Pathophysiological impact of diverse dysregulation of tonic inhibition in Angelman syndrome

Kiyoshi Egawa[1], Yoshihiro Hirata[1], Mitsuru Ishikawa[2], Hideaki Siraishi[1], Hideyuki Okano[2]

1. Department of Pediatrics, Hokkaido University Graduate School of Medicine.
2. Department of Physiology, Keio University School of Medicine

Recent studies have indicated that extra-synaptic GABAa receptor-mediated inhibition (tonic inhibition) is decreased in *Ube3a* knockout mice. However, its pathophysiological importance is still under elucidated. It has been shown that various kinds of protein such as GABAa receptor subunits and GABA transporters contribute to regulate tonic inhibition. Because its regulatory manner is different by brain region, the degree of deregulation can also differ with various brain regions in Angelman syndrome. To clarify this, we evaluated tonic inhibition in various brain regions and found that tonic inhibition was decreased in pyramidal neurons of the hippocampus and cortex, but not in thalamocortical relay neurons in the thalamus. We speculate that this discrepancy itself can contribute to the pathophysiology of symptoms coming from a disturbance of network processing, i.e. epilepsy or cognitive dysfunction. If so, positive allosteric modulators for α5 subunit containing GABAa receptor (PAM-α5GABAaR) may be effective for improving these symptoms because α5 subunit is exclusively expressed in the extra-synapse of the hippocampus and cortex. We are now evaluating this possibility by administrating PAM-α5GABAaR *in vivo* to compare its efficacy for cognitive dysfunction and EEG abnormality with that of gaboxadol, which enhances tonic inhibition globally. The deregulation of tonic inhibition can also differ with the different genotypes in Angelman syndrome because the deleted 15q11-13 region contains GABAa receptor α5 subunit encoding gene. To analyze the genotype-dependent differences in tonic inhibition, we established neurons differentiated from induced pluripotent stem cells of patients with various genotypes of Angelman syndrome and healthy controls. We confirmed comparable resting membrane and firing properties among genotypes and are now under preparation for investigating inhibitory functions in these neurons. We believe that the diverse deregulation of tonic inhibition would be one of the key for understanding the variety of symptoms and their severity in Angelman syndrome.