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The effect of MK801 on P-glycoprotein expression in limbic seizure rats' hippocampus

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Background and Objective: Seizures which cause glutamate acid release, could also induce overexpression of P-glycoprotein (P-gp) which contribute to the pharmacoresistance in refractory epilepsy. While NMDA receptor is one of the most important glutamate acid receptors, its activation by glutamate acid will induce the second messenger, Ca^{2+}, influx into the cells. As one of the important second messengers, Ca^{2+} has a great effect on the regulation of a lot of gene expression. We undertake this study to explore whether NMDA receptor play a role in the regulation of P-gp expression in hippocampus during limbic seizure.

Method: Limbic seizure rats model was made by lithium chloride and pilocarpine. Realtime quantitative RT-PCR (qRT-PCR) was employed to determine P-gp mRNA expression at 0 h, 3 h, 6 h, 24 h, and 72 h after seizure (n = 6). And P-gp mRNA expression at 6 h was also determined by qRT-PCR, while protein expression at 24 h was determined by immunohistochemistry for three groups, control, status epilepticus with MK801 intervention (MK801), and status epilepticus without intervention (SE) (n = 6).

Results and Discussion: The expression of multidrug resistance gene 1a (mdr1a) was much higher than control at each time point within 72 h after seizure, with highest expression level at 6 h. While the expression of mdr1b transiently increased at 2.18, 2.38, and 1.60 times respectively at 3 h, 6 h, and 24 h. Moreover, the expression of mdr1a and mdr1b were remarkably lower in MK801 group than in SE group at 6 h ($P<0.05$). The level of P-gp expression was also significantly lower in MK801 (26.58 ± 4.97) group than in SE group (39.03 ± 4.10, $P<0.01$) at 24 h.

The fact that MK801, an antagonist of NMDA receptor, down-regulates the overexpression of P-gp after seizure suggested that NMDA receptor may be involved in the regulation of P-gp expression during seizure. Therefore, it is possible to prevent the overexpression of P-gp after seizure by inhibiting NMDA receptor's overactivation effectively. It is thus possible in future, by determining some biomarkers indicating P-gp related pharmacoresistant epilepsy, to identify the subgroup of refractory epilepsy patients, for whom additional NMDA receptor antagonists may be effective.

Conclusion: An antagonist of NMDA receptor, MK801, could down-regulate the overexpression of P-gp after seizure not only on the mRNA level, but also on the protein level.

References

1. Edwards RH. Drug delivery via the blood-brain barrier. *Nat Neurosci* 2001; 4:221-2.
2. Eid T, Thomas MJ, Spencer DD, *et al*. Loss of glutamine synthetase in the human epileptogenic hippocampus: possible mechanism for raised extracellular glutamate in mesial temporal lobe epilepsy. *Lancet* 2004; 363(9402):28-37.