020P ACTIVITY OF THE SK POTASSIUM CHANNEL OPENER 1-ETHYL-2-BENZYLIMIDAZOLINONE (1-EBIO) IN ANIMAL MODELS OF SEIZURES

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The small conductance calcium-activated potassium (SK) channel is responsible for the afterhyperpolarisation observed in neurones following action potential firing and can therefore regulate the excitability of neurones. As modulation of such an action may have potential for the treatment of seizures, we tested the activity of the selective SK channel opener 1-ethyl-2-benzylimidazolinone (1-EBIO) in two murine seizure models, and on the rotarod apparatus as an indicator of potential ataxic side-effects.

Groups of 8 to 15 male NMRI mice (18-25 g) were used in these studies. 1-EBIO (suspended in a vehicle of 0.5% Tween-80; 10 to 80 mg/kg) was administered s.c., 30 min prior to testing. Maximal electroshock threshold was determined by administering a electroshock via the cornea. Starting with an initial stimulus intensity of 14mA, the current was adjusted down or up in 1mA steps, depending on whether the preceding animal did or did not show tonic hindlimb extension, respectively (Kimball et al., 1957). For each treatment group the median current (and 95% confidence intervals) for producing convulsions was determined by the method of Kimball et al. (1957). Differences between groups were considered significant when 95% confidence intervals did not overlap. Pentylenetetrazole (PTZ) threshold was determined by infusing PTZ (5 mg/ml) through a lateral tail vein at 0.5 ml/min, using time to first clonic seizure as the endpoint (Watson & Little, 1995). The mean threshold was calculated for each group and compared by one-way ANOVA followed by Dunnett's test. Ataxic effects were determined by measuring the time mice would stay on the rotarod apparatus (17 rpm, run time of 3 min), and analysed by one way ANOVA followed by Dunnett's test.

1-EBIO significantly elevated the maximal electroshock threshold at doses above 10 mg/kg and increased the threshold to pentylenetetrazole at 40 mg/kg; a dose range where marked ataxic actions were seen on the rotarod (Figure 1). Thus, whilst 1-EBIO clearly demonstrated dose-dependent anticonvulsant actions in these models, there was little selectivity seen between these doses and those where ataxic actions were seen.

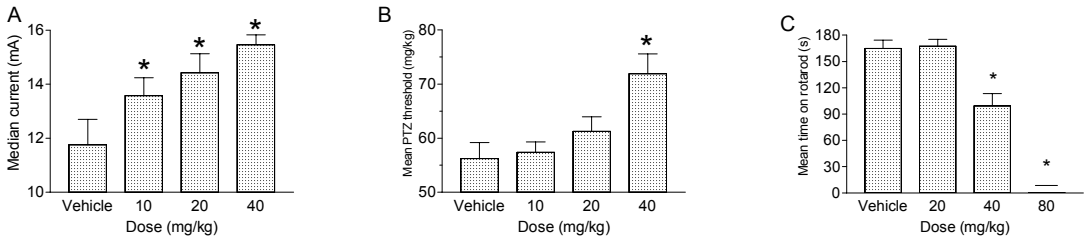

Figure 1. Effect of 30 min s.c. pre-treatment with 1-EBIO on A) Maximum electroshock threshold B) PTZ threshold and C) performance on rotarod in groups of 15, 14 and 8 mice, respectively. * indicates $P < 0.05$ compare to 0.5% Tween vehicle group.

Kimball, A.W. *et al.,* (1957) *Radiation Research* **7**, 1-12.
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