学位論文内容の要旨

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学位論文題名

Studies on neuronal function using voltage-gated Ca^{2+} channel Cav2.1α_1 subunit mutant mice

（Cav2.1 チャネルの神経機能における役割に関する研究 - Cav2.1α1 遺伝子変異マウスを用いて-）

Voltage-gated Ca^{2+} channel is widely distributed in central nervous system (CNS) and plays important role in Ca^{2+}-dependent cell functions. It is consisted of α_1, α_2/δ, β, and γ subunits. Glutamate is an important excitatory neurotransmitter mediated by Cav2.1 channel in CNS, essential for learning and memory. However, excessive glutamate induces excitotoxicity. Glutamate binds to specific receptors including, kainate/AMPA. Kainate administration is used in many studies to induce excitotoxicity model in the brain.

Mutation in human Cav2.1α_1 subunit (Cav2.1α_1) causes several neurologic disorders. The mutations have also been discovered in mice including *rolling Nagoya* and *tottering-6j* mice. These mice display similar neurologic disorders to those of human.

I examined the protective effect of Cav2.1 channel in kainate-induced and cryogenic brain injury using *rolling Nagoya*, and absence-like seizures and studied characteristics of *tottering-6j* mice.

Rolling Nagoya mouse is a recessive mutant strain and it shows 40% less Ca^{2+} current amplitude compared to wild-type (+/+) mice. It exhibits ataxia but not seizures. The mutant Cav2.1α_1 increases with age-dependent manner in heterozygous *rolling Nagoya* (*rol*/+) mice. The sensitivity of kainate-induced seizure has decreased in aged *rol*/+ mice than +/+ mice. Also neuronal damage and the number of reactive astrocyte in hippocampus were also decreased in aged *rol*/+ mice. In addition, western blot result showed significantly lower pp38 expression in aged *rol*/+ mice (Chapter 1). Cryogenic brain damages were induced in homozygous *rolling Nagoya* (*rol*/*rol*) mice. *rol*/*rol* mice showed smaller lesion, less neuronal damage and smaller number of reactive astrocyte after injury. Western blot of Cav2.1 channel inhibitor-post-treated mice showed lower level of pp38 expression than vehicle-treated mice (Chapter 2). The results of these studies indicate that Cav2.1 channel is related with p38 MAPK signaling, leading to decreasing neuronal cell death.

In this study, *tottering-6j* mouse showed absence-like seizure and pharmacological characteristic similar to those of human. Increased expression of TH, ZebrinII, and Ryr3, and decreased expression of Calb2 were found in the cerebellum of *tottering-6j* mice compared to +/+ mice. These results suggest that Ca^{2+} signaling is related with the seizure and cerebellar gene expression of *tottering-6j* mice (Chapter 3).

The studies using aged *rolling Nagoya* mice revealed that mutant Cav2.1 channel has a protective effect in seizure and p38 MAPK signaling is related with neuronal damage. Also, the results suggested that Cav2.1 channel and pp38 inhibitor could be used as therapeutic agents against seizure and brain injury. The study using *tottering-6j* mice showed that the different location of the Cav2.1α_1 mutation is important in seizure and gene expression in cerebellum. Thus, *tottering-6j* mice could be useful model for Cav2.1 channel function study.

I demonstrated that the difference of the mutation location in Cav2.1α_1 leads to different symptoms and gene expression. However, how Cav2.1 channel is related in certain disease, certain signaling cascade and certain gene expression is not known. Although further studies are warranted, I suggest that Cav2.1α_1 mutant mice would be useful models for researching Cav2.1 channel function and various Cav2.1 channel related neurological diseases and developing therapeutic agent.