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Electrophysiological characterisation of dorsal spinal neuronal responses and the inhibitory effect of aspirin triggered resolvin D1 in paclitaxel induced peripheral neuropathy in rats

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Introduction: The chemotherapeutic agent paclitaxel, widely used for the treatment of solid tumours, causes nerve damage leading to peripheral neuropathic pain (PPNP). Only few pharmacological management options for PPNP are clinically available. Here, we characterise evoked spinal neuronal responses in a rat model of PPNP and investigate the potential inhibitory effects of aspirin-triggered resolving D1 (AT-RvD1), a potent pro-resolving lipid mediator.

Method: Male Sprague-Dawley rats (200-250g) received intraperitoneal injection of 2mg/kg paclitaxel (n=15) or vehicle (10% Cremophor, 5% ethanol in saline, n=16) on four consecutive days[1]. Rats were prepared for single unit electrophysiology under anaesthesia[2] on day 28 when pain behaviour was maximal (hindpaw cutaneous mechanical allodynia and acetone-induced cold allodynia). Responses of lamina V-VI dorsal horn wide dynamic range (WDR) neurones were quantified following transcutaneous electrical (3 times of C- then Aβ fibre thresholds), mechanical (8-26g) and cold (100 ul acetone) stimulation onto the neuronal receptive field on the hindpaw. AT-RvD1 (15, 150 ng/50ul cumulatively) and then morphine (1 ug/50ul) were applied spinally. Comparisons of evoked WDR neuronal responses between groups and pre and post drug application were analysed with t-tests and repeated measure ANOVAs or relevant non-parametric statistics.

Results: Aβ and C-fibre thresholds of WDR neurones of paclitaxel-treated rats were lower than vehicle-treated, ($p<0.01$ (paclitaxel-treated n=27 neurones, vehicle-treated n=24 neurones)). A significantly larger proportion of neurones in paclitaxel-treated rats were acetone responsive (82% vs 66%), displayed post-discharge after non-noxious (8g) stimulation (74% vs 54%) and increased proportional spontaneous activity (40% vs 25%), (all $p<0.05$ compared to vehicle-treated rats). Spinal application of AT-RvD1 significantly ($p<0.05$) inhibited 8 and 10g mechanically evoked responses of neurones in paclitaxel-treated, but not in vehicle-treated rats (n=7-8 neurones/group). Acetone evoked responses were significantly ($p<0.05$) inhibited by AT-RvD1 in both groups of rats. Spinal AT-RvD1 had no significant effect on electrically evoked firing of WDR neurones. Spinal morphine had significant and generalised inhibitory effect upon WDR neurones to every stimulus modality.

Conclusion: Paclitaxel is associated with a phenotypic switch in the responses of WDR neurones in the dorsal horn, promoting increased spontaneous activity in WDR neurones, increased acetone responsiveness and greater post-discharge following low intensity mechanical stimuli. AT-RvD1 inhibited low intensity mechanical stimulus-evoked responses of WDR neurones only in paclitaxel-treated rats, suggesting this as a potential therapeutic target for treating mechanical allodynia in PPNP.

References:

1. Polomano RC et al. (2012). Pain 94: 293-304.
2. Chapman V et al. (1998) J Physiol 507:881-894.