第46回シグナル伝達医学グローバルCOE学術講演会

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Immature dentate gyrus as a candidate endophenotype of psychiatric disorders

Adequate maturation and integration of the adult-generated neurons into the circuit of the hippocampus would be crucial for normal cognitive functions and emotional behaviors. Disruption of the process could result in some disturbance in mental health. Previously, we reported that mice heterozygous for a null mutation of áCaMKII, a key molecule in synaptic plasticity, have profoundly dysregulated behaviors including hyper-locomotor activity and a severe working memory deficit, which are endophenotypes of schizophrenia and other psychiatric disorders. Surprisingly, we found that almost all the neurons in the dentate gyrus (DG) of the mutant mice failed to mature at molecular, morphological and electrophysiological levels, causing severe deficit in the synaptic plasticity at mossy fiber – CA3 synapses (Yamasaki et al., Molecular Brain, 2008; Matsuo et al., Front. Behav. Neurosci., 2009). Upon these findings, we have been trying to find the strains of mutant mice that have “immature dentate gyrus (iDG)” among approximately 120 strains of genetically engineered mice with which we have conducted our comprehensive behavioral test battery. So far, by using a simple real-time PCR assay using several iDG markers (Hagihara et al., JoVE, 2009; Ohira et al., Molecular Brain, 2010), we have identified four other strains of mutant mice that have a phenotype strikingly similar to iDG. We also found that chronic fluoxetine treatment can induce “dematuration” resulting in iDG-like phenotype in wild type mice (Kobayashi et al., PNAS, 2010). Some but not all the strains with iDG-like phenotype have decreased parvalbumin-positive interneurons in hippocampus and cortex, which is a well-known endophenotype of schizophrenia. Moreover, gene and protein expression patterns in the DG of these mice are similar to those found in the post-mortem brains of psychiatric patients, such as schizophrenia and bipolar disorder. Interestingly, a bioinformatics analysis revealed that the transcriptome pattern of the hippocampus of the mice with iDG-like phenotype had highly significant similarity to those obtained from the experiments involving injuries, infections, wounds, aging, and sleep deprivation, suggesting that iDG is associated with a phenomenon similar to inflammation. Based on these results, we propose that iDG in adulthood might serve as a promising candidate endophenotype of schizophrenia and its related psychiatric disorders.

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