

Effects of Perinatal Hypoxia Induced Seizures on Later Life Seizure Susceptibility and Neuronal Injury in the Developing Brain.

Abstract

The effect of early-life seizures on long term epileptogenesis has always been a controversial issue. In past years, lack of overt neuronal injury on the immature animal raised doubts about the postulated excitotoxicity caused by early-life seizures. However, recent studies demonstrate that these early seizures, while not causing acute neuronal death in the young animal, may still affect susceptibility to seizures and seizure induced neuronal injury later in life. This study uses the hypoxia-induced seizure model in Long Evans rats at postnatal day (P) 10 to determine future susceptibility to seizures and seizure-induced neuronal injury after administration of kainic acid (KA) (a potent convulsant and neurotoxin). KA was administered intraperitoneally to induce seizures in P14, P21, P28 and P45 rats that underwent previous hypoxic insult at P10 and animals were observed for changes in seizure threshold due to differences in latency to seizure onset and seizure severity. Animals were sacrificed and brain sections stained to detect neuronal loss via in situ end labeling (ISEL) of DNA fragmentation. Compared to controls, rats subjected to hypoxic insult at P10 had **significantly shorter** latency to seizure onset at all later ages. Also, average seizure severity was **significantly higher** among animals that were placed in earlier hypoxic conditions at P10. Furthermore while animals given KA at P14 failed to show cell death, P21 and P28 rats displayed greater DNA fragmentation in animals that had earlier hypoxia-induced seizures compared to their littermate controls who had not experienced earlier hypoxia-induced seizures. Positive nuclear labeling of ISEL showed that the DNA fragmentation occurred in vulnerable neurons predominantly in the CA1 hippocampal region. These observations indicate that the presence of generalized seizures due to hypoxic conditions in the immature brain, while resistant to cell death, has long term detrimental effects on behavior, seizure susceptibility and neuronal injury on the developing brain.