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Neuropathology of muscarinic receptor in the prenatal infection - rat model

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Abstract
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**Purpose**: There is substantial evidence to support the notion that prenatal infection is a risk factor for developing mental illness in offspring. Abnormal cholinergic neurotransmission has been observed in cognitive deficits and schizophrenia. However, the effects of maternal infection on the cholinergic neurotransmitter system are unknown. In this study, two different prenatal infection modes, bacterial (lipopolysaccharide; LPS) and viral (polynosinic-polycytidylic acid; poly IC) were utilised to investigate the M1/4 muscarinic receptor over 3 time points; neonatal pup, adolescent and adult.

**Methods**: Maternal Sprague-Dawley rats were injected intraperitoneally with saline solution (1 ml/kg, control), LPS (100 μg/kg) or poly IC (8 mg/kg) at embryonic days 15 and 16. Brains of female offspring were harvested at postnatal (PN) day 7, PN 35 and PN 126. Slide-based receptor autoradiography was then used to quantify acetylcholine M1/4 receptor density, using 10nM \[^{3}H\text{pirenzepine}\] as the specific and 10µM atropine as the non-specific ligand. M1/4 receptor binding densities were analysed by ANOVA with post-hoc Tukey’s HSD.

**Results**: M1/4 receptor binding density was significantly decreased in poly IC treated offspring on PN 7 within cortical, limbic, and subcortical brain regions including the: prefrontal cortex (23%, \(p<0.05\)), anterior cingulate cortex (54%, \(p<0.001\)), primary motor cortex (44%, \(p<0.001\)), secondary sensory cortex (43%, \(p<0.01\)); caudate putamen (24%, \(p<0.01\)) and nucleus accumbens (24%, \(p<0.01\)); hippocampus (33%, \(p<0.05\)) and amygdala (39%, \(p<0.05\)). However, many of these changes were not present at the adolescent and adult ages, except for the nucleus accumbens, hippocampus and amygdala. Prenatal LPS administration altered M1/4 receptor binding density only in the prefrontal cortex at PN 7.

**Conclusion**: This study has proved that M1/4 muscarinic receptor abnormality does occur in the prenatal infection model. Since the M1 receptor is involved in cognitive function, our finding supports the prenatal immune activation model as relevant to the aetiology of mental illness such as schizophrenia. Future study is required to examine the binding affinity, signalling molecules, and fine morphology of muscarinic receptors involved in brain development. The outcome of this study may contribute to drug identification for treating the cognitive deficits of schizophrenia and allied disorders.