

## ZONISAMIDE INDUCES A SLOW DOSE-DEPENDENT HYPERPOLARIZATION IN RAT OLFACTORY CORTICAL NEURONES *IN VITRO*

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Zonisamide (ZNS; Zonegran®) is a new generation antiepileptic drug (AED), which provides highly effective adjunctive treatment of refractory partial seizures in adults<sup>1</sup>. ZNS has multiple modes of action, a favourable pharmacokinetic profile and few drug–drug interactions. ZNS is a benzisoxazole derivative with a non-arylamine sulphonamide group and is chemically unrelated to other AEDs with the exception of the sulphonamide moiety, which is in common with Topiramate and Acetazolamide. Thus far, the cellular mechanisms underlying its anticonvulsant activity include block of sodium channels, binding preferentially to inactive channels producing use- and voltage-dependent blockade and slowing the rate of recovery<sup>2</sup> and reduction of low-threshold T-type calcium channel currents, ZNS is also reported to be a weak inhibitor of carbonic anhydrase<sup>3</sup>. It is thought to be 100–200 times less potent in this effect than acetazolamide<sup>3</sup>. We tested ZNS on transverse *in vitro* brain slices of olfactory cortex prepared from 200-250g male Wistar rats as previously described<sup>4</sup>. This 'limbic' area of the brain is known to be important in the development and maintenance of experimental kindled seizures 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 (60-80 MΩ). Data are presented as mean ± S.E.M. In neurones maintained at –70 mV membrane potential by steady current injection, bath-application of ZNS (10 μM; 20min; N=5) induced a slow, non significant, membrane hyperpolarization (mean peak amplitude = 2±0.46 mV), whereas, ZNS at 20 (N=5) and 40 μM (N=7) (bath application=20 min) induced a significant slow hyperpolarization of 4.21±0.72 mV and 9.47±0.43 mV, respectively. This hyperpolarization was accompanied by a decrease in membrane input resistance (22 ± 9 %). ZNS also produced a dose-dependent decrease in the number (but not amplitude) of action potentials elicited during a brief (160 ms) depolarizing current pulse; these effects of ZNS were usually fully reversed after a 30 min washout period. Such effects could contribute to the clinical antiepileptic efficacy of this drug.

<sup>1</sup>Brodie MJ. (2006). *Epilepsy Res.* 68: S11-6.

<sup>2</sup>Rock DM, Macdonald RL, Taylor CP. (1989). *Epilepsy Res.* 3:138-143.

<sup>3</sup>Masuda Y., Karasawa T. (1993). *Arzneimittelforschung* 43: 416-418.

<sup>4</sup>Russo E., Constanti A. (2004). *Brit. J. Pharmacol.* 141: 285-301.