Protection of fetuses from in utero inflammation: can MRI be the solution?

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Objectives: Prenatal inflammation is a major factor associated with altered brain development in the newborn leading to neurodevelopmental diseases and enhanced susceptibility to brain damage occurring at a later stage. There is currently no treatment to alleviate the impact of prenatal inflammation on the development of the newborn. This is mainly due to the lack of non-invasive tools to detect the prenatal inflammation and its role on the maternofetal interface. We used MRI as a detection technique to evaluate the impact of inflammation on the placenta and to determine an optimal therapeutic window for the administration of anti-inflammatory treatment.

Materials and methods: Studies were performed on a Lewis rat model of prenatal inflammation. The pregnant rats were injected with lipopolysaccharide (LPS, 200 µg/kg) or saline (Ctrl) either alone or in combination with anti-inflammatory treatment (antagonist of the receptor of interleukin-1; IL-1Ra, 10mg/kg) every 12h from gestational day 18 (G18) until G20. At G20, anesthetized animals were imaged using a small-animal 7T MRI scanner. A fast spin-echo pulse sequence (TR/TE_{eff}: 2000/12 ms, 8 echoes, FOV: 6 x 6 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 6 cm^2, matrix: $(128)^2$, α: 30°, NA: 4, 20 slices of 1.5 mm) for 50 min. 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 molecular analysis of cytokines expression.

Results: A rapid decrease in placental T_2-weighted signal intensity was detected as early as 3 h after intraperitoneal LPS administration to pregnant rats and was further decreased 12 h after the injection (Fig 1). The decreased signal intensity observed in T_2-weighted images was associated with a decreased placental perfusion rate, observed in T_1 experiments, but with a normal maximal contrast agent accumulation. Even though changes could be detected using MRI, no corresponding changes were seen by histological analysis of the placenta at 3 or 6 h after LPS administration and the tissue integrity was similar to control. Changes were significant only from 12 h and were characterized by macrophages infiltration and loss of tissue integrity. Further analysis of placental cytokines expression showed a significant increase in IL-1β as early as 3 h, correlating with the changes being detected by MRI. After a pre-determined delay following the first administration of LPS, rats were treated with an anti-inflammatory agent (IL-1Ra). Administration of IL-1Ra, even 24 h after the first injection of LPS partly restored the placental perfusion, limited macrophages infiltration and decreased the levels of IL-1β as compared to placentas from dams exposed to LPS only.

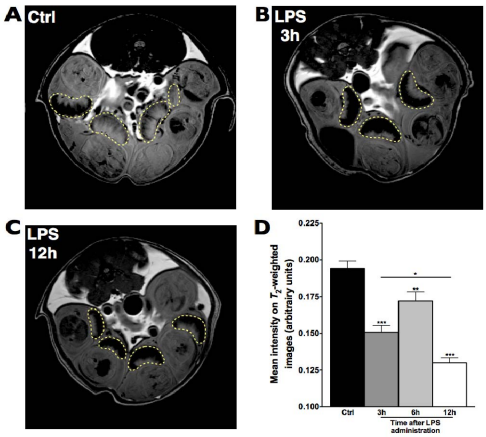

Figure 1: T_2-weighted images showing the decreased signal intensity in the LPS-exposed placenta as compared to control (A-C). Results are summarized in D.

Conclusion: Our results clearly show that MRI could non-invasively technique to detect placental inflammation *in utero* before any irreversible histological changes were induced. We therefore determined an optimal therapeutic window for the administration of an anti-inflammatory treatment that protected the newborn. Although the treatment is most efficient when administered at the earliest time possible (as we previously showed; Girard S, et al. J Immunol, 2010), it would be most clinically relevant to detect placental inflammation before administration of any treatment. Therefore, MRI detected *in utero* inflammation earlier than a commonly used technique (i.e. histological analysis of the placenta after birth). Earlier treatment was shown to protect the newborn rat.