S61-1 Depolarizing $GABA_A$ receptor signaling after febrile seizures forms aberrant neural circuits in the epileptic brain

◯Ryuta KOYAMA[1], Yuji IKEGAYA[1], Norio MATSUKI[1]

[1]Univ. of Tokyo. Grad. Sch. of Pharm. Sci.

Ectopic granule cells provide aberrant excitatory circuits in the dentate gyrus of patients with temporal lobe epilepsy (TLE). Thus, it is essential to clarify the cellular and molecular mechanisms underlying the emergence of ectopic granule cells. In this study, we tested the hypothesis that the disturbance of neuronal migration by febrile seizures (FS) results in the granule cell ectopia. We found that experimental FS in the rat pups resulted in the granule cell ectopia in the adulthood, a phenomenon blocked by the $GABA_A$ receptor antagonist picrotoxin. To directly examine whether $GABA_A$ receptor activation regulates the migration, we performed the cocultures of hippocampal slices prepared from transgenic rat pups expressing GFP, which enabled the time-lapse imaging of migrating granule cells. Immature granule cells had functional $GABA_A$ receptors and performed the radial migration to the granule cell layer. However, cells from FS rats often migrated reversely in the hilus, an event that was blocked by the $GABA_A$ receptor antagonist bicuculline. Importantly, these cells displayed a higher $GABA_A$ receptor immunoreactivity than control in the leading growth cone and the pharmacological activation of them induced the local calcium influx and slowed down or reversed the migration. Our findings revealed that depolarizing $GABA_A$ergic signaling induces the formation of aberrant neural circuits in the epileptic brain.