Evaluation of behavioral pain phenotype in the rat monoiodoacetate and medial meniscal tear models of osteoarthritis pain.

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In collaboration with the NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP), we examined a variety of pain behaviors in the rat monoiodoacetate (MIA) and medial meniscal tear (MMT) models of osteoarthritis to validate these models for the evaluation of novel assets. Adult male and female Sprague Dawley rats (n=10, each sex) were used in these studies and behavioral pain responses were evaluated for a period of 4 weeks. For the MIA model, intraarticular injection of MIA (1, 3 mg) into the hindlimb knee joint produced unilateral hind paw tactile hypersensitivity in male and female rats which was maximal at Week 2. Unilateral knee joint hypersensitivity to pressure and pinch stimuli was observed in female, but not male, rats at Week 2. Weight bearing deficits associated with the affected hind limb were modest when measuring static weight bearing, and were more pronounced when measuring dynamic weight bearing in male and female rats, with maximal effects observed at Week 1. Changes in gait were also observed in male and female rats following MIA injection, with significant differences observed in hind paw speed, rhythmicity, and paw position at Weeks 1 and 2. The optimal dose of MIA to examine pharmacological effects in this model was determined to be 1 mg, based on lower variability in weight bearing responses. Single administration of morphine (3 mg/kg s.c.) reduced hind paw tactile hypersensitivity and weight bearing deficits in male and female rats in the MIA model, whereas single administration of ketoprofen (6 mg/kg s.c.) or duloxetine (60 mg/kg p.o.) was partially effective or ineffective. In contrast, repeated administration of ketoprofen or duloxetine (4 days, b.i.d.) significantly reduced tactile hypersensitivity and weight bearing deficits. For the MMT model, male rats that had received MMT surgery displayed unilateral hind paw tactile hypersensitivity that was maximal at Week 3, while no changes in hind paw tactile sensitivity were observed in female rats. Knee joint sensitivity to a pressure stimulus was unaffected in male and female MMT rats, and dynamic weight bearing was also unaffected in male and female rats that had received MMT surgery. The results from this study demonstrate that a variety of pain behaviors associated with knee joint osteoarthritis can be measured using the rat MIA model, while pain behaviors in the MMT model were less robust or not observable. Evaluation of novel assets following single and repeated administration in the MIA model using multiple pain endpoints may be a viable strategy to accelerate the development of non-opioid, non-addictive therapeutics for the treatment of osteoarthritis pain.