with weekly intra-articular injections of specific peptide antagonists of ETA and/or BKB1 in either model at any time. Ipsilateral ATP3 expression was > contra-lateral in both DMM (D3) and mBSA (D7). In mBSA only, ipsilateral Tac1 (D14) was <, and Mor1 (D3 & D7) was > contra-lateral. In DMM only, ipsilateral TRPA1 (D3 and D112) and TRPV4 (D112) was > contra-lateral, and ipsilateral CGRP in DMM was > sham (D3 & D7).

Conclusions: More synovitis and SCB vascular invasion in the post-inflammatory arthropathy (mBSA) was reflected in greater change in limb loading, supporting a link between particular tissue pathologies and pain. However, changes in DRG expression of specific pain-related neuropeptides (CGRP, TRPV4, TRPA1) were only present in DMM. Interestingly, despite similar long-term progressive joint destruction, pain outcomes resolved in both models. Taken together our findings suggest there may be temporal and model-related differences in the type of pain, and its mechanisms. Using appropriate animal models will be critical to understanding what regulates OA pain and for developing improved analesgic therapies.

499 ENDOTHELIN AND BRADYKININ ANTAGONISM IMPROVES NOCICEPTIVE TOLERANCE AND PROTECTS CARTILAGE JOINT DEGARDATION IN OSTEOARTHRITIS


**Purpose:** Pain is the primary complaint of patients with Osteoarthritis (OA). Endothelin-1, a vasoconstrictor peptide, influences cartilage metabolism mainly via endothelin receptor type A (ETA). Along with the inflammatory nonapeptide vasodilator bradykinin (BK), which acts via bradykinin receptor B1 (BKB1) in chronic inflammatory conditions, these vasoactive factors potentiate joint pain and inflammation. Here we describe a preclinical study of the efficacy of treatment of surgically induced osteoarthritis with ETA and/or BKB1 specific peptide antagonists.

**Methods:** Osteoarthritis was surgically induced in rats by transection of the right anterior cruciate ligament. Animals were subsequently treated with weekly intra-articular injections of specific peptide antagonists of ETA and/or BKB1 (BQ 123 and R 954) . Hind limb nociception was measured by static weight bearing biweekly for two months post-operatively. Post-mortem, right knee joints were analyzed radiologically by X-ray and magnetic resonance, and histologically by the OARSI histopathology assessment system.

**Results:** Single and dual local ETA and/or BKB1 antagonist treatment diminished overall limb pain, and accelerated post-operative recovery after disease induction. Repeated measures analysis of variance of the static weight bearing data, followed by Tukey post-hoc hypothesis tests, demonstrated that treatment with R-954, or both BQ-123 and R-954, significantly ameliorated nociceptive tolerance in ACLT animals over the study period, as compared to saline-treated positive controls (0:0001 P0:0002). Treatments also protected joint radiomorphology and histomorphology. We found that single and dual ETA/BKB1 antagonist treatments decreased radiological disease indices, in terms of osteophyte formation, cartilage thinning, and subchondral bone remodelling, with dual antagonism being most protective. As well, cartilage T2, increased in ACLT animals, was decreased by antagonist treatment, which indicates a cartilage-preserving effect.

**Conclusions:** Using a rat surgically induced model of OA, we demonstrated that local treatment with specific peptide antagonists of ETA and/or BKB1 may slow or stabilize the development of radiomorphological and histomorphological changes occurring in OA pathogenesis. Furthermore, we showed that antagonist treatment accelerated recovery of, and improved long-term, nociceptive tolerance in ACLT animals. Taken together, our results indicate that blocking ETA and BKB1 improves OA prognostic indices, which implies that defective signalling might play a role in chronic OA pain. Our results also raise the possibility of targeted receptor antagonism as a relevant therapeutic option.

500 SPECIFIC KNEE PAIN PATTERNS ON THE KNEE PAIN MAP ARE ASSOCIATED WITH DIFFERENT LEVELS OF FUNCTIONAL PERFORMANCE - DATA FROM THE OAI

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**Purpose:** Knee osteoarthritis (OA) is the most common cause of knee pain (KP). While KP is the most cited complaint among older adults visiting primary care offices, the etiology of such pain is poorly understood. The purpose of this study was to examine the relationship between specific KP patterns and objective measures of functional performance.

**Methods:** We conducted a cross-sectional analysis of data from the 24-month follow up visit (OAI data release 2.1) for 4796 participants in the Osteoarthritis Initiative (OAI), a multicenter population-based cohort study designed to identify biomarkers of knee OA development and/or progression. The Knee Pain Map, an interviewer administered assessment of specific KP patterns, was used to identify local, regional, or global KP patterns vs. no KP. Functional performance was assessed based on times to complete a 20 meter walk, a 400 meter walk, and 5 repeated chair stands. Peak isometric quadriiceps strength and hamstring strength were also assessed. Data analysis was conducted using quintiles of performance as explanatory variables in multivariate multinomial logistic regression models. Controls were age, gender, race, BMI, depression, hand OA, history (Hx) of knee injury, Hx of knee surgery, family Hx of knee replacement, hip OA and Charlson Comorbidity score. Participants who did not complete the test were placed in the 5th (worst) quintile. Analysis was performed on a per-person basis for participants who reported experiencing KP in either knee on the day of their clinic visit or those who reported KP the past 30 days vs. no KP on the day of their clinic visit or no KP in either knee in the past 30 days, respectively. In individuals with bilateral KP, the knee with the most expansive pain pattern (i.e. global over regional and regional over local pain) was used as the index knee.

**Results:** Of the 3262 participants analyzed, on the day of the visit 2085 (63.9%) reported no pain in either knee, 493 (15.1%) reported local pain in their index knee, 383 (11.7%) reported regional pain in their index knee, and 301 (9.2%) reported global pain in their index knee. After controlling for covariates in multivariate analysis, using separate models for each performance measure, the worst quintiles of 20 meter walk time, 400 meter walk time, repeated chair stand time, and isometric quadriiceps strength showed significantly higher rates (vs. the best quintile) of localized KP vs. no KP (p < 0.001, p < 0.001, p < 0.001, respectively); regional KP vs. no KP (p < 0.001, p < 0.001, p < 0.001, respectively); global KP vs. no KP (p < 0.001, p < 0.001, p < 0.001, p < 0.001); and global KP vs. localized KP (p < 0.001, p < 0.001, p < 0.001, p < 0.001). Global KP vs. regional KP was only significant for the worst quintile of 400 meter walk time and quadriiceps strength (p < 0.030, p < 0.007). Interestingly, hamstring strength was significant only for the worst quintile and only for regional KP vs. no KP and regional KP vs. local KP comparisons (p < 0.001, p < 0.028). In a separate multivariate analysis using all performance variables in one model and controlling for covariates (see Table 1), the worst quintiles of chair time and isometric quadriiceps strength were significantly different from the best quintile for local KP vs. no KP (p < 0.002, p < 0.001) and global KP vs. no KP (p < 0.001, p < 0.001). For regional KP vs. no KP and global KP vs. local KP comparisons, only chair stand time was significant in the worst quintile of performance (p < 0.001, p < 0.001). An analysis with KP patterns more broadly defined as KP occurring within the past 30 days yielded similar results.

**Conclusions:** The data suggest that specific KP patterns are associated with different levels and types of functional disability. Performance on all tests except hamstring strength varied among the different KP patterns, and the strongest associations were seen with chair stand time and quadriiceps strength. In general, the worst quintiles of performance were most strongly associated with global KP, followed by regional KP, and local KP.