Hyperdopaminergic activity and abnormal auditory processing in a cytokine-induced schizophrenia model

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Abstract; Schizophrenia symptoms such as auditory hallucination typically emerge during and after the adolescent stage. However, the mechanism setting this timing of the disease onset remains to be elucidated. To explore this time dependency, we employed one of the cytokine-induced animal models for schizophrenia in which cognitive abnormalities are known to become apparent at the post-pubertal stage. Epidermal growth factor (EGF) was subcutaneously administered to neonatal mice and rats. This model as an adult exhibited most remarkable phenotypic changes in dopaminergic neurons. Electrophysiologically isolating dopaminergic neurons in the midbrain, we investigated the effects of neonatal EGF treatment on the development of spontaneous activity and spike properties of nigral dopaminergic neurons and assessed tone-induced neural activities in the auditory cortex by the flavin-brain imaging. Spontaneous activity was monitored in vivo in an anesthetic condition and spike properties were analyzed by patch clamping of midbrain slice preparations. In control animals, spontaneous firing activity was gradually elevated in both firing rates and burst ratios from juvenile to adolescence and reached plateau levels at the adult stage. In the same developmental time course of the EGF model, these indices more slowly increased, but continued to increase during the adolescent stage and exceeded the levels of control animals at the adult stage. In parallel, the EGF model exhibited abnormal auditory functions in basal hyperactivity as well as in offset responses. These results suggest that the temporal onset specificity of auditory impairments in schizophrenia might associate with aberrant postpubertal development of firing properties of midbrain dopaminergic neurons.