Selective hippocampal vulnerability to LPS-induced inflammation revealed by multi-parametric MRI

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Introduction/Purpose:

Cerebral inflammatory responses underlie the most morbid and prevalent neurological or traumatic disorders, including cancer, ischemia or neurodegeneration[1]. A better understanding of inflammation processes paves the way for more accurate diagnoses and effective therapies. However in many cases, bioimaging methods are not able to discriminate clearly between the pathology and the associated inflammatory response. On these grounds, the development of non-invasive methods to identify and characterize the contribution of the inflammatory component entails considerable therapeutic and diagnostic interest. We report here, for the first time to our knowledge, a longitudinal multi-parametric MRI 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). MRI studies of the mouse brain were carried out in a Bruker Pharmascan 7T/16 scanner. T1, T2, Apparent Diffusion Coefficient (ADC) in the head-foot (H-F), left-right (L-R) and the antero-posterior (A-P) directions, and Magnetization Transfer (MT) maps were routinely acquired before, one and three days after the LPS administration, when maximal inflammation develops[2]. Parametric values were determined using in house software and quantified in three brain regions: cortex, thalamus and hippocampus (Figure 1). Mice were perfused transcardially 21 days after the injection and brain sections were cut on cryostat (20 µm thick). The sections were immunostained with Rabbit anti IBA1 (1:1000, Wako Chemicals) and Mouse anti GFAP (1:400, Sigma-Aldrich).

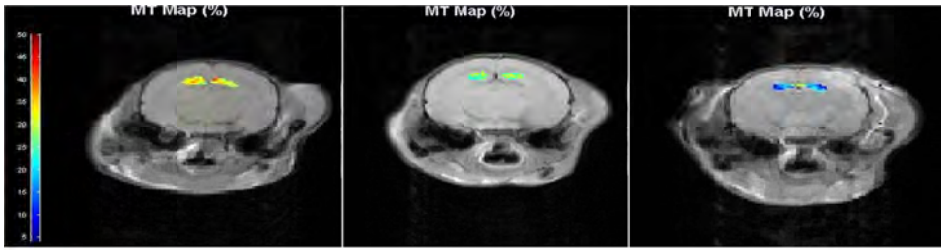

Fig. 1: Representative MT map of the hippocampus, before (left), one day (center) and three days (right) after the systemic LPS administration. Note the gradual decrease in average hippocampal MT after LPS injection.

Results:

LPS treatment induced significant variations in the A-P direction of the ADC and MT values in the hippocampus (p=0.03, p=0.02, respectively) and in the A-P and L-R direction of the ADC in the cortex (p=0.04, p=0.06) one day after the injection, appearing changes in T2 (p=0.001) and increasing the effects of MT and ADC (p=0.01, p=0.02) in the hippocampus after three days, but disappearing in the cortical region (Figure 2). Immunostaining results with GFAP showed astrogliosis exclusively in the hippocampus (Figure 3, upper right image). No increase in microglial immunoreactivity was observed 21 days after LPS treatment.

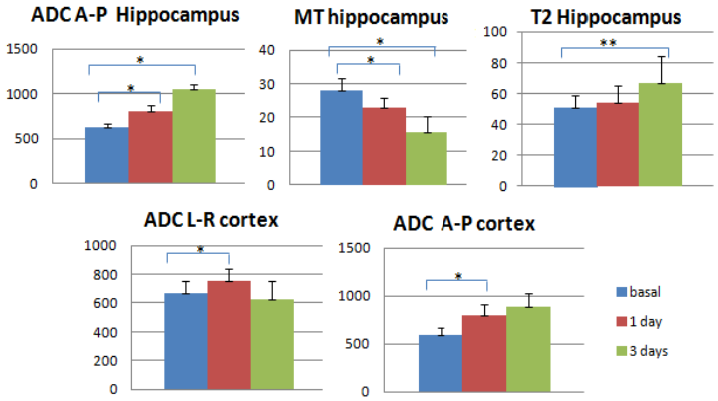

*Fig.2 Mean (±SD) values of ADC (A-P), MT and T2 for the hippocampus (upper panels) and ADC (A-P and L-R) for the cortex (lower panels); before (blue), one (red) and three (green) days after LPS administration. Paired t-test (basal with respect to one day and basal with respect to three days) are represented as *p<0.05 and **p<0.01*

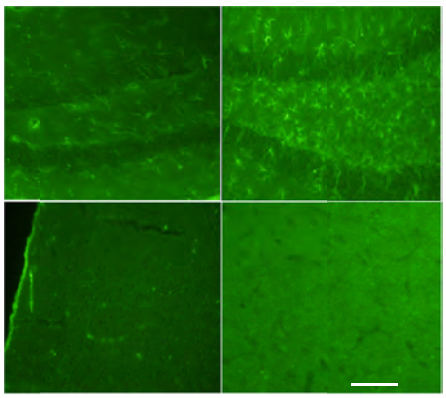

Fig.3 Representative results of immunostaining with GFAP. Upper left: Control mouse (CA1, hippocampus). Upper right: LPS-infected mouse (CA1, hippocampus). Lower left: LPS-infected mouse (cortical region). Lower right: LPS-infected mouse (thalamic region). Scale bar is 100 µm.

Conclusions:

Taken together our results allow characterizing by MRI the time evolution of cerebral inflammation after LPS administration. The inflamed regions depict longer T2, lower MT and higher ADC than the normal brain. The hippocampus appears to be the most vulnerable region, most probably undergoing a reactive vasogenic edema[3,4] to inflammation, with undetectable effects of LPS in the thalamus and smaller reversible damage in the cortical region. Immunostaining results correlate well with the MRI characterization, demonstrating hippocampal astrogliosis, reactive to astrocytic edema in this region.

References:

[1]Scrivo R. et al. 2011, Autoimmun Rev. 10(7):369-74, [2]Jeong HK, Jou I, Joe EH, 2010, Exp Mol Med. 31;42(12):823-32. [3]Loubinoux I. et al. 1997, Stroke. 28(2):419-26. [4]Tourdias T. et al. 2011, J Neuroinflammation. 19;8(1):143.