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The involvement of EAAC1 in diurnal variation of ischemic Zn^{2+} toxicity

Youichirou Higashi[1], Takaaki Aratake[1,2], Shogo Shimizu[1], Takahiro Shimizu[1], Motoaki Saito[1]

[1]Dept. Pharmacol., Kochi Med. Sch., Kochi Univ., [2]JSPS Research Fellow

Temporal changes in the severity of ischemic brain injury have been demonstrated, but the mechanism is not fully understood. In the post-ischemic hippocampus, massive amounts of Zn^{2+} accumulates in neurons, resulting in neuron death. On the other hand, excitatory amino acid carrier 1 (EAAC1), a cysteine transporter that plays an important role in GSH synthesis, reduces ischemia-induced hippocampal Zn^{2+} toxicity. Recently, it was reported that EAAC1 protein expression exhibits a diurnal change with a peak in the dark period in mesencephalon. In this symposium, we will introduce the involvement of EAAC1 in diurnal variation of post-ischemic injury. Male C57BL/6 mice were subjected transient global ischemia by clamping bilateral common carotid arteries at 09:00 (ZT4, in the light period) or 23:00 (ZT18, in the dark period), and Zn^{2+} accumulation was assessed by the Zn^{2+}-specific probe, TSQ. Compared to ZT4, the number of TSQ-positive cells were significantly decreased at ZT18. The protein levels of EAAC1 was found to be high at ZT18 than ZT14. Furthermore, pretreatment with TBOA, an EEAC1 inhibitor, increased the number of TSQ-positive cells at ZT18. These findings indicate that ischemia in the dark period reduces Zn^{2+} accumulation, and that this reduction might be mediated by temporal changes of EAAC1 protein expression.