(372) Exploring the actions of TRPV1 positive allosteric modulators in a peripheral inflammation model

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Small molecule pharmacological therapies focused on peripheral ion channels such as the transient receptor potential vanilloid-1 (TRPV1) may provide a novel therapy solution for patients in moderate to severe chronic pain. Previous studies in our lab have begun to characterize small molecule positive allosteric modulators (PAMs) of TRPV1 for pain relief. Like a potent, selective TRPV1 agonist such as resiniferatoxin (RTX), a TRPV1 PAM will act to induce calcium cytotoxicity in a clinically relevant sub-population of A-delta and C-fibers. Unlike RTX however, a TRPV1 PAM can be administered systemically since its effect relies on activity dependent vanilloid activation. To better understand its effect in an animal model of inflammation and hyperalgesia, we administered MRS1477 in combination with the TRPV1 agonist capsaicin to selectively deactivate nerves in the hindpaw. After 24 hours, we administered 4% carrageenan intraplantar (i.pl.). Behavioral experiments performed following carrageenan revealed increased paw withdrawal latency in response to thermal stimulation of the hindpaw compared to rats receiving capsaicin without MRS1477. Inactivation of TRPV1+ nerve endings by the combination of MRS1477 and capsaicin is consistent with the idea of a PAM mediated potentiation mechanism. These behavioral results indicate that a TRPV1 PAM in combination with a TRPV1 agonist may be useful in reducing nocifensive behaviors in an inflammatory pain model in rats and suggests that further investigation of TRPV1-PAM mechanisms may lead to new insights into the function of this ligand-gated ion channel. Supported by DIR, NIDCR.

(373) Targeting glutamate and opioid signaling by gene therapy in spinal cord injury-induced pain in rats

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Low efficacy of current pharmacotherapy for chronic neuropathic pain demands search for novel therapeutic targets and approaches. Enhanced glutamate signaling through NMDA receptors is one of the hypothesized mechanisms underlying development of neuropathic pain. However, although effective in animal models, clinical use of NMDA antagonists is limited by adverse effects such as hallucinations and motor dysfunction. Opiates have also been used in treatment of chronic pain with various successes, mostly due to unwanted side effects. Previous studies in our lab have shown NMDA antagonists activity of serine-histogranin (SHG), a synthetic analog of naturally occurring histogranin, lacking adverse effect. Transplantation of recombinant rat neuronal progenitors transduced with SHG construct reduced hypersensitivity induced by peripheral nerve injury. In addition, SHG can enhance opioid antinociceptive potency, thus reducing opioid doses and attendant side effects. Endomorphins (EMs) are endogenous opioid peptides with high selectivity for μ-opioid receptors. The aim of this study was to evaluate the antinociceptive potency of combined gene therapy with hexSHG (a 6 copy multi-SHG construct) and EM1 genes in rats with neuropathic pain symptoms. Spinal cord clip compression was used to induce central neuropathic pain. Five weeks post injury, lenti-hexSHG recombinant cells or lenti–EM1 constructs were intraspinally injected. Reduction of tactile and cold allodynia was observed in both groups of rats and analgesic effects were attenuated by SHG antibody or naloxone respectively. To evaluate combined therapy, SHG peptide was intrathecally delivered to lenti-EM1 injected animals at 7 weeks post injury. This further reduced tactile and cold allodynia compared to EM1-only treated animals. Intraspinal injection of both lenti-plasmids together nearly completely abolished cold allodynia and modestly attenuated tactile allodynia. These results encourage us to engineer compound constructs encoding both SHG and EM1 peptides in order to achieve better long-term analgesic outcomes in management of chronic neuropathic pain. Supported by NS51667 and CNF 190926.

(374) NP260, a novel GABA-A receptor antagonist, dampens neuronal hyperexcitability and relieves mechanical allodynia in a rat model of neuropathic pain

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We have identified a series of compounds that facilitate inhibitory neurotransmission and show analgesic activity through a novel mechanism. Oral dosing of one such compound, NP260 (15 – 100 mg/kg, 5 days, B.I.D.) to rats with spinal nerve ligation (SNL – Chung model) significantly reduced mechanical allodynia in a dose-dependent fashion on each day of behavioral evaluation. Tests 4 hours after the first dose increased the paw withdrawal threshold (PWT) from 2.5 ± 0.4g in vehicle treated animals to 3.8 ± 0.5 g in animals treated with 15 mg/kg NP260 ($n = 8$, $P < 0.05$, ANOVA). The same test on day 5 of chronic dosing generated PWTs of 2.2 ± 0.2 g in vehicle animals and 5.2 ± 0.8 g in the 15 mg/kg NP260 group ($P < 0.05$, ANOVA). In follow-up electrophysiology studies, acutely dissociated L4-L6 dorsal root ganglion (DRG) neurons, both contralateral and ipsilateral to the site of SNL surgery, exhibited robust GABA-evoked currents that were blocked by 10 μM NP260. NP260 also hyperpolarized the resting membrane potential of these neurons and increased the rheobase needed to elicit action potential firing. In longitudinal spinal cord slices, 10 μM NP260 reduced the amplitude of evoked EPSCs (71.4 ± 5.5% of control, $P < 0.001$, n=19), decreased the frequency (41.9 ± 4.4% of control, $P < 0.03$, n=8) and amplitude (58.9 ± 4.4% of control, $P < 0.05$, n=3) of spontaneous EPSCs, and increased the frequency of spontaneous IPSCs (182.9 ± 6.8% of control, $P < 0.001$, n=7) in lamina I/II neurons. In each case, the effect of NP260 was notably larger in neurons on the ipsilateral side compared to the contralateral side. Studies are ongoing to further investigate the electrophysiological actions of our compounds and determine their efficacy after chronic oral dosing in animals with neuropathy induced by oxaliplatin. Support provided by NeuroTherapeutics Pharma Inc.

(375) Double-blind, randomized study to evaluate efficacy, and safety of fulranumab in patients with moderate to severe, chronic knee pain from osteoarthritis: interim analysis results

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Efficacy and safety of fulranumab, an anti-nerve growth factor (NGF) monoclonal antibody, was evaluated in a phase 2, active- and placebo-controlled, randomized study in patients with osteoarthritis. Patients (aged 40 to 80 years), with moderate to severe chronic knee pain from osteoarthritis were randomized (1:1:1:1) to placebo, fulranumab 3- or 9-mgQ4week, or oxycodone controlled-release (CR) 20 to 50mg bid. After washout from prior analgesic medications, patients entered a 16-week double-blind efficacy phase. Due to US FDA clinical hold on anti-NGF trials, including fulranumab (December 23, 2010), only 196 of 300 planned patients were enrolled and included in this interim analysis (completed double-blind phase:39, withdrawn:50, ongoing in double-blind phase:107). Efficacy results were based on data obtained through the cut-off date (28 December 2010). Safety results were based on data collected before and for 6 months after the cut-off date. Primary efficacy endpoint was the responder rate curve from baseline to week 12 of double-blind phase between each fulranumab group versus placebo and oxycodone CR. Both fulranumab groups showed significant improvement in pain relief in the responder analysis versus oxycodone CR (nominal p-values: 0.008 [3mgQ4wk]; 0.012 [9mgQ4wk]); neither fulranumab group separated statistically from placebo group (nominal p-values: 3mgQ4wk = 0.74, 9mgQ4wk = 0.84), which had a high response rate. Mean changes in average pain intensity scores from baseline to week 12 were consistent with the primary endpoint results: -3.0 (placebo and fulranumab 9mgQ4), -2.9 (fulranumab 3mgQ4), and -1.6 (oxycodone CR). Rates of treatment-emergent adverse events (TEAEs) were: 63% (fulranumab 3mgQ4), 82% (fulranumab 9mgQ4), 80% (oxycodone CR), and 77% (placebo). The most common (≥10%) TEAEs for total fulranumab-treated patients were headache and nasopharyngitis. Fulranumab demonstrated better pain relief in these patients than oxycodone CR, but failed to separate statistically from placebo. Fulranumab was generally well tolerated in the studied patient population.