8. Summary

Opioid receptors (μ, δ, and κ) are synthesized in dorsal root ganglia (DRG) and transported into peripheral terminals of primary afferent neurons. Opioids mediate their analgesic effects by activating μ opioid receptors (MOR) not only within the central (CNS) but also on peripheral nervous system (PNS). The peripheral analgesic effects of opioids are best described under inflammatory conditions and has been shown in clinical and experimental studies. The current thesis investigated changes of the (MOR) expression and/or signaling at peripheral, spinal, or supraspinal neurons in an animal model of intraplantar Freund's complete adjuvant (FCA)-induced inflammation. Therefore, this study compared animals with and without inflammation to examine whether FCA inflammation 1) leads to differences in the distribution and density of MOR on peripheral, spinal, or supraspinal neurons 2) alters MOR binding on peripheral, spinal, or supraspinal neurons, 3) causes differences in the potency and efficacy of agonist coupling to MOR on peripheral, spinal, or supraspinal neurons, or 4) reveals differences in behavioral studies for the partial MOR agonist buprenorphin (BUP). Our results show that painful inflammation leads to differential alterations of MOR receptor expression in Hypothalamus (HT), spinal cord (SC) and DRG. Unilateral FCA inflammation of one hindpaw induced a significant upregulation of MOR receptor sites only in DRG but not in HT or SC. This upregulation was time-dependent, restricted to the inflamed side, and showed a peak at 24 h. It is associated with an upregulation of MOR receptor expression mainly in small sized primary afferent neurons, but not in the CNS. This suggests that a locally applied inflammation can affect neurons that are innervating the region of inflammation. This has functional relevance because the efficacy of MOR receptor agonists in G protein coupling is enhanced in these primary afferent fibers. Inflammation resulted in significant increases in the voll agonist (DAMGO) induced MOR receptor G protein coupling only in membranes of DRG, but not in HT, SC, or DRG on the contralateral side of inflammation. In contrast, the partial agonist (BUP) showed no detectable G-protein coupling in DRG of animals without FCA inflammation; however, partial agonist activity of BUP-induced MOR G-protein coupling was detectable in animals with FCA inflammation. In behavioral studies administration of BUP produced significant antinociception only in inflamed but not in noninflamed paws.

These findings indicate that clinical treatment of patients with opioids in inflammatory diseases is different from patients with noninflammatory painful conditions. The known increased analgesic efficacy of locally applied opioids could be explained by a selectively increased numbers as well as Gprotein coupling efficacy of MOR receptor in primary afferent neurons.