Frequency-dependent inhibition of antidromic hippocampal compound action potentials by anti-convulsants

Adrianna Teriakidis¹, Jon T. Brown¹,², Andrew Randall¹,²

¹Neurology and GI CEDD, GlaxoSmithKline Research and Development Ltd, New Frontiers Science Park (North), Harlow, Essex, CM19 5AW, UK
²Present address: MRC Centre for Synaptic Plasticity, University of Bristol, University Walk, Bristol, BS8 1TD, UK

Abstract:
Using rat hippocampal slices, extracellularly recorded antidromic compound action potentials (cAP) were produced in CA1 pyramidal cell populations by electrical stimulation of the alveus at 0.5 Hz. These responses were additionally examined across a range of stimulus frequencies between 0.5 and 100 Hz. Anticonvulsant drugs in clinical use were applied via perfusion of the recording chamber. Three anticonvulsants produced a concentration-dependent inhibition of the cAP evoked at low frequency (0.5 Hz). The following IC₅₀ values were observed: lamotrigine, 210 µM (interpolated); carbamazepine, 210 µM (interpolated); phenytoin, 400 µM (extrapolated). The extent of inhibition produced was increased when trains of 30 cAPs were evoked at frequencies ≥ 30Hz. This frequency dependence was quantified by measuring a response integral for a range of compound concentrations. Three other compounds valproate (5 mM), topiramate (500 µM) and levetiracetam (500 µM) produced no clear effect at any stimulus frequency tested. Using this simple neurophysiological assay it has been possible to compare the use-dependent inhibition of hippocampal action potentials by a range of anticonvulsants, providing a useful adjunct to patch clamp studies of such molecules at Na⁺ channels. There is no clear correlation between the activity in this model and the clinical efficacy of these drugs in different forms of epilepsy.

Key words:
epilepsy, drug, seizure, ion channel, use-dependent block