

The NIH HEAL Initiative Preclinical Screening Platform for Pain (PSPP) efforts to validate rodent models of pain and migraine

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Background

The Preclinical Screening Platform for Pain (PSPP) program aims to accelerate the discovery and development of new non-opioid, non-addictive pain therapeutics. Towards that goal, PSPP accepts small molecules, biologics, natural products and devices from industry, academia or government asset owners from across the world. PSPP evaluates assets in a range of in vitro functional assays, pharmacokinetics, side effect profile, abuse liability as well as preclinical pain models. PSPP is collaborating with PsychoGenics, Inc. to validate preclinical models and endpoints to advance profiling of novel assets. Towards that goal, we describe the validation of monoiodoacetate (MIA) model of osteoarthritis pain, the paclitaxel and oxaliplatin models of chemotherapy-induced peripheral neuropathy (CIPN) in the rat, and the dural stimulation model of migraine in the mouse.

Methods

Adult male and female Sprague Dawley rats (N=10, each sex) were used for the MIA and CIPN studies. MIA: MIA was injected intraarticularly into the left hindlimb knee joint. Tactile sensitivity, weight bearing, changes in gait, and paw pressure were systematically evaluated in both sexes for 4-6 weeks. Pharmacological validation of the model was established using morphine, duloxetine, and ketoprofen after acute and repeated dosing. CIPN: Paclitaxel was injected at several doses on alternate days to determine the optimal dose and route of administration. Oxaliplatin was injected 2 days per week for 4 weeks. Hind paw tactile sensitivity and cold sensitivity were evaluated. Dural stimulation: Six-week-old female (C57Bl/6 and CD-1) or male (CD-1) mice received dural injections of inflammatory soup (IS; pH 4-5; 1mM bradykinin, 1 mM histamine, 1mM serotonin, 100 uM PGE2) or vehicle (SIF; pH 7.4). Following injection, periorbital and hindpaw von Frey were assessed.

Results

MIA: Intraarticular injection of MIA into the hindlimb knee joint produced unilateral hind paw tactile hypersensitivity and changes in weight bearing. Acute subcutaneous injection of morphine reduced hind paw tactile hypersensitivity and weight bearing deficits in male and female rats, whereas acute oral administration of ketoprofen and duloxetine were less effective. Repeated treatment with ketoprofen or duloxetine significantly reduced these endpoints. CIPN: Both the paclitaxel and the oxaliplatin models showed reproducible bilateral hind paw tactile and cold hypersensitivity in male and female rats which were significantly inhibited by morphine. Dural stimulation: Female C57Bl/6 mice showed only modest changes in paw withdrawal frequency following injection of IS. In male CD-1 mice, IS produced a minor statistically significant increase in periorbital response frequency, but this was only evident at 30 minutes – 1 hour after injection. A similar effect was not observed in female mice using 1mM pH 5 IS, but was observed when using 2mM pH 4 IS.

Conclusions

The results from these carefully validated studies using evoked and non-evoked endpoints in the rat MIA model and using both mechanical sensitivity and cold allodynia in the CIPN models suggest that these models may be used to identify and differentiate novel therapeutics for treatment of osteoarthritis and chemotherapy induced neuropathic pain. Compared to the MIA and CIPN models, the dural inflammation requires further optimization and validation to incorporate into the profiling program. These efforts within the NIH HEAL Initiative will accelerate the development of novel non-opioid non-addictive pain and headache therapeutics.

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