Acute excitatory effects of calcitonin gene-related peptide on joint associated afferent neurones are enhanced in the monosodium iodoacetate (MIA) model of osteoarthritic pain

Craig Bullock[1,2], David, A. Walsh[1,4], Victoria Chapman[1,3], Ali Mobasheri[1,5], Sara Kelly[1,2]

[1]Arthritis Research UK Pain Centre, Clinical Sciences Building, City Hospital, Nottingham, NG5 1PB, UK, [2]School of Biosciences, University of Nottingham, Sutton Bonington, LE12 5RD, UK, [3]School of Biomedical Sciences, University of Nottingham, Nottingham, NG7 2RD, UK, [4]School of Clinical Sciences, University of Nottingham, Nottingham, NG5 1PB, UK, [5]School of Veterinary Medicine and Science, Sutton Bonington, LE12 5RD, UK

Background: Peripheral sensitization contributes to pain in knee osteoarthritis (OA) and knee joint afferents are sensitized to mechanical stimuli in the monosodium iodoacetate (MIA) rat OA pain model. The mechanisms of this sensitization are not well understood. Expression of calcitonin gene-related peptide (CGRP) in knee afferent neurones and joint structures is increased following MIA injection. CGRP has a role in neurogenic inflammation and direct excitatory effects on sensory neurones. This study investigated the effects of CGRP on the excitability of knee joint nociceptors in the MIA model of OA.

Methods: Male Sprague-Dawley rats (212±8g) were injected (left knee) with MIA (1mg/50µl; n=11) or saline (50µl; n=10). Pain behaviour (hind-limb weight bearing and hind paw von Frey withdrawal thresholds) was tested at days 0, 3, 7 and 14 post-injection. 14 days post-injection rats were anaesthetised with isoflurane (3.5% in O_2) and the jugular vein, carotid artery, trachea and femoral artery were cannulated. Anaesthesia was maintained using pentobarbital (30-40mg/kg/hr). Extracellular recordings (1 fibre per rat) were made from knee joint-associated afferents (receptive fields (RFs) over the knee) in response to von Frey stimulation (0.16-15g, 5s each/5mins). Once responses were stable, CGRP (0.5 and 1µg/100µl) (n=9) or vehicle (2 x 100µl saline) (n=12) was peripherally injected (close intra arterial) and effects followed for 60mins. Any burst firing or spontaneous activity evoked by CGRP was also studied. Conduction velocities were estimated (RF electrical stimulation; range = 0.39-13.60ms^{-1}; A- and C-fibres).

Results: Injection of MIA, but not saline, reduced ipsilateral hind-limb weight bearing and lowered ipsilateral von Frey paw withdrawal thresholds up to day 14 post-injection. On day 14 local administration of CGRP (0.5, 1µg) altered mechanically-evoked responses of joint associated afferents in MIA-treated (4/5 fibres) and saline-treated rats (3/4 fibres). In both groups of rats CGRP produced either a sensitization, or a desensitization, of mechanically-evoked responses. Administration of CGRP was associated with afferent firing in MIA rats only, and evoked spontaneous activity following injection in a greater proportion of fibres in MIA-treated rats (3/5 fibres) compared to saline-treated rats (1/4 fibres). Injection of saline did not alter responses in either group of rats.

Conclusion: Our data indicate that locally administered CGRP modulates mechanically-evoked responses of knee joint associated afferents. The acute excitatory effects of CGRP on joint afferents were only observed in MIA rats suggesting an enhanced sensitivity to the effects of CGRP in this model of joint pain. We have previously demonstrated that CGRP antagonists attenuate the sensitization of knee joint afferents in MIA-treated rats and together with the present data support our hypothesis that CGRP plays an important role in the peripheral mechanisms of OA pain.