Abnormal firing activity of midbrain dopaminergic neurons of a schizophrenia animal model established by perinatal EGF treatment: implication for their social interaction ability

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Epidermal growth factor (EGF) is one of ligands for the ErbB receptors expressed by midbrain dopamine neurons. Excessive signals of this cytokine EGF in the perinatal stage perturb the postnatal development of dopamine neurons, resulting in the post-pubertal behavioral endophenotypes relevant to schizophrenia (such as reduced PPI and social deficits). To explore the contribution of their dopaminergic abnormality to social behaviors as well as to stress vulnerability, we investigated the firing activity of dopamine neurons in the ventral tegmental area (VTA). Single unit recording in an anesthetic condition revealed that the mean firing rate of VTA dopaminergic neurons was increased in EGF-pretreated rats (EGF rats). Subchronic treatment with the antipsychotic drug risperidone ameliorated both social deficits and the firing abnormality. Social defeat stress mimicked the effects of EGF pretreatment; it elevated the mean firing rate and conversely reduced social interaction scores in control rats. In contrast, the stress responses were less evident in those of EGF rats. In order to further explore the above pathophysiological phenomena, we performed single-unit recordings and in vivo microdialysis in free-moving conditions. We confirmed that the firing activity of EGF rats was higher in the basal state than that of controls but was less elevated than control during social interactions. In agreement, microdialysis revealed that dopamine efflux in the medial prefrontal cortex was less responsive to the social interaction stimuli. These results suggest that the dynamic range of dopaminergic responses to stressors is one of the crucial determinants for their social interaction ability and its reduction contributes to the social negativity of the schizophrenia model.