S51-2 Epilepsy with heterozygous SCN1A mutations of voltage-gated sodium channels

◯Iori OHMORI[1], Keiichiro HAYASHI[1], Hideki MATSUI[1]

[1]Department of Physiology, Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama University

Voltage-gated sodium channels are responsible for the generation and propagation of action potentials in the brain. Mutations in genes encoding sodium channel α1 subunit ($Na_v1.1$) have been associated with various types of epileptic syndromes, including severe myoclonc epilepsy in infancy (SMEI) and generalized epilepsy with febrile seizure plus (GEFS+). Approximately 80% of SMEI patients and 5-10% of GEFS+ patients have the heterozygous *SCN1A* mutations.

Regarding types of mutations, truncated mutations such as nonsense mutations and frame shift mutations were detected in SMEI patients while missense mutations were mostly detected in GEFS+ patients. Missense mutations were located in the pore region and the voltage sensor of $Na_v1.1$channel. These findings suggested the *SCN1A* mutations lead to the significant dysfunction of $Na_v1.1$ channel. The electrophysiological study of the mutant channels were carried out by using the patch clamp method in the HEK cells which heterologously expressed *SCN1A* cDNA. The *SCN1A* mutations revealed the alternations of activation, inactivation, persistent currents, and current density. Most of the mutant channels lost their function partially or completely.

Scn1a KO mice which exhibit epilepsy and ataxia have been generated recently. $Na_v1.1$ channels were dominantly expressed in the GABAergic interneurons. Dysfunction of inhibitory neurons might lead to epileptic seizures. In addition, rats harboring the *Scn1a* missense mutation which shows hyperthermia induced seizure susceptibility were generated. These rodent models will be useful to elucidate the mechanism of the *SCN1A* mutation-associated epilepsies and contribute to the development of the novel antiepileptic drugs.