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ANALGESIC EFFICACY OF CR4056, A NOVEL I2-IMIDAZOLINE RECEPTOR LIGAND, IN THE RAT MONOSODIUM IODOACETATE MODEL OF OSTEOARTHRITIC PAIN

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Purpose: Joint pain is the earliest symptom of osteoarthritis (OA) although clinical data suggest that it poorly correlates with OA radiological features. Interestingly, recent studies show that OA pain is driven by both nociceptive and neuropathic mechanisms. CR4056 is a promising analgesic drug that binds to imidazoline-2 receptors and that was previously reported to be effective in several animal models of inflammatory, neuropathic, and postoperative pain. The aim of this study was to evaluate the effect of CR4056 in a well-established model of OA pain mimicking the painful components of human OA. The model consisted in the injection of monosodium iodoacetate (MIA) into the knee joint of rats, which produces cartilage degeneration and pain.

Methods: Unilateral pain was induced by a single intra-articular injection of 1mg/50ul MIA in the infrapatellar area of the right knee of male Wistar rats (6 animals/group). Pain thresholds were determined as mechanical allodynia (Dynamic Plantar Aesthesiometer - electronic Von Frey test) and mechanical hyperalgesia (Pressure Application Measurement - PAM device) on day 1 before MIA injection, and on day 7, 14 and 21 after MIA injection. CR4056 (2, 6 mg/kg) or 10 mg/kg naproxen were administered orally, as single treatment on day 7 post injury and from day 14 to day 21, once daily, as sub-chronic treatments. Statistical analysis was performed by Two-way RM ANOVA, followed by Dunnett’s multiple comparisons test.

Results: Intra-articular injection of MIA induced both mechanical allodynia of the ipsilateral paw and mechanical hyperalgesia of the ipsilateral knee, either compared with the contralateral paw and knee or the saline control. Since 7 days after the induction with MIA the difference of pain behaviour between sham and arthritic rats was highly statistically significant both for allodynia (mean ± SEM: 36.4 ± 0.82 g vs. 26.5 ± 0.98 g, respectively) and for hyperalgesia (1086 ± 13.3 g vs. 692 ± 26.6 g, respectively). The difference between sham and MIA rats remained constant throughout the study. Acute oral administration of CR4056, 7 days after MIA, induced a dose-dependent reversal of MIA induced pain behaviours evaluated 90 minutes after treatment, that attained statistical significance (p<0.05) for the 6 mg/kg dose (40% and 33% reversal for allodynia and hyperalgesia, respectively). Naproxen at 10 mg/kg produced a lower and non-significant analgesia. Even more interestingly, as illustrated in the Figure, subacute treatment from days 14 to 21 after MIA with CR4056 (both doses) and naproxen, showed statistically significant anti-hyperalgesic effects (90% after treatment). Subacute 10 mg/kg Naproxen and 6 mg/kg CR4056 were also significantly effective against allodynia. Moreover, the rats treated for 7 days with 6 mg/kg CR4056 showed a significant reduction of both basal pain behaviours (allodynia and hyperalgesia), demonstrating either a long lasting effect or, even, a true symptom modulating effect. A similar effect was observed after naproxen, but this was only limited to hyperalgesia.

Conclusions: The data here presented show that the imidazoline I2 ligand CR4056 could represent a new highly effective treatment option for OA pain.

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SUBSTANCE P EXPRESSION IN THE MURINE LUMBAR DORSAL ROOT GANGLIA: EFFECT OF CHRONIC INFLAMMATORY ARTHRITIS KNEE PAIN AND TREATMENT WITH IA VANILLOIDS

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Purpose: Capsaicin (CAP) and Resiniferatoxin (RTX) are vanilloid receptor agonists that when given by intra-articular (IA) injections, can normalize Evoked Pain Scores (EPS) and Automated Dynamic Weight Bearing (ADWB) measures in carrageenan-induced acute inflammatory arthritis. To determine whether these vanilloid receptor agonists might have benefit in chronic inflammatory arthritis pain, we measured changes in ADWB and EPS due to joint pain in mice with Complete Freund’s Adjuvant (CFA) induced chronic inflammatory arthritis with and without treatment with IA injections of CAP and RTX.

Methods: Chronic inflammatory arthritis was produced by IA injection of 30 μl of CFA into the left knee of C57BL6 male mice 3 weeks prior to pain behavior testing. Mice were injected with IA RTX (10μl of 0.001%) or 10μl of 0.01% IA CAP 7 days prior to measurement of EPS and ADWB. Evoked pain behavior was measured by tallying fidgets and vocalizations per one minute with repeated palpation of the knee at 15.6 psi. ADWB (%weight on each limb and %time on each limb) was measured using an Automated Dynamic Weight Bearing apparatus (Bioseb, Vitrolles, France). Following pain behavior testing, animals were euthanized with CO2 and L2-5 dorsal root ganglia (DRG) were harvested from ipsilateral and contralateral sides after perfusion with 4% paraformaldehyde. DRG sections were incubated with primary anti-SP followed by fluorescent secondary antibody. DRG neurons expressing SP were counted manually after imaging with confocal fluorescent microscopy as a proportion of total DRG neurons.

Results: Chronic inflammatory arthritis induced by IA CFA resulted in a significantly increased EPS (3.5) and a decrease in left to right ADWB ratios for weight (0.76) and time (0.93) when compared with naive controls. Treatment with IA CAP 7 days prior to pain behavior testing resulted in minimal improvement in EPS (2.94) and no improvement of left to right ADWB ratios for weight (0.72) or time (0.83) when compared to the chronic inflammatory arthritis model. Treatment with IA 0.001% RTX 7 days prior to the exam led to improved EPS (1.71) and improved left to right ADWB ratios for weight (0.88) but no change in time (0.95) when compared to the chronic inflammatory arthritis model, but these improvements were not statistically significant. IA injection of CAP and RTX into naïve knees produced no increase in EPS or decrease in ADWB measures. DRG staining for SP showed an increase in the percent neurons expressing SP after development of arthritis from 16.7 to 31.2%. Pretreatment with CAP reduced this to nearly normal (21%) in spite of the lack of analgesic effect. Treatment with CAP and RTX in nonarthritic mice had no effect on expression of SP in the DRG.

Conclusions: Using ADWB and EPS, we were able to quantitate pain in a murine chronic inflammatory arthritis model. Chronic inflammatory arthritis produced a significant increase in EPS and decrease in ADWB measures in the affected limb. Treatment with RTX in these mice resulted in a non statistically significant improvement in pain measures as assessed.
by EPS and ADWB. CAP did not improve ADWB or EPS. These results are different than those found in mice with acute inflammatory arthritis that were pretreated with vanilloids. SP expression in the DRG of arthritic mice was increased compared to naïve but IA treatment with CAP normalized this expression. The use IA RTX or CAP for analgesia in chronic inflammatory arthritis will require additional consideration of optimal dose and timing of administration which has yet to be determined.

RELEVANCE OF IMAGING IN ANTI NERVE GROWTH FACTOR INHIBITOR (ANGF) STUDIES WITH A FOCUS ON ELIGIBILITY AND ON-STUDY SAFETY – A PICTORIAL OVERVIEW

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Purpose: Monoclonal antibodies that bind and inhibit nerve growth factor (NGF) have demonstrated both good analgesic efficacy and improvement in function in patients with osteoarthritis (OA). Anti-(a)NGF therapies offer potential as the first new class of analgesics for many years. Despite promising efficacy data, trials in OA were suspended due to concerns over accelerated rates of OA progression in some patients. However, continued development of aNGF drugs with rigorous safety screening criteria in future trials is planned and imaging will play a crucial role. Imaging will be used to define the eligibility of potential participants and to monitor safety during the course of these studies in order to identify subjects at risk for rapidly progressive OA (RPOA) prior to inclusion or to withdraw subjects from treatment early due to the occurrence of joint safety events such as RPOA.

Fig 1A. Baseline radiograph shows a normal medial and lateral joint space width.

Fig 1B. 6 months follow-up radiograph depicts definite medial joint space narrowing (JSN; arrows) with persistent absence of osteophytes medially consistent with RPOA.

Fig 2. Coronal T1 weighted MR image shows typical metaphyseal osteonecrosis (arrows) with central fat-like signal (asterisk).