Early increases in Glu/Gln, Tau and tCho 1H MRS resonances in vivo, anticipate later imaging repercussions of the cerebral inflammatory response in a mouse model of LPS-induced endotoxemia

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Introduction:

Cerebral inflammatory responses underlie the most prevalent neurological disorders, including cancer, ischemia or neurodegeneration[1]. In many cases, bioimaging methods are not able to discriminate clearly between the pathology and the associated inflammatory response, making it difficult to evaluate the effect of anti-inflammatory strategies. On these grounds, the development of non-invasive methods to identify and characterize the contribution of inflammatory components entails considerable therapeutic and diagnostic interest. We report here, for the first time to our knowledge, a longitudinal MRI and MRS characterization of the cerebral inflammatory component developed after the systemic administration of Lipopolysaccharide (LPS).

Subjects and Methods:

Adult male mice C57BL/6 (n=6) received an i.p. injection of LPS from Escherichia Coli Serotype 0127:B8 (5mg/kg). MRS studies (Bruker Pharmascan 7T/16) of mouse brain were acquired from two cerebral regions (Figure 1). ^{1}H-spectra were quantified with LCModel (20% Cranmer-Rao rejection limit) relative to the total-creatine (tCr) resonance using PRESS sequences (TE/TR/NS: 35ms/3000ms/128), before, after injection, one and three days after LPS administration[2]. MR T2W, T1W, Diffusion Weighted Imaging (DWI), and Magnetization Transfer (MT) images were also acquired in the same study (for the same time points from the same mice and scanner). Parametric maps were computed using in house software and quantified in cortex, thalamus and hippocampus. Finally, mice were perfused transcardially 21 days after LPS injection. Brain sections were cut on cryostat (20 µm thick) and immunostained with Mouse antiGFAP for histological evaluation.

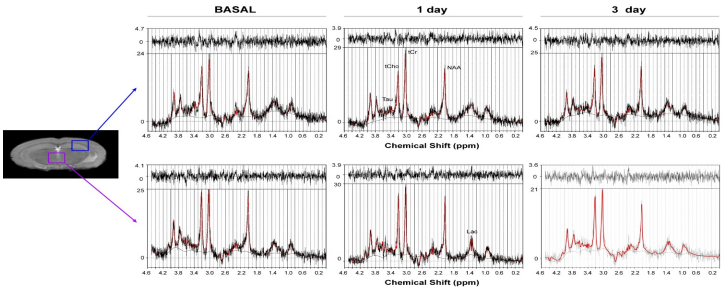

Fig.1: *The two regions selected: cortex/hippocampus (in blue), subcortical (in purple). Right: Representative spectra obtained with LCModel at different measured times*

Results:

LPS administration triggered a significant increase in levels of total-choline (tCho), taurine (Tau), and glutamate+glutamine (Glu+Gln), immediately after LPS injection in the cortical/hippocampal region (Figure 2). One day after, Tau and tCho, decreased significantly to lower levels than the basal state, and Glu+Gln decreased to normal levels in both regions investigated. On the third day, tCho increased slightly compared to basal, Tau recovered only in the subcortical region. Lactate (Lac) was only detectable in all mice in the cortical/hippocampal region three days after the injection (Figure 3). *N*-acetylaspartate (NAA), and lipids did not suffer significant variations. Image analyses revealed one day after LPS administration, significant changes in hippocampal MT and Apparent Diffusion Coefficient (ADC) and in the cortical ADC. On the third day; the magnitude of the MT and ADC effects augmented and an additional T2 increase became detectable in the hippocampus, disappearing all effects previously detected in the cortex (Figure 4). Immunostaining results confirmed a reactive astrogliosis to LPS induced endotoxemia, exclusively in the hippocampus (not shown).

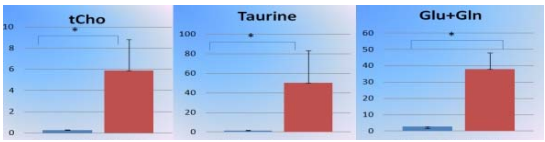

Fig.2: *Mean ± SD of the statistically significant metabolites in the cortex/hippocampus region just after the injection of LPS (in red). Paired t-student significance is represented as *p<0.05.*

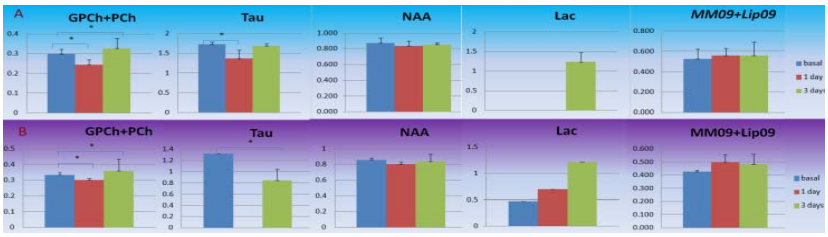

Fig.3: *Mean ± SD of tCho, Tau, NAA, Lac and total macromolecules and lipids around 0.9 ppm (MM09+Lip09) measured in the cortical/hippocampal region (A: upper panel) and the subcortical (B: lower panel). Blue bar represents basal state, red; one day after the injection and green three days after the injection.*

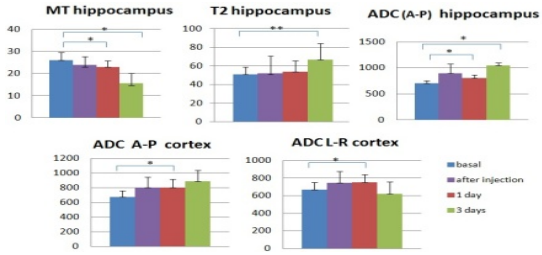

Fig.4: *Mean ± SD of the MT, T2, ADC in the Antero-Posterior (A-P) for the hippocampus (upper panel) and ADC in the A-P and the Left-Right (L-R) in the cortex. Statistical significance is represented as *p<0.05 and **p<0.01.*

Conclusions:

In-vivo spectroscopy reveals very early severe metabolic changes in Tau, tCho, Glu+Gln resonances. These observations suggest that LPS induced cerebral inflammation proceeds with altered osmolite and phosphoplipid metabolism, as well as a very early concomitant increase of the Glu+Gln levels, followed by a later increase in Lac, probably reflecting an LPS induced neurotoxic response[3,4]. Notably, the spectroscopic changes appear to be maximal immediately after the LPS insult, while the imaging changes peak 72h after in the hippocampus. Our results indicate that the metabolic changes detected by in-vivo spectroscopy precede the functional consequences detected later by imaging and histology.

References:

[1]Scrivo R, Vasile M, Bartosiewicz I, Valesini G. Autoimmun Rev. 2011;10(7):369-74, [2]Jeong HK, Jou I, Joe EH. Exp Mol Med. 2010;42(12);823-32, [3]Tokés T, Eros G, Bebes A, Hartmann P, Várszeqi S, et al. Shock. 2011;36(5):458-65, [4]Schuller-Levis GB, Park E. FEMS Microbiol Lett. 2003;226:195-202