The effects of fetal asphyctic preconditioning on pro- and anti-inflammatory cytokine levels in the placenta

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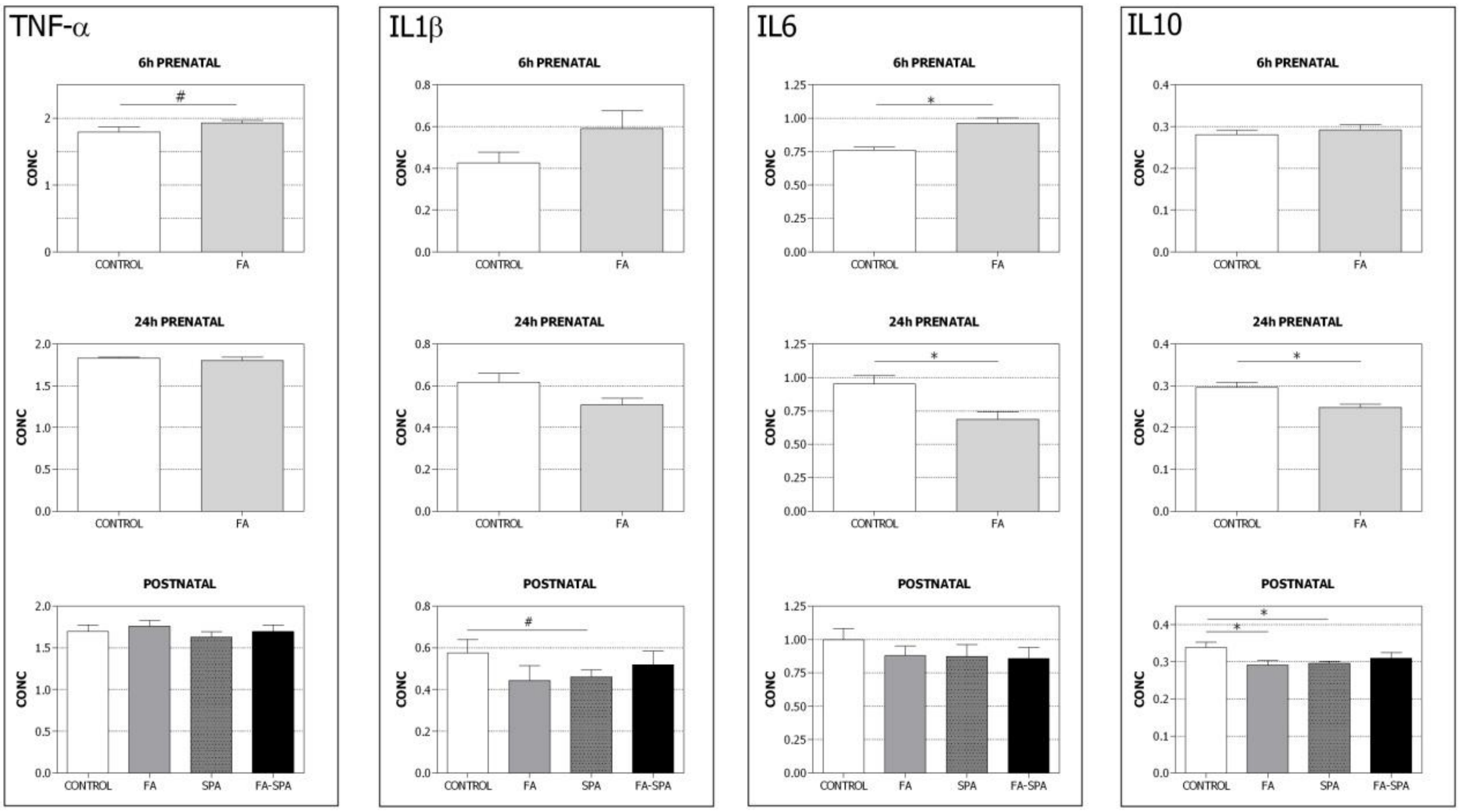
Background: Perinatal asphyxia is a major cause of neonatal mortality and morbidity, contributing to neuronal injury leading to long-term motor and cognitive problems. Research has shown that in the rat brief episodes of sub-lethal fetal asphyxia (FA) may elicit neuroprotection against a subsequent more severe perinatal asphyctic insult (PA) at birth. This is called fetal asphyctic preconditioning (PC). Recent evidence shows a down-regulation of inflammatory cytokines in the brain after PC, implicating that PC induces neuroprotection at birth. However, the exact mechanisms underlying PC are not yet elucidated. Since the placenta is also subjected to the asphyctic insult, and is a critical organ related to fetal wellbeing, it might play a role in fetal PC as well. **Objective:** To investigate changes in the placental cytokine response after fetal asphyctic PC in the rat. **Methods:** Fetal asphyctic PC was induced in the rat at 17 days of pregnancy (E17) by clamping the uterine circulation for 30 min. The second hit, PA, was induced at E21/22 by submersing the uterine horns in a saline bath (37ºC) for 19 min. Placental IL-1β, IL-6, TNF-α and IL-10 protein concentrations among 50 mg of tissue homogenates (Sigma protocol) were measured by ELISA method at 6 and 24 hours after FA, and at birth after PA. Two groups will be studied prenatally (control, FA), and 4 groups at birth (control, FA, FA+PA, PA). A total of 39 placental samples were analyzed.

Results: TNF-α levels were not significantly different in the placentas, though as compared to the SHAM-6 group a prenatal down-regulation trend was observed for this analyte in FA-6 (p=0.095). Equally, placental IL-1β levels showed no significant differences; however, as compared to the SHAM group a postnatal down-regulation trend (p=0.095) was found for this analyte at birth after severe PA. Prenatal placental IL-6 levels showed significant differences in both FA-6 (p=0.016) and FA-24 (p=0.016) as compared to the SHAM-6 and SHAM-24 group, respectively. The FA-6 group showed a placental IL-6 up-regulation trend, whereas the FA-24 group demonstrated a down-regulation. Placental IL-10 levels displayed significant differences: prenatally a down-regulation was observed 24 hours after FA (p=0.016) and postnatally a significant decrease in both the FA group (p=0.016) and the severe PA group (p=0.016). **Conclusion:** Asphyxia preconditioning affects placental cytokine concentrations (IL-6 and IL-10) especially prenatally, maintaining similar IL-10 (anti-inflammatory) concentrations as in controls, which may modulate placental inflammatory responses and contribute to the neuroprotective effects previously reported in the literature.

Figure: Mean cytokine levels in the homogenized placental rat samples



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