Prenatal PolyIC and LPS exposure alters serotonin transporter and 5-HT2A receptor binding densities in rodents: implications for schizophrenia

Yinghua Yu  
*University of Wollongong, yinghua@uow.edu.au*

Rory Watsford  
*University of Wollongong, rnw535@uowmail.edu.au*

Christopher Bell  
*University of Wollongong, cjb692@uowmail.edu.au*

Zehra Boz  
*University of Wollongong, zb010@uowmail.edu.au*

Hongqin Wang  
*University of Wollongong, hongqin@uow.edu.au*

*See next page for additional authors*
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Authors
Yinghua Yu, Rory Watsford, Christopher Bell, Zehra Boz, Hongqin Wang, and Xu-Feng Huang

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**Abstract Title:** Prenatal PolyIC and LPS exposure alters serotonin transporter and 5-HT$_{2A}$ receptor binding densities in rodents: implications for schizophrenia

**Background:** Epidemiological studies have reported a strong association between prenatal infection and an increased incidence of schizophrenia. The serotonergic system has been implicated in the pathogenesis of schizophrenia. Alterations in the expression of serotonin transporter (5-HTT) and receptor 2A (5-HT2A) have been reported in the brain of schizophrenia patients. Rodents treated with PolyIC (polyinosinic-polycytidylic acid; PolyI:C) and LPS (lipopolysaccharide; LPS) show behavioral changes resembling certain aspects of schizophrenia. In this study, we investigated 5-HTT and 5-HT2A receptor binding densities in the brain of adult rats treated with PolyIC and LPS at prenatal period.

**Methods:** Maternal Sprague-Dawley rats were injected intraperitoneally with saline solution, LPS, or PolyI:C at embryonic days 15 and 16. Open field (OF) and novel object recognition (NOR) tests were performed in offspring from postnatal day (PN) 118. Cognition was evaluated by a discrimination index in the NOR test reflecting recognition memory. The receptor binding densities of 5-HTT and 5-HT2A were detected by [3H]-paroxetine and [3H]-ketanserin binding autoradiography. The prefrontal cortex (PFC), cingulate cortex (Cg), striatum, nucleus accumbens (Acb), hippocampus and amygdala were examined.

**Results:** Prenatal PolyI:C decreased the 5-HTT binding density in the striatum and M1 in adult offspring, but increased 5-HTT binding density in the amygdala. Prenatal LPS significantly decreased 5-HTT binding density in the striatum, Cg, M1 and S1, but increased 5-HTT binding density in the amygdala. However, neither prenatal PolyI:C nor LPS significantly altered 5-HT2A receptor binding density in these brain regions. In the NOR test, adult prenatal LPS offspring showed a 74% decrease in discrimination index compared to saline control (p=0.011). Prenatal injection of PolyI:C significantly increased peripheral rearing activity of adult offspring in the OF test (p=0.034).

**Conclusions:** Both bacterial and viral prenatal infection decreased 5-HTT binding density in the striatum and increased 5-HTT binding density in the amygdala, suggesting serotonin was increased in the striatum and decreased in the amygdala. Serotonin in the striatum is believed to be involved in the positive symptoms of schizophrenia, while serotonin in the amygdala is an important region for cognitive function. Cognitive deficit was observed in prenatal LPS offspring, and prenatal PolyI:C induced hyperlocomotor activity indicating schizophrenia-like positive symptoms. Therefore, the alteration of 5-HTT binding density and neurobehavioral changes imply that the prenatal infection may a risk of disrupted neurodevelopment.