HERSTON HEALTH PRECINCT SYMPOSIUM 2021

6 - 10 September 2021 Education Centre RBWH

DISC-0052

Ibuprofen treatment improves neurovascular unit alterations in the growth restricted newborn

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BACKGROUND: Fetal growth restriction (FGR) is commonly caused by placental insufficiency, resulting in abnormal neurodevelopment of the brain.

- No treatment exists to protect the FGR newborn brain.
- Inflammation is a key mechanism in progression of brain impairment in the FGR newborn and may disrupt the neurovascular unit (NVU)
- We investigated whether ibuprofen, a NSAID, could reduce NVU disruption and brain neuropathology in FGR newborns using a pre-clinical pig model.

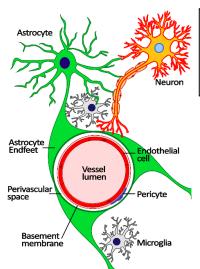


Figure 1. Cellular composition of the NVU. Resting glial cells form a tight functional unit that regulates the homeostasis of the brain environment

METHODS: Normally grown (*NG*) and *FGR* (<10th centile) piglets were collected on day of birth and assigned to treatment groups:

<u>Ibuprofen</u> was administered orally at each morning feed (day 1: 20mg/kg; days 2 and 3: 10mg/kg).

Animals were euthanised on day 4. Brain outcomes were examined suing histology and molecular approaches (minimum *n* = 5 per group).

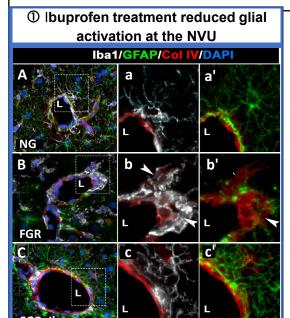


Figure 2. FGR display astrocyte and microglial activation at the micro vessels interface, indicative of an inflammatory response. This was supported by increased cytokine expression (data not shown).

RESULTS

② Reduced disruption of the NVU after ibuprofen treatment, with less infiltration of serum proteins and ③ peripheral immune cells (T-cells) into the brain parenchyma



Figure 3. Presence of IgG in the brain parenchyma indicates altered integrity of the blood brain barrier in FGR. These alterations coincide with decreased astrocyte (GFAP) interaction with the vasculature (Collagen IV)

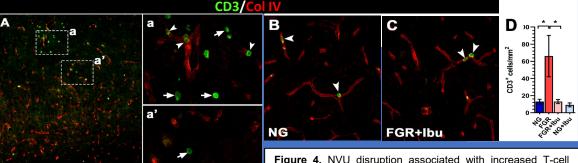


Figure 4. NVU disruption associated with increased T-cell (CD3*) infiltration into brain parenchyma of FGR. Reduced cell infiltration observed in ibuprofen treated FGR newborns.

CONCLUSION: Postnatal administration of ibuprofen on day of birth modulates the inflammatory state improving interaction between vasculature and astrocytic end-feet to restore NVU integrity in FGR newborns preventing entry of peripheral infiltrates. These changes to the FGR brain microenvironment may be key to neuroprotection. Long-term studies are required to determine whether these improvements persist.















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