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Prenatal stress on *Gad1*-heterozygotes selectively perturbs GABAergic neurogenesis, GABAergic synapse function and behavioral phenotypes.

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【Background】

Exposure to prenatal stress (PS) and mutations in *GAD1*, which encodes the GABA synthesizing enzyme glutamate decarboxylase (GAD) 67, are both risk factors for psychiatric disorders. Using GAD67-GFP knock-in mice (GAD67^{+/GFP}) subjected to PS from embryonic day 15.0 to 17.5, we previously reported disruption of GABAergic neurogenesis in the MGE and loss of PV neurons in the mPFC, hippocampus and somatosensory cortex of GAD67^{+/GFP}-PS mice. Nevertheless, little is known about the mechanisms underlying the changes in fetal brain programming, as well as the long-lasting effects inducing psychiatric disorders by PS and *Gad1* gene mutation.

【Methods】

Using GAD67^{+/GFP}-PS model, we performed RNA expression microarray and DNA methylation profiling as well as behavioral test. Functional implications of the double-hits condition on inhibitory synapse was examined by inhibitory postsynaptic current (IPSC) and electrocorticogram (EcoG) recordings.

【Results】

RNA expression microarray analysis showed enrichment of differentially expressed genes (DEGs) functionally associated with neurogenesis, behavior, cell proliferation and differentiation. In addition, genome-wide DNA methylation profiling revealed some of DGEs may be affected due to epigenetic regulation. We examined the behavioral phenotype and found lack of social novelty recognition in a 3-chambered social approach task. Furthermore, impairments in prepulse inhibition of startle response were observed in GAD67^{+/GFP}-PS mice. The frequency of mIPSCs was decreased without significant changes in amplitude and decay time constant in layer V pyramidal neuron of mPFC in GAD67^{+/GFP}-PS mice. We also demonstrated that the amplitude, frequency and decay time constant of spontaneous IPSC as well as GABA_AR-mediated tonic current were significant increased in GAD67^{+/GFP}-PS mice. Finally, EcoG recording showed reduction in mean power spectrum density at gamma-frequency range in mPFC of double-hits mice.

【Conclusions】

Our data indicated a possible role of epigenetic mechanisms induced by *Gad1*-PS double-hits. Inhibitory synaptic inputs and post synaptic alterations in our model suggested GABAergic dysfunction underlying the behavioral deficit. These findings may provide new insights into mechanisms of the pathogenesis of psychiatric disorders.