Glia activation, neuroinflammation and oxidative stress are concomitant pathogenic events in an infantile rat model of epileptic encephalopathy

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BACKGROUND
Neuronal status epilepticus (SE) may result in long-term neurological outcomes. There is urgent need of animal models to study the pathologic mechanisms induced by unmitigating seizures in the immature brain that lead to cognitive deficits and epilepsy. Since neuroinflammation and oxidative stress are triggered by activated glial cells and may contribute to disease development, we investigated this brain response in an infantile rat model of epileptic encephalopathy. This is a condition in which epileptic activity itself may contribute to cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and it can worsen over time1.

AIM
To characterize in depth an infantile rat model of epileptic encephalopathy induced by de novo status epilepticus to study mechanisms and test novel disease-modifying treatments.

METHODS

EXPERIMENTAL MODEL: Status epilepticus (SE) was induced in postnatal day 10 (P10) P10 Sprague Dawley rats by bilateral injection of kainic acid (KA, logEC50 = 5). Of the animals (14 days after injection) 4 groups of rats were compared depending on the age of the experiment: 1) Sham (control); 2) KA: KA was prepared and injected in the animals (14 days) 3) KA: KA was prepared and injected in the animals (14 days) 4) KA: KA was prepared and injected in the animals (14 days). The animals were then divided into control and experimental groups (n=6 for each group) and behavioral assays were performed for 5 weeks. Histology was performed for 5 weeks.

RESULTS

NEURONAL LOSS: At 2 months post SE, there were significant decreases in the number of CA1 and CA3 neurons in the hippocampus of SE-exposed animals compared to controls. These results are consistent with previous findings in other animal models of SE.

Epileptiform activity was observed in the SE-exposed group, as indicated by increased EEG power in the theta range. This activity was not observed in the control group.

NEUROINFLAMMATION: Inflammation markers were elevated in the hippocampus of SE-exposed animals compared to controls. These results suggest that inflammation plays a role in the pathogenesis of SE.

Oxidative stress markers were also elevated in the hippocampus of SE-exposed animals compared to controls. These results are consistent with previous findings in other animal models of SE.

CONCLUSIONS

SE-exposed rats show changes in brain and cognitive function compared to controls. These changes are consistent with previous findings in other animal models of SE.

RT-qPCR analysis showed an increase in mRNA levels of neuroinflammatory (GFAP, CD-11b, HMGB1) and oxidative stress (Nrf2) markers in the hippocampus 24h-1 week post SE.

Histological and biochemical analyses of neuroinflammation and oxidative stress in the acute phase post-SE

Astrocytes and microglia are activated in the hippocampus, thalamus, caudate putamen and cortex (not shown) at 6-72h post SE. This activation is unilateral at the site of kainite injection at 6h, thereafter it becomes bilateral. IL-1β is induced in caudate putamen in microglia at 6-24h.

Summary

The rat model recapitulates some salient features of the clinical condition:

- age of animals (early childhood of human life)
- development of epilepsy
- cognitive decline and brain atrophy which worsens with epilepsy

Neuroinflammation and oxidative stress, two pathologic processes involved in the progression of epilepsy4, develop in the aftermath of SE. MRI parameters prospectively differentiate rats with and without spontaneous seizures.

Conclusions

This model can be used for mechanistic studies and for testing novel drugs.

Since the model provides rats with and without spontaneous seizures (although all animals are similarly injured), it can be exploited to identify biomarkers of epileptogenesis.

Reference

Supported by

 leans on "The impact of water maze training on spatial memory in rats with kainic acid-induced seizures" by Di Sapio et al. (2012).