Induction of mild inflammation leads to cognitive deficits related to schizophrenia

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Researchers at the Institute for Comprehensive Medical Science, Fujita Health University and the National Institute for Physiological Sciences, Japan, along with colleagues from 9 other institutions, have identified an exceptional mouse model of schizophrenia. After screening over 160 mutant mouse strains with a systematic battery of behavioral tests, they identified a mutant mouse lacking the Schnurri-2 protein (Shn-2 KO) that exhibits behavioral deficits and other brain features consistent with schizophrenia. Shn-2 is an NF-kappaB site-binding protein that binds enhancers of major histocompatibility complex class I genes and inflammatory cytokines, which harbor common variant single nucleotide polymorphisms associated with schizophrenia. The Shn-2 KO mice display behavioral abnormalities that resemble the symptoms of human schizophrenia, including working memory deficits, impaired nest building behavior (a measure of self-neglect), decreased social behaviors, and anhedonia (loss of the ability to experience pleasure).

Drs. Tsuyoshi Miyakawa, Keizo Takao, and their colleagues found that Shn-2 deficiency results in mild chronic brain inflammation, which leads to a unique alteration of a specific region in the brain, the dentate gyrus. The "immature Dentate Gyrus (iDG)", as it is referred to by the researchers, is presumed to produce schizophrenia-related phenotypes, such as working memory deficits and impaired nest-building behavior, as reported online February 6th in *Neuropsychopharmacology*.

The transcriptome patterns in the prefrontal cortex of the Shn-2 KO mice and post-mortem schizophrenia patients are surprisingly similar,

with 100 commonly altered genes. Interestingly, 11 of the top 20 ranked genes with altered expression levels are involved in inflammatory or immune function. The brains of the mutant mice also exhibit numerous schizophrenia-related phenotypes, including decreased parvalbumin and GAD67 levels, increased theta and decreased gamma power on electroencephalograms, activation of astrocytes, and a thinner cortex.

The researchers also succeeded in rescuing the working memory deficit, impaired nest-building behavior, and some features of iDG in the brain of this schizophrenia model mouse by chronically administering anti-inflammatory drugs. This finding highlights the possibility that genetically-induced changes in the immune system may be a predisposing factor in schizophrenia, providing the groundwork for further studies to elucidate the pathogenesis and pathophysiology of schizophrenia using this model.

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