## Latent sensitization is masked by spinal mu and kappa, but not delta opioid receptor analgesia in a preclinical model of postoperative pain

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Tissue or nerve injury elicits a sustained silent form of neuronal plasticity that increases the susceptibility to chronic pain, entitled latent sensitization (LS). Our laboratory previously demonstrated that injury tonically activates spinal μ-opioid receptors, which in turn opposes nociceptive transmission, preventing the transition from acute to chronic pain (Corder et al, Science, 2013). However, whether other opioid receptors contribute to the maintenance of the remission phase of LS remains uncertain. Moreover, preclinical and clinical studies indicate a sexual dimorphism in the responsiveness to the analgesic effects of ƙ-selective agonists. Therefore, we investigated whether there are sex differences in endogenous ƙ- (and also δ- and μ-) opioid receptor-mediated inhibition of LS. To help to answer these questions, we intrathecally administered opioid subtype-selective antagonists after the behavioral hypersensitivity of postoperative pain had resolved, e.g., 21-28 days after surgical incision of the plantar skin plus damage to the flexor digitorium brevis muscle. We found that ƙ-selective antagonists nor-BNI (0.1μg -10μg i.t.) or LY2456302 (0.1μg -10μg i.t.), or the μ-selective antagonist CTOP (0.001μg-0.1μg i.t.), but not the δ-selective antagonists naltrindole (1μg/5μl i.t.) or TIPP [psi] (1μg -10μg i.t.), reinstated pain-like behavior in a dose-dependent manner. Mu and kappa antagonist-induced reinstatement was observed in both male and female mice. There were no significant differences in von Frey thresholds after LY2456302 (10μg i.t.) at 1h (females 0.41 ± 0.11 vs males 0.69 ± 0.21, mean ± SEM), 4h (females 0.41 ± 0.15 vs males 0.69 ± 0.24), and 96 h (females 1.86 ± 0.34 vs males 1.66 ± 0.38) post injection (n=6-7 animals per group); nor on von Frey thresholds after CTOP (0.1μg i.t.) at 30min (females 0.56 ± 0.18 vs males 0.51 ± 0.22), 120min (females 1.23 ± 0.35 vs males 1.04 ± 0.26), and 180min (females 2.00 ± 0.32 vs males 1.80 ± 0.36) post injection (n=8 animals per group). We conclude that mechanical hyperalgesia after plantar incision in the mouse is maintained in state of remission through ƙ- and μ-, but not δ-opioid receptor subtypes, and is sex -independent. We are currently investigating whether lower doses of ƙ- and μ-opioid antagonists will reinstate mechanical or heat hyperalgesia in a sex-dependent manner. We also aim to investigate whether injury up-regulates the expression of opioid receptors on excitatory interneurons within the superficial laminae of dorsal horn.