The involvement of EAAC1 in diurnal variation of ischemic Zn²⁺ toxicity

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[Aim] It was reported that temporal changes in severity of ischemic brain injury, but the mechanism is mostly unknown. In ischemic hippocampus, extracellular Zn²⁺ accumulates in neurons, resulting in neuron death. Excitatory amino acid carrier (EAAC) 1 reduces zinc toxicity. Here, we examined the involvement of EAAC1 in temporal changes in ischemic zinc toxicity.

[Methods] Mice (12 weeks) were subjected to ischemia at 09:00 (ZT4) or 23:00 (ZT18). At 72 h after, zinc accumulation was assessed by Zn²⁺ probe, TSQ, and the number of neurons were examined by immunostaining. Diurnal changes in hippocampal EAAC1 expression were assessed by western blot. Mice were subjected to ischemia at ZT18 after an EAAC1 inhibitor, TBOA, injection (i.c.v.) and we examined zinc accumulation and the number of neurons.

[Results] Ischemia induced TSQ(+) cells in hippocampus and the number of TSQ(+) cells were less at ZT18 than ZT4. Compared to ZT4, a decrease in neuron death were observed at ZT18. EAAC1 expression was higher at ZT18 than ZT4. Besides, TBOA increased TSQ(+) cells and decreased neuron death at ZT18.

[Conclusion] These results suggest temporal changes in severity of ischemic neuronal damage might be mediated by zinc accumulation via diurnal variation of EAAC1 expression.