Validation of a maternal immune activation (mIA) model of schizophrenia: effects of strain and dose of poly I:C on inflammatory profiles of rats and their offspring.

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Introduction

• There is accumulating evidence for the role of neuroinflammatory processes in the aetiology of neuropsychiatric disorders. In particular, maternal immune activation (mIA) is emerging as a key model for neurodevelopmental disorders including schizophrenia¹.

• The viral-mimetic polyribonucleic-polyribosylribidicylic acid (poly- I:C) has been used to elicit mIA. However, differences in dose, strain and route of administration exist in the literature, which may contribute to the behavioural and neurochemical variations observed in the offspring².

• Gestational and early postnatal day physiological changes in the development of offspring from poly I:C treated mothers have yet to be fully explored in rat models of poly I:C induced mIA.

Methods

Drug administration.
Acute systemic inflammation was induced in female Wistar, hooded-Lister and Sprague-Dawley rats (n=8; 180-190 g; 18-weeks old) intraperitoneally (i.p) with poly I:C 10, 15 or 50mg/kg. Sigma, UK or saline.
Chronic systemic inflammation was induced in female Wistar rats (n=8) by poly I:C i.p. 10, 25, 5 or 100mg/kg saline for 5 consecutive days.

Maternal immune activation was induced in pregnant Wistar rats (n=8) by poly I:C i.p. 10mg/kg or saline for gestational day GD15.

Fever response: Fever was measured by rectal probe recordings in saline-treated baseline, 3h and 6h post-injection.

Protein expression: Blood samples were taken following poly I:C or saline administration at 3h and changes in IL-6, TNFα, IL-1β expression were measured in the plasma by ELISA.

Fetal measurements: At GD21 pup weight, head circumference, length and abdominal circumference were measured.

qPCR: A selection of myelination (myelin basic protein, MBP), blood-brain barrier (BBB) integrity (major facilitator superfamily domain 2a, Mfsd2a) and axonal guidance (Semaphorin 3a, Sema3a) genes were measured in the brains of GD21 pups via the qRT-PCR method of RNA isolation. Target genes were normalised to endogenous reference genes (GAPDH and SDHA) and then to a calibrator (sample with the lowest expression) using the 2^-ΔΔCt method.

Acute administration of poly I:C (10mg/kg) is optimal dosing regime

Poly I:C (10mg/kg: i.p) evokes a robust immune response in Wistar rats

Figures 1: qRT-PCR expression in plasma at 3h post poly I:C injection (i.p) in female Wistar rats (n=8) on GD17. *p<0.001 vs saline; **p<0.01 vs poly I:C 10mg/kg; ***p<0.001 vs poly I:C 15mg/kg; ****p<0.001 vs poly I:C 50mg/kg. #p<0.05 vs saline; ##p<0.01 vs poly I:C 10mg/kg; ###p<0.001 vs poly I:C 15mg/kg.

Poly I:C (10mg/kg: i.p) causes an inflammatory response in pregnant Wistar rats

Figures 2. IL-1β expression in plasma at 3h post poly I:C injection (i.p) in female Wistar (A), Sprague-Dawley (B) and Lister Hooded (C) rats (n=8). Changes in temperature at 3 and 6h post-injection in female Wistar (D); Sprague-Dawley (E) and Lister Hooded (F) rats (n=8). Non-parametric one-way ANOVA followed by Dunn’s multiple comparison test. *p<0.05, **p<0.01, ***p<0.001. Data presented as mean±SEM.

Poly I:C induced mIA alters offspring neurodevelopment at GD21

Myelin Basic Protein (MBP) - Myelination

Major facilitator superfamily domain containing 2a (Mfsd2a) – BBB integrity during early development

Figures 3: effects of saline or poly I:C administration (i.p) at GD15 in pregnant Wistar rats on male and female pups. (A) Myelin basic protein (MBP) myelination. (B) Myelin basic protein (MBP) myelination in normal female offspring. (C) Major facilitator superfamily domain containing 2a (Mfsd2a) expression was altered at GD21 when compared to nil-poly I:C. (D) Pup numbers (vehicle n=35, poly I:C n=30; Student t-test. Data presented as mean±SEM. *p<0.05)

Figures 4: Effects of saline or poly I:C administered (i.p) at GD15 in female Wistar rats on male and female pup weight (A); abdominal weight (B); pup length (C) and head circumference (D). (E) Myelin basic protein (MBP) myelination. (F) Major facilitator superfamily domain containing 2a (Mfsd2a) expression was altered at GD21 when compared to nil-poly I:C. (G) Pup numbers (vehicle n=35, poly I:C n=30; Student t-test. Data presented as mean±SEM. *p<0.05)

Conclusion

• These data demonstrate that, under our experimental conditions, acute administration of 10mg/kg poly I:C (i.p) to female Wistar rats is the optimal dosing schedule and strain to induce a robust systemic inflammatory response for mIA studies.

• Acute administration of 10mg/kg poly I:C (i.p) also elicits a robust immune response in pregnant Wistar rats at GD15.

• Acute administration of 10mg/kg poly I:C (i.p) in pregnant Wistar rats at GD15 does not affect litter size or pup mortality rates but results in pups with smaller allometric measurements prior to parturition.

• Furthermore, maternal immune activation results in changes to gene expression in the brains of pups born to poly I:C treated mothers.

• Differences in myelination, BBB integrity and axonal guidance genes were observed at GD21.

• Acute administration of 10mg/kg poly I:C (i.p) induces a robust systemic inflammatory response in both naïve and pregnant Wistar rats.

Poly I:C induced mIA results in pup and placenta growth restriction alongside early neurodevelopmental changes.

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