Effect of a Blocking Antibody to Adrenomedullin on Pain-Like Behaviour in Inflammatory Pain Models

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Adrenomedullin (ADM) is a 52 amino acid peptide member of the CGRP family of peptides. Like CGRP, ADM exerts a hypotensive effect when administered systemically and is best known for its role in cardiovascular function (Bunton et al., 2004). However, ADM is also reported to be involved in inflammatory processes exerting both pro- and anti-inflammatory effects. ADM has recently been described as a pain inducing neuropeptide since intrathecal administration of ADM has been shown to induce pain-like behaviour in rats (Ma et al., 2006). In the current study we have sought to investigate the effect of a blocking antibody to ADM (MOR6292) on pain-like behaviour in three rat models of hyperalgesia in which inflammation is present – the Complete Freund’s adjuvant model (CFA), the ultraviolet induced hyperalgesia model (UVIH) and the moniodoacetate model (MIA).

Male Sprague Dawley rats (175-250g, CRUK) were used for all studies and induction of each of the lesions was carried out under isoflurane anaesthesia. For induction of CFA-induced hyperalgesia, CFA (100μg in 100μl) was injected into the right hind paw. For UVIH, the right hind paw was exposed to ultraviolet irradiation using the Saalmann CupCube system (300mj/cm² irradiation of a 8x12mm plantar area) and for the MIA model, 2mg/50μl MIA was injected intra-articularly into the right knee. For the CFA and UVIH models, thermal hyperalgesia was assessed from 24h and 48h post injury respectively using the Hargreaves’ plantar test (paw withdrawal latency, PWL, s). For the MIA model, mechanical hyperalgesia was assessed from 11 days post injection using the digital Randall Selitto apparatus (withdrawal threshold, g). MOR6292 was injected subcutaneously at 24h post CFA injection (0.8mg/kg, 8mg/kg) and directly after exposure to the ultraviolet stimulus (1mg/kg & 8mg/kg). For the MIA model, mechanical hyperalgesia was assessed from 11 days post injection using the digital Randall Selitto apparatus (withdrawal threshold, g). MOR6292 was injected intravenously at 11 days post MIA injection (1mg/kg, 8mg/kg & 22mg/kg). The non-steroidal anti-inflammatory drug ibuprofen (100mg/kg, po) served as a clinical comparator in the UVIH study and celecoxib (30mg/kg, po) in the MIA study. All experiments were conducted under fully blind protocols.

Administration of MOR6292 at 24h post CFA resulted in a significant reversal of thermal hyperalgesia at 48h post dose (PWL of 5.8+/-.3s for vehicle (n=10) vs 7.1+/-.05s for 0.8mg/kg (n=11) and 7.9+/-.06s for 8mg/kg (n=5) (p<0.05). In the UVIH model, MOR6292 prevented the onset of thermal hyperalgesia (PWL of 4.2+/-.06s for vehicle vs 7.8+/-.09s for 8mg/kg, p<0.01, n=9). In the MIA model, MOR6292 was ineffective in reversing mechanical hyperalgesia (3, 8 and 22mg/kg p>0.05, n=10) when tested at 11-21 days post MIA injection.

In summary, we have shown that a blocking antibody to ADM is effective in reversing thermal hyperalgesia following intraplantar injection of CFA and in preventing the onset of hyperalgesia following UVIH exposure, but was without effect in the MIA model of joint pain. The pain-like behaviour in all three of these models can be reversed using standard anti-inflammatory drugs. However, the results of the current study suggest that the underlying mechanisms and the involvement of ADM in the pain phenotype of these models differ.