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AED sensitivity in a novel model of acquired epilepsy in organotypic entorhinal-hippocampal slices

Peter Massey, Jessica Carpenter, Alex Lench, Roland Jones. University of Bath, Bath, UK

Epilepsy is a common neurological disorder that affects over 500,000 people in the U.K. In order to develop effective therapeutic treatments it is crucial to better understand the pathophysiological changes that take place in the brain during its initiation and development. Epilepsy research relies heavily on in vivo animal models of epilepsy, but this approach has a number of serious drawbacks. We have developed a novel in vitro model of chronic acquired epilepsy in cultured organotypic hippocampus-entorhinal slices in which acute seizure-like events (SLEs) are initially evoked by exposing cultures to an external medium containing high potassium/low magnesium (12 mM K^+/0.5 mM Mg^{2+}; HKLM; (1)). Slice cultures treated in this way can then be returned to normal conditions and monitored for the appearance of chronic, recurrent, spontaneous activity. We have now demonstrated that by three weeks post-treatment the majority of treated slices exhibit spontaneous paroxysmal-like events (SPLE) whilst matched control slices do not. This model therefore allows longitudinal assessment of seizure development following insult in a single animal and has a number of other major advantages over traditional models. We are currently characterising the pharmacological profile of the acute phase of the model and investigated the effectiveness of some clinically effective antiepileptic drugs (AEDs).

Acute brain slices were prepared as described (2) from neonatal (P10-14) rats, and then maintained in organotypic culture using the interface method (3). Spontaneous extracellular field potentials were recorded from entorhinal cortex (EC) of cultured brain slices (14-30 days in vitro) and SLEs induced by perfusion of HKLM aCSF. AEDs were bath applied for 30 minutes following establishment of stable baseline activity. Phenytoin (100 µM; n = 8), gabapentin (100 µM; n = 6) and lamotrigine (100 µM; n = 4) significantly suppressed both SLE amplitude and frequency ($P<0.05$) whilst remacemide (100 µM; n = 6) significantly suppressed SLE amplitude ($P<0.05$) but not frequency. In contrast, ethosuximide (200µM; n=3), an AED commonly used to treat absence seizures, was ineffective. Thus, the acute phase of the model exhibits unusual sensitivity to clinically useful AEDs. It remains to be determined whether treatment with these AEDs during or after the acute phase would effectively impact on the development of long-term chronic epileptiform activity. In conclusion, this model has potential as a tool for evaluating the effectiveness of AEDs during epileptogenesis and has a number of advantages over traditional models.

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References

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