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Physiological Roles of Phosphorylation of Brain Specific K^+-Cl^- Cotransporter, KCC2, Studied by Using Dephosphomimetic Mutant Mice.

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Summary

A transient increase in $[Cl^-]_i$ can reverse the direction of Cl^- permeation, causing a reversal from inhibitory GABA action to excitatory, and can cause spatial recruitment of oscillations involving many circuits. KCC2, which rapidly pumps out the influx of Cl^-, is extremely important, and the phosphorylated state of T906 and T1007 regulates KCC2 function and, as a result, regulates GABA action. It is necessary that the dynamic change of the phosphorylation state of KCC2 is maintained in order to keep it in an appropriate range. In order to investigate its physiological regulation, a missense mutation that replaces a threonine residue with arginine was introduced, and KCC2-T906A/T1007A ($KCC2^{A/A}$) mice, in which this site was constitutively dephosphorylated, were generated. Using this mouse, we prove that the normal phosphorylation state of KCC2 is essential for the normal development and function of the brain.

In $KCC2^{A/A}$ homozygous mouses, the ability of KCC2 to pump Cl^- out of cells was enhanced. Birth and adult body weight, respiratory rate, and fertility were normal. Pain, muscular endurance, spontaneous locomotor activity, compulsive repetitive behavior, and sociability were normal, but startle response, anxiety-like behavior, and social novelty cognition were impaired. The seizure scale and EEG measurement showed an increase in the seizure index. In addition, the activity of the γ-band in standard state decreased, and the synchrony of the neuronal activity increased.

In $KCC2^{A/A}$ mice, the function of KCC2 was enhanced and the inhibitory power of GABA was strengthened, resulting in changes in behavior. The decrease in the γ-band of EEG and the abnormal cognitive function as well as the increase in the synchronization of the neuronal activity as a mechanism prone to seizures, are consistent with the enhancement of the inhibitory action and its robustness by enhancing the KCC2 function. Thus, appropriate regulation of phosphorylation of Thr906 and Thr1007 of KCC2 was found to be important for the development of inhibitory neurotransmission and maintenance of normal brain function.