IMPAIRED EXPLORATORY BEHAVIOR IN THE ACUTE POST-ICTAL PERIOD IN DEVELOPING RATS

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Prolonged seizures in early life are associated with an increased risk for the development of long-term cognitive deficits, memory impairment, learning disabilities, and attentional problems. They are also associated with microglial activation . However, the existence of such behavioral deficits in the acute period following seizure and their relationship to microglial activation have not been well-established. Using a kainic acid (KA)-induced model of status epilepticus, we investigated changes in exploratory behavior and microglial activation in young rats in the acute period (1-7 days) following seizures.

On postnatal day (P) 15, 21, or 30, male Long Evans rats were injected with KA (3 mg/kg, 10mg/kg, 10 mg/kg, respectively, *i.p.*) or saline. Beginning 24 hours after injection, exploratory behavior was quantified in an open field, and reassessed at 24 hour intervals for up to seven days. At 24 and 240 hours post-seizure, animals were sacrificed and their brains processed for immunocytochemical detection of microglia using anti-Aif1 Ab.

24-48 hours after seizure, P21 rats failed to explore in an open field, remaining nearly immobile and paralyzed (24 hrs: KA=1.8±2.2, control=72.4±19; $p < 0.0001$). By day 3, however, they showed behavioral recovery, exploring similarly to littermate controls. In P30 animals, on the other hand, this deficit persisted as long as 7 days (the extent of testing; day 7: KA=24.7±21.6, control=72.2±29.85, $p<0.05$). In contrast, when P15 pups were placed in an open field away from their dams 24 hours after seizure, they exhibited significantly increased exploratory behavior relative to littermate controls (KA=84.9±24.1, control=24.5±21; $p<0.05$). This behavior normalized by 48 hours. In P21 and P30 animals, the time course of impaired exploratory behavior was paralleled by microglia activation, while P15 animals showed no detectable changes in microglia.

Behavioral deficits are evident in the acute period following prolonged seizures, and are significantly modulated by age at seizure onset. Younger animals (P15) initially show hyper-exploratory behavior, while older animals (P21 and P30) show exploratory deficits. While the behavioral impairments of P21 animals are transient, they persist in P30 animals. Transient (P21) or persistent (P30) microglial activation parallel these impaired exploratory behavior. Our results suggest that modulation of microglia activation may hasten recovery of behavioral changes following prolonged seizure. There may be a role for anti-inflammatory therapy in reversing the essential behavioral comorbidity in children with epilepsy.