Region specific-alteration of blood-brain barrier development caused by prenatal exposure to inflammation

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Objectives: Perinatal inflammation affects brain development and has long-term consequences. The permeability of the developing blood-brain barrier (BBB) of neonates has not been characterized such that treatment of brain damage using anti-inflammatory drugs is limited. So far, most of the animal studies testing the efficiency of neuroprotective drugs used invasive (e.g., intracerebral) injection. Transfer of treatment options to the clinic first requires a better understanding of the BBB development and of its permeability. We therefore undertook this study to evaluate postnatally the developing variations of BBB permeability to a contrast agent using MRI and to an anti-inflammatory treatment using histology and protein extract. We also evaluated the modulation of the BBB permeability by prenatal exposure to inflammation.

Model: Rat pups were prenatally exposed either to saline (Ctrl, n=12) or to a bacterial component (lipopolysaccharide, LPS, 200 μg/kg/12h at the end of gestation, from G18 until birth, n=18). Anesthetized animals (isoflurane 1%) were imaged using a small-animal 7T MRI scanner from postnatal day 1 (P1) up to P30. A bolus of Gd-DTPA (2 μmol/g) was injected i.p. with simultaneous and continuous monitoring by T_1-weighted images (TR/TE: 135/2.5 ms, FOV: 2.5 x 2.5 cm^2, matrix: (128)^2, α: 30°, NA: 8, 10-15 slices of 1 mm) for a time period of 2 hours. Brains were also harvested at the same time points as the scan, to correlate the *in vivo* data with histology and protein extracts. The transfer across the BBB of an anti-inflammatory treatment (recombinant human antagonist of IL-1 (IL-1Ra), 10 mg/kg, i.p.) was also correlated at each time point.

Results: We first studied the kinetic of BBB developmental permeability in Ctrl animals. All brain regions studied had a similar permeability to Gd-DTPA at the earliest time point (P1-5). By P16-20 they were all impermeable to the contrast agent. On the other hand, prenatal exposure to LPS altered the BBB permeability in a region-specific manner (Fig 1A). At P1-5, the cortex and hippocampus showed a more pronounced signal enhancement than other brain regions and this regionally increased level of permeability was higher than in Ctrl animals (Fig 1B). The same experiments repeated from P6-15 revealed a reduced BBB permeability in all brain regions. Later (P16-30), the prenatal exposure to LPS led to a sustained and higher contrast agent delivery in all brain regions studied, whereas the Ctrl animals had an impermeable barrier at this point. Those results are consistent with our previous findings that showed developmental vulnerability of the animals to the aggressions. Those results were confirmed by histology using markers of BBB permeability, glial cells development and also by studying the transfer of an anti-inflammatory drug across the BBB at the same time points.

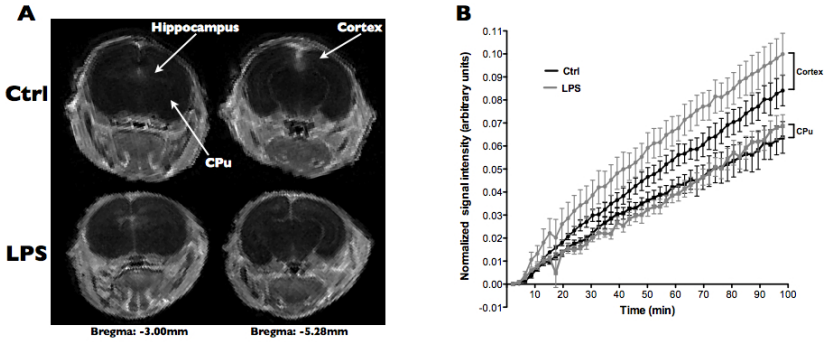

Figure 1: (A) Representative T_1-weighted images of the signal enhancement post-contrast injection observed in the cortex and hippocampus as compared to the caudate putamen (CPu) at P3 and (B) graphical representation of the normalized signal intensity (P1-5).

Conclusion: *In vivo* MRI clearly revealed for the first time a decrease in BBB permeability during development and that this permeability was modulated in a region-specific manner by prenatal exposure to inflammation. Such region-specific modulation of BBB permeability provides new insights into the mechanisms explaining the vulnerability to inflammation/aggressions in newborns causing brain damage.