A novel double-hit animal model of schizophrenia: behavioural assessment in male and female mice

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Background: A growing body of evidence supports that maternal prenatal infections represent a risk factor for schizophrenia in offspring [1]. Moreover, stressful events during critical neurodevelopmental periods, such as adolescence, may trigger the onset of the disease in predisposed individuals [2]. Thus, a prenatal priming event (i.e., maternal infection during pregnancy) that would induce vulnerability, followed by a second stressful hit in peripuberty may lead to the onset of schizophrenia [3].

Aim: We aimed to develop and characterise a novel double-hit animal model of schizophrenia in male and female CD1 mice, based on prenatal maternal immune activation (MIA) followed by social isolation (SI) in the peripuberal period.

Methods: Polyriboinosinic-polyribocytidilic acid [Poly (I:C)] (7.5 mg/kg i.p.) or saline (5 ml/kg i.p.) was administered to pregnant dams at gestational day 9.5. At post-weaning (postnatal day 21), offspring were either housed in groups (4 animals per cage) or isolated during at least 8 weeks until behavioural assessment. The four experimental arms generated (MIA, SI, MIA+SI and control) in both, male (n = 12/arm) and female (n = 12/arm) mice, were tested for social behaviour—Social Preference Test (SPT)—and cognitive status—Novel Object Recognition Test (NORT) and Y-Maze Spontaneous Alternation Test (YMSAT)—. Additionally, in a subsample of mice (n = 6/sex/arm), locomotor response to acute amphetamine administration (5 mg/kg i.p.) was evaluated during a 120-minute period. Data were analysed using non-repeated or repeated measures three-way ANOVAs as appropriate.

Results: In the SPT, social exploration time was significantly reduced by MIA (F[1,82] = 9.48; p<0.01) and SI (F[1,82] = 7.92; p<0.01). Non-social exploration was not affected by any of the two hits (MIA: F[1,82] = 0.10; p = 0.75; SI: F[1,82] = 0.44; p = 0.51). A significant effect of sex on both social (F[1,82] = 19.69; p<0.001) and non-social (F[1,82] = 11.89; p<0.001) exploration time was found, with higher exploration times in males than in females. The NORT discrimination index (DI) was significantly impaired by MIA (F[1,85] = 10.93; p<0.001) and SI (F[1,85] = 7.46; p<0.01). DI scores were significantly influenced by sex (F[1,85] = 17.27; p<0.001), being higher in females than in males. Of note, both male and female double-hit groups (MIA+SI) showed worse scores in SPT and NORT compared to single-hit groups. Spontaneous alternation in the YMSAT was not affected by any of the hits or sex (MIA: F[1,88] = 0.67; p = 0.42; SI: F[1,88] = 1.28; p = 0.26; sex: F[1,88] = 2.52; p = 0.12). No
significant “sex x hit”, “hit x hit” or “sex x hit x hit” interactions were found in neither SPT, NORT nor YM-SAT. A time dependent locomotor response to amphetamine was found in all male (F[3.05, 60.92] = 6.49; p<0.001) and female (F[2.41, 45.82] = 10.88; p<0.001) experimental groups. The hyperlocomotion induced by amphetamine was significantly increased by SI in female (F[1,19] = 5.36; p<0.05) but not in male (F[1,20] = 0.82; p = 0.38) mice. No significant “time x hit”, “hit x hit” or “time x hit x hit” interactions were found in locomotor response to amphetamine.

Conclusion: These results showed a significant impact induced by MIA and SI on schizophrenia related behaviours at adulthood in both sexes. These data support the double-hit model as a valuable translational tool in schizophrenia research.

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References


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