Impact of anti-inflammatory treatment on placental and neurodevelopmental defects monitored in utero by MRI

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Objectives: Perinatal inflammation affects newborns, especially when they are preterm, leading to neurodevelopmental diseases and enhanced susceptibility to later occurring brain damage. Cytokines, mainly the interleukin-1 (IL-1) system, are believed to be important mediators linking maternal inflammation and fetal brain damage. There is currently no therapeutic strategy to protect the newborn brain against maternal inflammation. This is mainly due to the lack of non-invasive tools to detect the impact of inflammation on the maternofetal interface and the effects of anti-inflammatory treatment. We used MRI to visualize the impact of inflammation on the placenta and to test the prevention of placental and neurodevelopmental defects by an anti-inflammatory treatment targeting the IL-1 system.

Materials and methods: Studies were performed on a Lewis rat model of prenatal inflammation. Anesthetized animals were imaged using a small-animal 7T MRI scanner at gestational day 17 (G17). A fast spin-echo pulse sequence (TR/TE_{eff}: 2000/12 ms, 8 echoes, FOV: 6 x 5 cm^2, matrix: $(256)^2$, NA: 8, 20 slices of 1.5 mm) was first performed. A bolus of Gd-DTPA (500 µl) was then injected i.v. (tail vein) with simultaneous and continuous monitoring by T_1-weighted images (TR/TE: 197/2.5 ms, FOV: 6 x 5 cm^2, matrix: $(128)^2$, α: 30°, NA: 4, 20 slices of 1.5 mm) for a time period of 50 min. The pregnant rat was then injected every 12 hours either with lipopolysaccharide (LPS, n = 6) or saline (Ctrl, n = 6) until G20 when the MRI procedure was repeated. The anti-inflammatory treatment (recombinant human antagonist of IL-1 (IL-1Ra), 2, 10 or 20 mg/kg) was administered 30 min before each LPS injection. After imaging, placentas were removed; half were stained or processed for immunohistochemistry, to determine the histological correlates of LPS-induced inflammation; the other half were used for cytokines analysis.

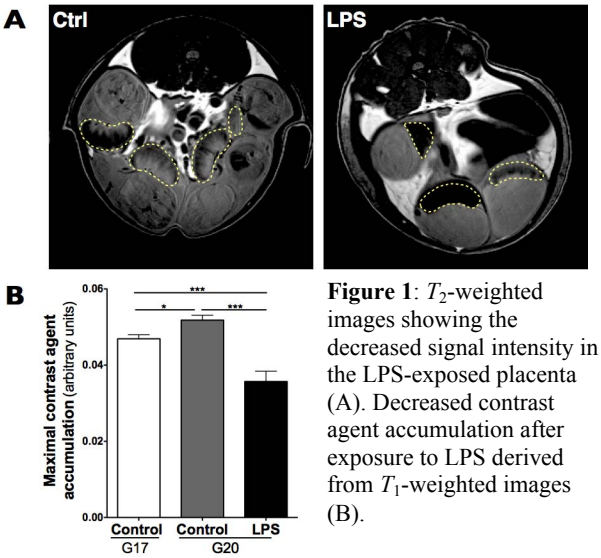

Figure 1: T_2-weighted images showing the decreased signal intensity in the LPS-exposed placenta (A). Decreased contrast agent accumulation after exposure to LPS derived from T_1-weighted images (B).

Results: A decrease in placental T_2-weighted signal intensity was detected in LPS-treated pregnant rats compared to controls (Fig 1A). This was related to major changes in the placental tissue: apoptosis, calcification, macrophages infiltration and massive cytokines production (especially IL-1β). The placental function was evaluated with dynamic contrast-enhanced T_1-weighted images. LPS induced a decrease in both placental perfusion and clearance rate and also a decrease in the maximal contrast agent accumulation in the tissue (Fig 1B). The protective effect of the IL-1Ra treatment was evaluated with MRI, which showed a dose-dependent recovery of placental perfusion and an increase in the T_2-weighted signal intensity. This *in utero* improvement in function was confirmed by the preservation of the placental tissue integrity, decreased inflammation and increased pups survival.

Conclusion: Our results clearly indicate that MRI could be used as a non-invasive technique to detect placental inflammation *in utero* without injection of a contrast agent. The follow up and monitoring of the impact of anti-inflammatory treatment on the tissue integrity and function is also of great clinical interest and could be achieved as demonstrated here with the protective effects of the IL-1Ra administered during gestation. This non-invasive methodology is expected to be useful for the assessment of novel treatments aimed at preventing brain damage in newborns.