15-Deoxy-Delta-12,14-prostaglandin J2 activates peripheral Peroxisome proliferator-activated receptor gamma gamma and opioids receptors to reduce infl

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Peroxisome proliferator-activated receptor gamma (PPARγ) receptors are emerging as a promising target for the treatment of inflammatory and neuropathic pain. As with administration of peripherally-acting opioid receptor agonists, peripheral administration of PPARγ agonists reduces behavioral signs of persistent pain. However, the contribution of peripheral PPARγ activation to muscle pain and its modulation by opioid receptors remains unknown. The aim of this study was to determine whether activation of peripheral PPARγ receptors by the endogenous ligand 15d-PGJ2 reduces inflammatory muscle pain in rats in an opioid receptor-dependent manner. Inflammatory muscle hyperalgesia was induced by injection of carrageenan into the gastrocnemius muscle. Mechanical muscle hyperalgesia was quantified with a Randal Sellito pressure analgesimeter, applied to the gastrocnemius muscle. Male Wistar rats were used and methods were approved by the Ethics Committee in Animal Research of the UNICAMP (protocol n. 3919-1). To investigate the contribution of PPARγ receptors to muscle pain, 15d-PGJ2 was injected into gastrocnemius muscle 30 min before carrageenan. As 15d-PGJ2 can exert both PPARγ-dependent and PPARγ- independent effects, we pretreated rats 30 min. prior to 15d-PGJ2 with either vehicle or GW9662, a selective PPARγ receptors antagonist. To test the hypothesis that 15d-PGJ2 recruits opioid analgesic system, Naloxone, a non-selective opioid receptor antagonist, was injected into gastrocnemius muscle 30 min. before 15d-PGJ2. Carrageenan (100μg) produced mechanical muscle hyperalgesia 3 h after its injection ($p<0.05$, T test). 15d-PGJ2 (1, 10 and 100ng) prevented the mechanical muscle hyperalgesia induced by carrageenan when injected in the ipsilateral muscle in a dose-dependent manner ($p<0,05$, ANOVA, Tukey test) but not in the contralateral muscle ($p>0.05$). Pretreatment with GW9662 (3 or 9 ng) or Naloxone (0.1 or 1μg) reversed the anti-hyperalgesic effect of 15d-PGJ2 in a dose-dependent manner ($p<0,05$, ANOVA, Tukey test, n=4). GW9662 or Naloxone didn't alter the nociceptive threshold when injected alone ($p>0,05$, T test, n=4). These data demonstrate that 15d -PGJ2 increases mechanical response thresholds in the carrageenan model of inflammatory muscle pain. This anti-hyperalgesic effect is dependent on activation of peripheral PPARγ and opioids receptors. We speculate that activation of PPARγ leads to the subsequent activation of peripheral opioid receptors, leading to inhibition of inflammatory muscle pain. We conclude that local PPARγ receptors are important pharmacological targets for the pharmacotherapy of inflammatory muscle pain.