Adolescent Loss of Lis1 Results in Defective Hippocampal Morphology and Distinct Behavioral Deficits Resembling a Schizophrenic-Like Phenotype

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In this project I established the Lis1 gene as a potential novel target for pharmaceutical treatment of schizophrenia. 80% of schizophrenics currently comply poorly with medication regimens, making new medications desirable. The Lis1 gene, which encodes beta subunit platelet−activating factor acetylhydrolase (PAFAH1B1), plays a crucial role in neuronal migration during development. However, its role in post−migrational neurons remains unknown. Interestingly, Lis1 expression is decreased in adult brains of schizophrenic patients. To investigate Lis1's role in the adult brain, four mouse mutant models were generated by the Cre/loxP gene targeting system: Lis1fl/+, Lis1fl/fl (~25% Lis1 reduction), CamKII−Cre;Lis1fl/+(~50% Cre−expressing cell reduction), and Lis1cko, a Lis1 conditional knockout(100% Lis1 reduction). Examining the interneuron density of adult Lis1cko mutants using immunohistochemistry showed that adolescent loss of Lis1 results in decreased density of Parvalbumin−expressing interneurons within the CA1 region. This morphological change is a key indicator of schizophrenia in human patients. To further understand this morphological phenotype, I examined Lis1cko using a battery of behavioral assays: sucrose preference test, modified open field, and basal locomotion. Results revealed that adolescent loss of Lis1 results in negative, positive, and cognitive behavioral symptoms consistent with the schizophrenic−like phenotype. Establishing the role of Lis1 in regulating adult hippocampal interneuron and linked behaviors marks Lis1 as a potential novel target of therapeutic treatments for schizophrenia.