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Analgesic effects of vascular endothelial growth factor-A_{165}b in a model of osteoarthritis in rat

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Introduction Osteoarthritis (OA) is the leading cause of musculoskeletal pain in the world[1], which is still inadequately managed[2]. Vascular endothelial growth factor-A alternative splice variants have pro- (VEGF-A_{165}a) and anti-nociceptive (VEGF-A_{165}b) effects[3-5]. Alternative splicing of VEGF-A is controlled by serine-arginine protein kinase 1 (SRPK1). This study investigated the effects of VEGF-A_{165}b and SRPK1 inhibition on pain behaviour in the monosodium iodoacetate (MIA) model of OA in rats.

Methods Fifty-six male Wistar rats (200-250g) were used. In the first study, arthritis was induced with intra-knee-joint injection of MIA (1 mg/50 µl saline, n=23) under isoflurane anaesthesia (2-3% in O_2). Controls were untreated (n=9). Rats were treated with: VEGF-A_{165}b (20 ng/g body weight, days 0-14) followed by PBS (days 15-28, (MIA/VEGF14), twice weekly intra-peritoneal (I.P.)), or PBS (d0-14) followed by VEGF-A_{165}b (d15-28 I.P., MIA/VEGF28). In the second study, arthritis was induced as above (n=16) and rats treated with SRPK1 inhibitor (SRPK1i, 0.8 µg/g body weight in 1% DMSO, MIA/ SRPK1i). Weight bearing asymmetry and mechanical withdrawal threshold were measured twice weekly. Rats were euthanized with pentobarbital overdose (100 mg I.P.) on day 28.

Results MIA/VEGF14 rats had significantly reduced weight bearing asymmetry on days 25 and 28 compared to control (weight borne on ipsilateral hindpaw in MIA/VEGF14 rats 44.74 ± 2.66% vs. MIA/PBS 38.62 ± 2.68% on day 25, $p<0.05$, and 45.46 ± 1.86 vs 36.59 ± 2.17% on day 28 respectively ($p<0.001$, 2 way ANOVA, post-hoc Tukey's tests). MIA/PBS rats had significantly lowered mechanical thresholds (d28 7.168 ± 1.21 vs 14.23± 0.57 at baseline), and this was reversed by VEGF-A_{165}b treatment (d28 8.46 ± 1.16g, mean ± SEM). There was no significant effect of SRPK1 inhibitor on nociceptive behaviour.

Conclusions Systemic VEGF-A_{165}b has an anti-nociceptive effect in the MIA model of OA in rat when given early, but not later, in the development of the disease. The lack of effect of SRPK1 inhibition on OA pain could be attributable to the early stage of drug development.

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