

DOES HIPPOCAMPAL NEUROGENESIS AFTER KAINATE-INDUCED APOPTOSIS IN NEONATAL RATS REPLACE LOST NEURONS?

Hippocampal Neurogenesis Follows Kainic Acid-Induced Apoptosis in Neonatal Rats

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The effects of kainic acid (KA) on neurogenesis in the developing rat hippocampus were investigated. Neonatal [postnatal day (P) 7] rats received a single bilateral intracerebroventricular infusion of KA (50 nmol in 1.0 μ L) or vehicle. At P14, P25, P40, and P60, the spatial and temporal relations between the neurodegeneration and neurogenesis induced by KA were explored by using terminal deoxynucleotidyl transferase-mediated biotinylated UTP nick-end labeling (TUNEL) to detect the dying cells and 5-bromodeoxyuridine (BrdU) to label newly generated cells.

There was progressive loss of neurons in the cornu ammonis (CA) 1 and CA3 subfields of the hippocampus at all time points in KA-treated rats. TUNEL staining identified dying cells at P14 through P60, mainly in the CA3 subfield. The number of TUNEL-positive cells decreased with age. Neurogenesis also was observed in the KA-treated hippocampus. The number of BrdU-positive cells in the dentate gyrus was significantly decreased at P14, when the number of TUNEL-positive cells is highest. However, at later time points (P40 and P60), the number of BrdU-positive cells in the dentate gyrus was significantly increased. In addition, the number of BrdU-positive cells was increased in the CA3 subfield at P40 and P60 in KA-treated rats. A substantial proportion (40%) of the newly generated cells in CA3 also expressed markers of immature and mature neurons (class III β -tubulin and neuronal nuclei). Newly generated cells in the CA3 subfield only rarely expressed glial markers (8%).

These results suggest that a single exposure to KA at P7 has both immediate (inhibition) and delayed (stimulation) effects on neurogenesis within the dentate gyrus of developing rats. KA administration resulted in both neu-

ronal apoptosis and neurogenesis within the CA3 subfield, suggesting that the purpose of neurogenesis in the CA3 is to replace neurons lost to apoptosis.

COMMENTARY

Considerable interest has been directed at the hypothesis that neurogenesis of dentate granule cells after status epilepticus may contribute to synaptic reorganization and epileptogenesis in the adult rat hippocampus (1,2). More recently, studies have provided evidence that *neonatal* seizures lead to a *reduction* in neurogenesis (3). The work of Dong and co-workers suggests that apoptosis *without* recorded seizures is followed by a long-lasting period of neurogenesis that produces neurons in the dentate gyrus and CA3 areas. These authors propose that neurogenesis, during apoptosis without apparent seizures, replaces neurons that were lost after the excitotoxic insult.

Dong et al. gave neonatal rats single bilateral intracerebroventricular infusions of kainic acid or vehicle at postnatal day 7, resulting in two key findings. First, dying apoptotic neurons were found primarily in the CA3 area shortly after the kainate treatment, whereas progressively fewer apoptotic neurons were seen at later times after the excitotoxic insult. Second, the number of newborn neurons in the dentate gyrus and CA3, relative to controls, was significantly increased several weeks after the insult. The researcher's data suggested that the newborn cells were primarily neurons and not glia. Thus neurogenesis occurred after the kainate-induced apoptosis, which is their basis for speculating that the neurogenesis essentially replaced apoptotic neurons.

Based on earlier data, the authors argue that the kainate-infusion protocol in P7 rats does not induce seizure activity (4). Thus this work implies that kainate treatment in this model caused neuronal death *without seizures*. The issue of whether kainate is capable of causing seizures in immature rats has been controversial. A difficult but important question, based on these data, is the nature of the electrical activity that presumably occurred during the kainate treatment. It is difficult to rule out the possibility that unrecorded seizures may have played a role in the delayed

neuronal death (i.e., apoptosis) induced by intracerebroventricular kainate. Whether subsequent neurogenesis occurred independent of intense kainate-induced depolarization and electrical activity associated with neurotoxicity deserves further investigation.

The authors raise the question whether neurogenesis serves to repair the brain and/or contributes to subsequent pathology. The authors' results suggest the hypothesis that the cell proliferation replaces the specific types of neurons that are lost (e.g., CA3 pyramidal cells), which warrants further investigation.

by F. Edward Dudek, Ph.D.

References

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