TOPIRAMATE DOSE-DEPENDENTLY MODIFIES SLOW INHIBITORY POST SYNAPTIC POTENTIALS EVOKED IN RAT OLFACTORY CORTICAL NEURONES IN VITRO

Russo Emilio, De Sarro G., Constanti A.

Chair of Pharmacology, Department of Experimental and Clinical Medicine, Faculty of Medicine and Surgery, University of Catanzaro, Catanzaro, Italy;
Pharmacology Department, School of Pharmacy, University of London, London, UK.

Topiramate (TPM) is a new generation antiepileptic drug, licensed for patients with partial and secondarily generalized seizures. Thus far, its cellular mechanisms include: blockade of voltage-activated Na\(^+\) channels, modulation of HVA Ca\(^{2+}\) channels, potentiation of GABA\(_A\) currents inhibition of AMPA/KAI glutamate currents and a K\(^+\)-dependent hyperpolarization\(^1\). We tested TPM on transverse in vitro brain slices of olfactory cortex prepared from Wistar rats as previously reported\(^2\). This 'limbic' brain area is known to be important in the development and maintenance of experimental kindling and also has a potential role in the genesis and spread of certain forms of human epilepsy e.g. temporal lobe epilepsy with partial seizures. Stable intracellular recordings were made from neurones in the deep cell layer II-III using 4M K acetate-filled microelectrodes. Data are presented as mean ± S.E.M. As previously reported, in neurones maintained at −70 mV membrane potential by steady current injection, bath-application of TPM induced a slow membrane hyperpolarization, which was accompanied by a decrease in membrane input resistance\(^2\). Synaptic stimulation was delivered through a bipolar nichrome wire electrode (25μm diameter; 15μm inner core diameter) placed in cortical layer I, in order to activate afferent and association fibres projecting to layer II/III. Postsynaptic potentials (PSPs) were evoked in response to stimuli of increasing intensities (5–20 V, 0.2 ms) delivered by a Digitimer isolated DS2 stimulator. Stimulus strength was adjusted so that the synaptic response was just sub-threshold for evoking orthodromic action potentials. All measurements were performed before, during and after bath-application of TPM, so that each neurone served as its own control. Control PSPs recorded at -70mV were usually characterized by a fast excitatory component (fEPSPs) and a slow inhibitory component (sIPSPs). Control sIPSPs were characterized by a averaged peak amplitude of -6.47±0.73 mV with a averaged time to peak of 229.7±31 ms. TPM 10μM induced an increase in peak amplitude (+74.75%) and in the time to peak (+20.33%). Inversely, TPM 20 and 40μM induced a decrease of peak amplitude -46.58% and -61.73% for 20μM and 40μM, respectively. The latter dose reduced significantly also the time to peak of -28.38%. At the dose of 50μM, TPM induced a complete block of the sIPSPs these effects of TPM were usually fully reversed after a 30 min washout period. Such effects could contribute to the clinical antiepileptic efficacy of this drug.


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