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Abstract

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# *Changes in midbrain dopaminergic circuitry in the maternal immune activation rat model of schizophrenia: ultrastructural stereological analyses*

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Schizophrenia is a debilitating neuropsychiatric disorder with ~1% prevalence. Despite extensive research, little is known about the microscopic changes in neural circuits that may contribute to the behavioural manifestations of schizophrenia. We have identified a complex pattern of inputs onto the dopaminergic neurons in the posterior ventral tegmental area (pVTA) of the midbrain, involving inhibitory inputs from the rostromedial tegmental nucleus (RMTg), which in turn are modulated by excitatory glutamatergic inputs. Here, we investigated the hypothesis that an underlying causal mechanism of schizophrenia is altered synaptic input onto pVTA dopaminergic neurons, which results in a characteristic excessive release of dopamine. We combined lentiviral vector technology and peroxidase-immunogold double labelling methods to selectively label pVTA dopaminergic neurons and RMTg GABAergic neurons. Three-dimensional serial transmission electron microscopy was used to analyze the synaptic inputs to the pVTA in the maternal immune activation (MIA) rat model of schizophrenia versus controls. In identified synapses between RMTg GABAergic neurons and pVTA dopaminergic neurons, we found a statistically significant decrease in the volume of both the presynaptic terminal and the postsynaptic density in MIA rats versus controls. For excitatory synapses on the RMTg GABAergic inputs, we found a statistically significant decrease in the thickness of the postsynaptic density in MIA rats versus controls. All anatomical deficits correlated significantly with decreased pre-pulse inhibition. These data suggest that in schizophrenia, impaired inhibition of pVTA dopaminergic neurons could result in excessive release of dopamine, leading to a hyperdopaminergic state of the brain and the manifestation of schizophrenic symptoms.