Department of Basic Medical Sciences

Division of Neuronal Network
神経ネットワーク分野

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Our major research interest is the molecular mechanisms of higher brain functions in mammals such as emotion, and learning and memory. We are especially focusing on the roles of functional molecules localized in synapses, for instance, neurotransmitter receptors, signal transduction molecules and adhesion molecules, in neuronal information processing. We are examining receptor functions, synaptic transmission and plasticity, and their roles in the whole animal with electrophysiological, biochemical, molecular genetic and behavioral approaches. We are also trying to elucidate fundamental aspects of psychiatrical and neurological disorders using model animals.

1. Behavioral abnormalities and impairments in GluA1 trafficking in Lmtk3 KO mice

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Accumulating evidence suggests that glutamatergic signaling and synaptic plasticity underlie one of a number of ways psychiatric disorders appear. The present study reveals a possible mechanism by which this occurs through highlighting the importance of lemur tyrosine kinase 3 (LMTK3) in the brain. Behavioral analysis of Lmtk3 knockout (KO) mice revealed a number of abnormalities that have been linked to psychiatric disease such as hyper-sociability, deficits in pre-pulse inhibition and cognitive dysfunction. Treatment with the antipsychotic clozapine suppressed these behavioral changes in Lmtk3 KO mice. As synaptic dysfunction is implicated in human psychiatric disease, we analyzed long-term potentiation (LTP) of excitatory synaptic transmission in Lmtk3 KO mice and found that its induction was severely impaired. Further investigation revealed abnormalities in trafficking of the α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA)-receptor subunit GluA1 after AMPA stimulation in Lmtk3 KO neurons, along with a reduction in GluA1 expression in the postsynaptic density. Therefore, we hypothesize that LMTK3 is an important factor involved in the trafficking of GluA1 during LTP, and that disruption of this pathway contributes to the appearance of behavior associated with human psychiatric disease in mice.

2. Analyses of the vanishing white matter disease model mouse

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Vanishing white matter disease (VWM) is an auto-

somal recessive neurological disorder caused by mutation(s) in any subunit of eukaryotic translation initiation factor 2B (eIF2B), an activator of translation initiation factor eIF2. VWM occurs with mutation of the genes encoding eIF2B subunits (EIF2B1, EIF2B2, EIF2B3, EIF2B4 and EIF2B5). However, little is known regarding the underlying pathogenetic mechanisms or how to treat patients with VWM. Here, we describe the identification and detailed analysis of a new spontaneous mutant mouse harboring a point mutation in the *Eif2b5* gene (p.Ile98Met). Homozygous Eif-2b5I98M mutant mice exhibited a small body, abnormal gait, male and female infertility, epileptic seizures and a shortened lifespan. Biochemical analyses indicated that guanine nucleotide exchange activity on eIF2 was decreased in the mutant eIF2B protein with the Eif2b5I98M mutation, and the level of the endoplasmic reticulum stress marker activating transcription factor 4 was elevated in the 1-month-old Eif-2b5I98M brain. Histological analyses indicated upregulated immunoreactivity of glial fibrillary acidic protein in the astrocytes of the Eif2b5I98M forebrain and translocation of Bergmann glia in the Eif-2b5I98M cerebellum, as well as increased mRNA expression of an endoplasmic reticulum stress marker, C/EBP homologous protein. Disruption of myelin and clustering of oligodendrocyte progenitor cells were also found in the white matter of the Eif2b5I98M spinal cord at 8 months old. Our data show that Eif-2b5I98M mutants are a good model for understanding VWM pathogenesis and therapy development.

3. Store-operated Ca^{2+} entry and insulin secretion mediated by GPR40 via the IP3R1/STIM1/Orai1 pathway in pancreatic β-cells

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The long-chain fatty acid receptor GPR40 plays an important role in potentiation of glucose-induced insulin secretion (GIIS) from pancreatic β-cells. Previous studies demonstrated that GPR40 activation enhances Ca^{2+} release from the endoplasmic reticulum (ER) by activating inositol 1,4,5-triphosphate (IP3) receptors. However, it remains unknown how ER Ca^{2+} release via the IP3 receptor is linked to GIIS potentiation. Recently, stromal interaction molecule (STIM) 1 was identified as a key regulator of store-operated Ca^{2+} entry (SOCE), but little is known about its contribution in GPR40 signaling. We show that GPR40-mediated potentiation of GIIS is abolished by knockdown of IP3 receptor 1 (IP3R1), STIM1 or Ca^{2+}-channel Orai1 in insulin-secreting MIN6 cells. STIM1 and Orai1 knockdown significantly impaired SOCE and the increase of intracellular Ca^{2+} by the GPR40 agonist fasiglifam. Furthermore, β-cell-specific STIM1 knockout mice showed impaired fasiglifam-mediated GIIS potentiation not only in isolated islets but also in vivo. These results indicate that the IP3R1/STIM1/Orai1 pathway plays an important role in GPR40-mediated SOCE initiation and GIIS potentiation in pancreatic β-cells.

Publications

Montrose, K., Kobayashi, S., Manabe, T. and Yamamoto, T. (2019). Lmtk3-KO mice display a range of behavioral abnormalities and have an impairment in GluA1 trafficking. *Neuroscience* 414:154-167.

Terumitsu-Tsujita, M., Kitaura, H., Miura, I., Kiyama, Y., Goto, F., Muraki, Y., Ominato, S., Hara, N., Simankova, A., Bizen, N., Kashiwagi, K., Ito, T., Toyoshima, Y., Kakita, A., Manabe, T., Wakana, S., Takebayashi, H. and Igarashi, H. (2019). Glial pathology in a novel spontaneous mutant mouse of the Eif2b5 gene: a vanishing white matter disease model. *J. Neurochem.* https://doi.org/10.1111/jnc.14887

Usui, R., Yabe, D., Fauzi, M., Goto, H., Botagarova, A., Tokumoto, S., Tatsuoka, H., Tahara, Y., Kobayashi, S., Manabe, T., Baba, Y., Kurosaki, T., Herrera, P., Ogura, M., Nagashima, K. and Inagaki, N. (2019). GPR40 activation initiates store operated Ca^{2+} entry and potentiates insulin secretion via the IP3R1/STIM1/Orai1 pathway in pancreatic β-cells. *Sci. Rep.* 9:15562.