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Abstract

Introduction: Preterm birth (delivery <37 weeks) is the main cause of neonatal mortality in the UK and worldwide. It is associated with high rates of adverse neurodevelopmental outcome and cerebral palsy, of which males are at greater risk than females. Approximately 40% of cases of spontaneous preterm birth have been associated with infection. Delaying preterm birth and improving the outcome of the premature babies has proved a great challenge and current therapies are ineffective. Our objective was to investigate the extent of neuroinflammation in pups from pregnant mice following the ascent, from the vagina to the uterine cavity, of either a non-pathogenic strain of E. coli (K12) or a strain associated with clinical meningitis (K1).

Methods: On embryonic day (e) 16.5, intravaginal administration of either K12 (20µl of 1x109 CFU; n=15 from 5 dams) or K1 E. coli (20µl of 2x102; n=15 from 5 dams) or PBS control (20µl; n=10 from 5 dams) was performed. Dams (C57BL/6 Tyrc-2J) were imaged at 0 hours (h), 24h and 48h to monitor the ascension of the bioluminescent E. coli strains. Fetal tissues were harvested 48h following infection. Neuroinflammation was assessed by multiplex ELISA for a panel of inflammatory mediators.

Results: Imaging confirmed the ascension of both E. coli strains from the vagina into the uterus. The following inflammatory mediators were increased in perinatal brains from non-pathogenic K12 E. Coli infected dams in comparison to PBS treated mice; IFNγ ($p=0.0072$), IL-1β ($p=0.017$), IL-4 ($p=0.0179$), IL-12p70 ($p=0.0354$) and IL-5 ($p=0.0292$). When dams were infected with pathogenic K1 E. Coli, TNFα ($p<0.0001$) and IL-1β ($p=0.0245$) production were elevated in comparison to the PBS group. Specifically, these increases were associated with the male pups exposed to K1 (TNFα $p=0.0006$ vs PBS, IL-1β $p=0.0496$ vs PBS). There was no significant difference between the female pups exposed to K1 compared to females exposed to PBS.

Conclusion: Both strains of E. coli induced perinatal neuroinflammation and in some cases, this effect was specific to the male pups. However, the non-pathogenic K12 strain increased the production of more inflammatory mediators than the pathogenic K1 strain. Future studies will further characterise this model of perinatal neuroinflammation by assessing the neurodevelopment of these pups at the molecular and behavioural level. We are also investigating an antimicrobial peptide gene therapy approach with the aim of preventing both early delivery and perinatal brain damage.