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Age and gender susceptibility to ischemic neonatal seizures: Role of chloride co-transporters in refractoriness?

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Ischemia in the neonatal brain is an important cause of refractory seizures. Exact timing of neonatal stroke occurrence is usually unclear and the diagnosis delayed until presentation with seizures a few to several hours later. Developmental profiles of chloride co-transporter expression and function in immature brains have been proposed to underlie the efficacy of GABA-agonists to act as hyperpolarizing agents. To investigate the anti-seizure efficacy of the first line anticonvulsant and GABAA-agonist phenobarbital (PB) and NKCC1 antagonist bumetanide (BTN) as adjunct treatment on neonatal ischemic-seizures, we utilized unilateral carotid-ligation to produce ischemia and acute ischemic-seizures in postnatal day 7 and 10 CD1 mice. Quantitative video-EEG and western blot quantification of the adult-form electroneutral chloride co-transporter KCC2 assessed efficacy of the treatment.

Age and sex dependent susceptibility to ischemic seizure severity was detected. Inefficacy of PB for P7 ischemic seizures was supported by published studies indicating a chloride co-transport dependent developmental reversal of depolarizing to hyperpolarizing action of GABA by the age of P8-9 in rodents. The age-dependent increase in the hyperpolarizing effects of the GABAA agonists have been shown to depend on the increasing KCC2 expression profile detected in the maturing CD1 mouse brains and was supported by the efficacy of PB for P10 seizures. However, this study showed a down regulation of KCC2 after cerebral ischemia that may further decrease the efficacy of drug actions that are dependent on a hyperpolarizing chloride gradient for their anticonvulsant action that failed to be rescued by blocking NKCC1 by BTN.

Biography

Dr. Kadam completed her Ph.D. from Colorado State University working with Dr. F.E. Dudek who is a world renowned epilepsy researcher. She completed her post-doctoral training at Johns Hopkins University School of Medicine and is now an independent researcher with the Department of Neurology. She has established a small animal EEG core and begun collaborations investigating epileptogenesis both in models of pediatric acquired and genetic epilepsies. Her current research investigating mechanisms underlying neonatal seizure refractoriness is funded by an Epilepsy Foundation research grant. She has published 11 papers in reputed journals and is serving as a scientific program review committee member for the American Epilepsy Society.