EFFECT OF LAMOTRIGINE ON NETWORK AND CELLULAR EXCITABILITY IN THE RAT ENTORHINAL CORTEX *IN VITRO*

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The anticonvulsant, lamotrigine, has been suggested to act by blocking Na and/or Ca channels, and consequently reducing presynaptic release of glutamate (Leach *et al,* 1986; Wang *et al*, 1996). Using patch clamp recordings of spontaneous synaptic currents in the rat entorhinal cortex (EC) we have shown that the drug reduces spontaneous glutamate release, but increases GABA release, although neither effect is related to Na or Ca channel blockade (Cunningham *et al* 2000). Technical limitations of the patch clamp approach do not allow us to determine what the overall effect of the drug on background synaptic inhibition and excitation in cortical neurones is, or how this may alter neuronal excitability. To address these questions we utilised a novel approach described by Rudolph *et al* (2004), which derives global background inhibitory and excitatory conductances from membrane potential fluctuations using sharp electrode intracellular recordings.

Intracellular recordings were made from pyramidal cells in layer III in slices of EC obtained from male Wistar rats (50-60g). At intervals of five minutes the membrane potential was manually clamped to two depolarised levels by direct current injection via the recording electrode. Analysis of the membrane voltage fluctuations recorded at these two levels were then used, in conjunction with knowledge of the leak conductance and reversal potentials of synaptic excitation and inhibition, to estimate quantitatively the global network inhibitory and excitatory conductances (Rudolph et al, 2004). At intervals between the direct current injections, families of depolarising current pulses were applied to generate action potentials to measure cellular excitability via action potential threshold and spike train characteristics.

In 4 layer III neurones the mean (±sem) global excitatory conductance was 1.18±0.32 nS, whereas that for inhibition was 3.92±0.88 nS. After 15 min perfusion with lamotrigine (20μM) the excitatory conductance had decreased to 0.76±0.07 nS, whilst inhibition had dramatically increased to 10.82±2.29 nS. Thus, the average inhibition:excitation ratio changed from 3.9±1.2 to 15.1±4.3 in favour of inhibition. At the same time, action potential threshold increased from 25.3±3.3 mV to 29.1±3.8 mV positive to resting potential. In addition, when spike trains were evoked by a supra-threshold (250ms) depolarising pulse, the number of spikes decreased from 5.3±0.9 to 1.3±0.6. There was no change in spike amplitude either when evoked singly or in trains. The results suggest that the changes in spontaneous GABA and glutamate release seen in patch clamp experiments with lamotrigine result in a change in global background conductances in further favour of inhibition. This may be responsible for the change in cellular excitability and underlie, in part, the anticonvulsant action of lamotrigine.

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