Epidemiological evidence supports an association between maternal infection and the risk of neurodevelopmental disorders in offspring (e.g. ASD and schizophrenia) 1

Poly(I:C)-induced maternal immune activation (mIA) in rodents is a key model for the investigation of maternal infection during pregnancy

Studies in rodents have shown early gestational exposure to mIA can produce phenotypes relevant to ASD 2

Further validation of this model is required in rats at early gestational time points (gestational day (GD): 12.5) to explore both early neurobiological, neurodevelopmental and behavioural changes in male and female offspring

Aims and Objectives
Provide a comprehensive evaluation of the poly(I:C) model of mIA at GD12.5
- Perform behavioural phenotyping
- Explore early neurodevelopmental changes within this model

Methods

Behavioural testing: All offspring from poly(I:C) and saline treated dams were tested in the open field test (OFT) and social interaction test. Social communication was monitored at PD9 during brief (3 min) isolation of individual pups from the nest.

qPCR: mRNA expression was normalised to SDHA housekeeping gene and expressed as fold change from a calibrator (naïve brain tissue) using 2-ΔΔCt.

Statistics: For comparisons between offspring of poly(I:C) and saline-treated pups, a nested-ANOVA was performed with litter treated as a random variable. The homoscedasticity (Levene's test) and normality (Shapiro-Wilk test) of each data set were tested.

To prevent litter effects skewing data where nested analysis was not possible, mean values per litter are presented (Figure 4-5). Student’s test was performed or a Mann-Whitney test was used when parametric analysis was not applicable.

Results: Maternal response
10 mg/kg poly(I:C) induces a variable immune response in pregnant Wistar rats at GD12.5

Figure 1. A subset of the Wistar rats treated with poly(I:C) showed a detectable level (125 pg/mL) of IL-6. Data are presented as mean ± SEM, n=15-18 dams (some data points below detectable level).

Results: Behavioural phenotyping
10mg/kg poly(I-C) at GD12.5 reduces risk-taking behaviour of male adolescent offspring in the OFT

Figure 2. 10mg/kg poly(I-C) reduced risk-taking behaviours at PD20 but had no significant effect on social play behaviours at PD24. Data are presented as mean ± SEM. *P<0.05

Results: Social communication
mIA induces no change in early communication in poly(I-C) offspring

Figure 3. Following 10mg/kg poly(I:C) male and female offspring from poly(I:C) dams vocalised more but this effect did not reach significance. Background grey data points represent individual male/female offspring from n=6-8 dams; foreground data points represent litter means. Data are presented as mean ± SEM.

Results: Morphological changes GD21
mIA induces a reduction in placental weight in female offspring

Figure 4. A-B) 10 mg/kg poly(I:C) induces no change to offspring body weight or brain weight at GD21. C) Placental weight was significantly reduced in female offspring. Data presented as mean ±SEM; n=6 (litter means); *P<0.05

Results: qPCR
mIA alters expression of Otfm3 (microglial marker) in male offspring frontal cortex at GD21

- MIA at GD12.5 did not induce any significant change in astrocyte marker GFAP (glial fibrillary acidic protein), Mef2c a synaptic pruning marker (myocyte-specific enhancer factor 2c), or synaptic scaffold protein Shank3.
- There was a significant increase in microglial marker Otfm3, (olfactomedin like 3) in male offspring at GD21.

Conclusions
- 10mg/kg poly(I:C) on GD12.5 reduced risk-taking behaviour in male offspring but did not significantly affect other behavioural parameters
- 10mg/kg poly(I:C) on GD12.5 induced significant reduction in female placental weight but no change to other morphometric parameters
- Expression of Otfm3 (microglia marker) was increased in frontal cortex from male offspring at GD21
- This study provides an in depth longitudinal evaluation of this mIA model. This is the first study to use GD12.5 mIA in Wistar rats for investigation of NDDs

References

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