Maternal and offspring P2X7 receptors drive autism-like behavior in mice

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Maternal immune activation is a principal environmental risk factor contributing to neurodevelopmental psychiatric disorders, including autism spectrum disorder (ASD). Maternal infection is associated with the later emergence of ASD compromising foetal brain development at critical periods of pregnancy, and the elevation of maternal pro-inflammatory cytokines has been causally linked to perinatal brain reprogramming. However, the molecular signalling pathway that converts maternal immune activation to pathologically relevant neurodevelopmental abnormalities in the offspring has been unclear until now. The NLRP3 inflammasome signalling pathway, triggered by the co-activation of P2X7 purinergic receptors is an intracellular multiprotein complex responsible for the conversion of innate immune response to inflammation in response to exogenous and endogenous danger signals. Here we report that activation of maternal P2X7 receptors is necessary and sufficient to transduce maternal immune activation (MIA) to autistic phenotype in the offspring. We show that whilst maternal immune activation by poly(I:C) injections to pregnant wild-type mouse dams elicits autism-like phenotype in their offspring, including social deficit, impairment of sensorimotor coordination, repetitive behaviours, atrophy of cerebellar Purkinje cells and destruction of synapses, no such alterations are observed in mice genetically deficient in P2X7 receptors. The effect of P2X7 gene deficiency could be reproduced by maternal treatment with specific P2X7 receptor antagonist JNJ7965567 (20 mg/kg i.p.). Genetic deletion and pharmacological inhibition of maternal P2X7 receptors also effectively counteracted the induction of IL-6 in the maternal plasma and foetal brain, whilst postnatal P2X7 receptor inhibition alleviates behavioural and morphological alterations in the offspring. Our results offer a therapeutic possibility for early prevention and treatment of ASD, the increasingly prevalent psychiatric disorder in children.