

001P INVESTIGATION OF THE ANTAGONIST ACTION OF NOVEL POLYAMINE ANALOGUES ON SPERMINE INDUCED CNS EXCITATION IN MICE *IN VIVO*

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Direct administration of 100µg spermine into the cerebral ventricles of female *Laca* mice leads to the development of CNS excitation in the form of tremor, which worsens over time and culminates in tonic convulsions (Doyle et al, 1998). Polyamines have two modulatory binding sites on the NMDA receptor complex, and have been implicated in the pathophysiology of epilepsy. The aim of this investigation was to evaluate the antagonist potential of 6 novel polyamine analogues on spermine induced CNS excitation (drugs A-F). N1-coumaroyl-1,12-dodecanediamine (A), N1-coumaroyl-1,4bis(aminopropyl) piperazine (B), N1-coumaroyl-4,9-dioxo-1,12-dodecanediamine (C), (2E)-N-[3-({2-[(3-aminopropyl) amino]cyclohexyl} amino) propyl]-3-(4 hydroxyphenyl)prop-2-enamide (D), 2E)-N- {3-[4-aminocyclohexyl]amino}propyl}-3- hydroxyphenyl)prop-2- enamide (E), and (2E)-N-[3-{2-(3-aminopropyl)amino}cyclohexyl} amino)propyl]-3-(4-hydroxyphenyl)prop-2-enamide (F), (from Brock University). Female *Laca* mice weighing 20—25g were housed in groups of 4-6 under a 12 hour light/dark cycle (light 7am-7pm) and given food and water *ad libitum*. 100µg spermine, dissolved in 0.9% sterile saline, was administered directly into the cerebral ventricles (i.c.v) in a volume of 20µl, using a Hamilton microlight syringe and a 27-gauge needle to a depth of 3mm. The injection site was 1mm to the left of the midline and 2mm rostral to a line joining the anterior base of the ears.

Administration of the analogues was achieved by either co-

administration with spermine (i.c.v) or via the i.p. route, 30 minutes prior to spermine injection.

Assessment of CNS excitation in the spermine treated mice used a scoring system (score from 1 to 5) to quantify the degree of tremor produced (Doyle et al, 1998), every 30mins for 7.5 hours. The median (+/- interquartile range) CNS excitation score for each treatment was calculated. Statistical significance of the difference between test and control was calculated using the Mann-Whitney U-test. Spermine treatment in the absence of antagonist produced a median score of 5 (+/-0.25) (n=18), 7.5hr after spermine administration. Co-administration of a 20µg dose of Drug A (n=28) or C (n=20) significantly reduced CNS excitation to a median value of 2 (+/-3.5), P<0.001. Compounds E and F (10µg, i.c.v), (n=12) were more potent, producing a median of 1(+/-1), P<0.0001. In contrast compounds B, (n=17) and D, (n=38) were without effect in this model even at 20µg, i.c.v. The effect of the most potent analogues was assessed following i.p administration. Drug E dose-dependently reduced the median value to 3 (+/-2, P<0.001), (20mg, n=18), and to 2 (+/-1, p<0.0001), (30mg/kg, n=16). Drug F (5mg/kg, n=36) reduced the median to 3 (+/-3.75, P<0.001), while 10 or 20mg/kg reduced the median score to 2 (+/-2, P<0.0001).

In summary, drugs E and F showed the most potent antagonism of spermine induced CNS excitation when administered i.c.v, although drug A and C also showed some antagonism. In addition, drug E and F have shown antagonistic potential when administered i.p. In conclusion, polyamine analogues that are effective polyamine antagonists have been developed, and may have therapeutic potential.

1. Doyle K.M & Shaw G.G. (1998) *Br. J. Pharmacol.*, **124**:386-390.