

Post-transcriptional Modification of AMPA Receptors Following Neonatal Seizure

Abstract

Many factors controlling seizure susceptibility in the neonatal brain are developmentally regulated. During early brain development there is intense synaptogenesis, pruning of the vast synaptic network and axonal myelination. A neonate's steep learning curve requires incredible plasticity leading to greater vulnerability to hyperexcitability and seizures following hypoxic insult. These events may increase a newborn's susceptibility to epileptogenesis later in life. The aims of this study were (1) to determine whether the sequelae following neonatal seizure include mechanisms similar to those employed during learning and memory processes such as phosphorylation of AMPA receptors (AMPA receptors) and (2) to assess the efficacy of AMPA antagonists in preventing or reversing this phosphorylation. In order to characterize AMPAR phosphorylation events, a global hypoxia neonatal seizure model was employed using Long Evans hooded rats at postnatal day 10-12 when they are considered developmentally similar to the newborn human. Rat hippocampal lysates were immunoprecipitated with aGluR1 antibody. By using phosphospecific antibodies in western blot incubations, I found that there were increased levels of phosphorylation on two serine residues, Ser831 and Ser845, in AMPAR subunit GluR1 in hypoxic rats as compared to normoxic control littermates. These same sites, and additionally Ser818, are known to be analogously phosphorylated during long-term potentiation contributing to a modification of ion channel properties and the synaptic incorporation of AMPARs. These results suggest a pathway shared between the mechanisms of learning and those of epileptogenesis that may contribute to hyperexcitability following hypoxia-induced seizure. The reversible nature of the phosphorylation events observed may suggest a novel route for the therapeutic intervention. I investigated the effect of known anti-epileptic drugs, NBQX and topiramate (TOPAMAX) on these phosphorylation levels and found that 30mg/kg intraperitoneal topiramate treatment over an extended period of time following hypoxia-induced seizures decreased phosphorylation of Ser831 residues on AMPAR subunit GluR1 as compared to vehicle treatment.