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Reciprocal release profile between hippocampal monoamines and acetylcholine releases in a novel spontaneous epilepsy model, mu3B deficient mice

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Purpose: Recently, it has been shown that the neuron-specific adaptor protein complex type-3B (AP-3B) may be involved in de novo synaptic vesicle biogenesis from endosomes. Homozygous mice deficient in mu3B-subunit of AP-3B (mu3BKO) show spontaneous epileptic seizures. Toward the understanding of mechanism of seizure in mu3BKO, we determined neurotransmitter releases in mu3BKO and wildtype mice, using hippocampal mini-slices in vitro. **Methods:** The experimental protocol used in this study has been approved by the Ethical Committee of Hirosaki University. The hippocampal mini-slices (350 x 350 micron thickness) were incubated in 0.5 ml artificial-cerebrospinal-fluid (ACSF) for 5 min. The levels of dopamine, serotonin and acetylcholine in ACSF were determined by ECD-HPLC system. After confirming the stabilization of basal release, 50 mM potassium-evoked stimulation were performed for 5 min. **Results:** There was no significant difference in the basal releases of dopamine and serotonin between mu3BKO and wildtype mice, whereas the basal acetylcholine release in mu3BKO was lower than that in wildtype. By contrast, potassium-evoked release of monoamines in mu3BKO was lower than that in wildtype, whereas potassium-evoked acetylcholine release in mu3BKO was higher than that in wildtype. **Conclusion:** This study demonstrated that a reverse relationship between monoaminergic and acetylcholinergic transmission in mu3B deficient mice, namely a reduction of monoaminergic release and an increase of acetylcholinergic release. Therefore, the present results suggest that the imbalance between these two transmission may be, at least partially, involved in the mechanisms of spontaneous seizures in mu3B deficient mice.

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The Ih blockers, CsCl and ZD7288, can suppress the inherited epilepsy of Mongolian Gerbil

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Background: In our acute experiments, CsCl and ZD7288 (4-ethylphenylamino-1, 2-dimethyl-6-methylaminopyrimidinium chloride), which were blockers for hyperpolarization-dependent cationic current (Ih), increased the threshold of electrically induced paroxysmal discharge. We examined the anti-convulsant effects of Ih blockers on inherited epilepsy of Mongolian gerbil. **Methods:** In administration test of CsCl, a total of 13 gerbils (♂:5, ♀:8) were employed, whereas 9 gerbils (♂:4, ♀:5) were used in evaluating ZD7288. They were tested by the falling-stimuli once or twice a week for 5-6 weeks before, during, and after orally administering CsCl (10mM) or ZD7288 (100μ M) solution. The behavioral responses were classified into four stages modified from Loskota et al. We measured the ratio of each response to total examination. **Result:** The average score in the CsCl test was 0.73±0.01(mean±S.E.) before administration, 0.38±0.06 during administration, and 0.54±0.07 after administration, respectively. This agent reduced the frequency of grade 3 (generalized seizure) significantly from 10.4±2.56% to 0 %. In the ZD7288 test, the average score was 1.00±0.09 before administration, 0.67±0.05 during administration, and 0.71±0.06 after administration. It also reduced the frequency (10±2.6%; n=88) of generalized seizure in control to 0% (n=71), while it increased the frequency (24±2.5%) of no responses to 46±2.9%. **Conclusion:** Statistical analyses showed that CsCl and ZD7288 have a potent anti-epileptic effect.