan for histological analysis (ongoing study, not reported in these preliminary results): IL1-ß (a proinflammatory cytokine and marker for neuroinflammation), IBA-1 (activated microglia) and GFAP (astrocytes).

RESULTS

Of the metabolites examined, we find the clearest change in myoinositol levels. Baseline levels did not differ (data not shown), but interestingly, the response in WT vs. AD animals is different (Genotype*time interaction: $F(4,32) = 2.65$, $p=0.05$): Ins in WT animals (n=5) decrease over time to 5 ± 3 % at 4h, whereas in AD mice (n=5), at 4 hours, we observe a 10 ± 2 % increase at 4h ($p=0.006$ vs baseline and $p=0.002$ vs WT mice).

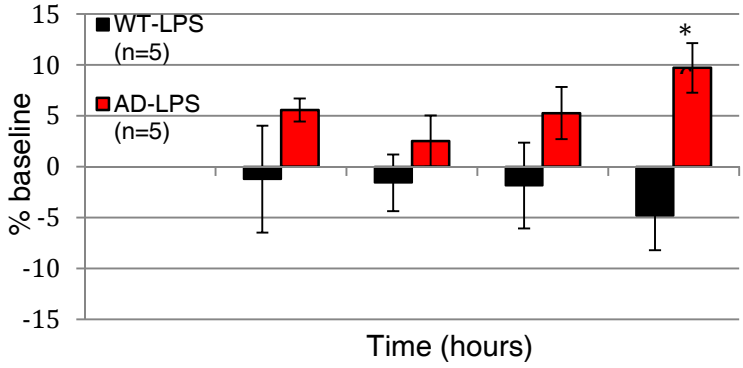

Fig 1. Myoinositol levels assessed by MRS change differentially following LPS administration, decreasing in WT animals, while increasing in AD models mice, aged 4.5-10.5 months. (* denotes statistical significance, $p < 0.01$)

DISCUSSION

We show a differential change in Ins levels after LPS, suggesting, as expected, a stronger inflammatory effect of LPS in chronic disease mouse models. The decrease of myoinositol levels, a marker of glial activation, in healthy controls however is unexpected, and is not explained by anaesthesia effects (no change following vehicle administration, data not shown). Ongoing histological analysis will allow to establish whether the increase in Ins simply reflects glial activation or selectively correlates with expression levels of the pro-inflammatory cytokine IL1-ß.