Modulation of PPARγ receptors regulates tolerance to morphine analgesia

G. de Guglielmo[1], G. Scuppa[1] M. Kallupi[1], S. Stopponi[1], R. Ciccocioppo[1]

[1]School of Pharmacy, Pharmacology Unit, University of Camerino, via Madonna delle Carceri, Camerino 62032 Italy

Opioids are essential medications for pain treatment. They are largely used to treat acute severe pain following trauma, extensive burns or surgery. In these time-limited situations, the efficacy of opiates is extensively documented and broadly accepted. However, opioid use for the treatment of chronic pain is still controversial. The main barrier to the prescription of opioids for prolonged period is the rapid development of tolerance to the analgesic effect of these drugs, which requires dose escalation to maintain adequate analgesia. In turn, using higher doses of opioids could increase the risk to develop drug dependence and possibly addiction and exacerbate their side effects. Identification of innovative strategies to attenuate opioid tolerance development could offer important benefit in the management of chronic pain treatment. Peroxisome Proliferator Activated Receptor gamma (PPARγ) is a ligand-activated transcription factor of the nuclear hormone receptor super-family, involved in the regulation of sugar and lipid homeostasis. PPARγ controls also the expression of pro-inflammatory mediators by both peripheral macrophages and microglia in the central nervous system (CNS). Recent evidence from our laboratory has demonstrated that activation of PPARγ by pioglitazone, a drug currently used to treat insulin resistance in Type II diabetes, reduced the addictive potential of alcohol in the rat including occurrence of physical withdrawal symptoms. Considering the similarities between some CNS effects of alcohol and opioids we sought interesting to investigate the role of PPARγ on morphine pharmacology with focus on analgesic tolerance. Experiments were conducted with pioglitazone and GW 9662 (selective PPARγ antagonist). For induction of morphine tolerance mice were treated with morphine (30 mg/kg) twice daily for 9 consecutive days. The analgesic response was monitored by the tail-immersion test, performed 45 min after the evening injection of morphine. The results showed that pioglitazone reduced the development of tolerance to morphine, an effect prevented by GW 9662 co-administration. Notably, chronic treatment with GW 9662 alone accelerated the development of morphine tolerance. Consistent with antagonism data, conditional neuronal PPARγ knockout (KO) mice showed faster development of morphine tolerance. While pioglitazone significantly attenuated the development of tolerance to the analgesic effect of morphine in the wild type (WT) mice, it was ineffective in KO mice. Overall, these results indicate that PPARγ plays an important role in the modulation of tolerance to morphine and strongly support the potential of pioglitazone in reducing opiate tolerance. Clinical trials to test this possibility are relatively easy to conduct because pioglitazone is a drug already available for clinical use.