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Neurodevelopmental impact of antiepileptic drug exposure

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Epilepsy management in neonates and infants represents a particular challenge because we have little information about the adverse effects of either seizures or antiepileptic drugs (AEDs) on the developing brain during the early postnatal period. As we and others have shown over the past decade, certain AEDs (including phenobarbital, phenytoin, valproate, and clonazepam) induce pronounced apoptotic neuronal death in specific regions of the neonatal rodent brain. Moreover, some AEDs (including newer drugs, topiramate and lamotrigine) exhibit a profound synergistic effect on neuronal apoptosis when applied in combination even in doses that are below threshold for inducing apoptosis when given individually. The long-term functional consequences of these effects on apoptosis remain unknown but have been assumed to be deleterious. To support this assumption, we have recently found that exposure of seizure-free rat pups to certain AEDs results in long-term behavioral and cognitive abnormalities in adulthood. For some AEDs, certain long-term abnormalities were seen following a single drug administration to the pups. In the rat model these abnormalities ranged from decreased seizure threshold in adulthood to profound schizophrenia-like phenotypes and cognitive/emotional deficits. The discussion will focus on: 1) interactions between effects of seizures and AEDs; 2) the neural substrates in which enhanced neuronal apoptosis is detected and their correlation with the neural substrates of behavioral and cognitive abnormalities, and 3) our search for AEDs that may be devoid of deleterious effects in the immature brain as a strategy to avoid long-term adverse behavioral consequences.

Biography

Dr. Kondratyev obtained his Ph.D. in 1986 from the Institute of Molecular Biology, Moscow, Russia. He performed his postdoctoral studies at the National Institute of Child Health and Child Development and then at the Department of Radiation Medicine at Georgetown University. In 1996, he joined the faculty at Georgetown and is currently an Associate Professor of Pediatrics and Director of the Epilepsy Research Program. His research focuses on the basic mechanisms of neuronal injury following glutamate-mediated excitation and seizures, as well as on the neurodevelopmental aspects of antiepileptic drug exposure.

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