SUMMARY

Opioids play an outstanding role in the treatment of acute, postoperative and tumor-caused pain frequently associated with tissue inflammation. The opioid mediated activation of peripheral μ-receptors modulates voltage-gated calcium channels and thus inhibits afferent neuron excitation. However, it is unclear if opioids affect the ligand-gated ion channel *transient receptor potential vanilloid 1* (TRPV1). TRPV1 is crucially involved in the development of pain and thermal hypersensitivity associated with tissue inflammation and is particularly sensitized by inflammatory mediators and protein kinase mediated phosphorylation processes. In this study, the effects of μ-receptor activation on TRPV1 ion channel function was analyzed in dorsal root ganglion (DRG) neurons and in μ-receptor and TRPV1 expressing HEK293-cells. For the first time we could show that μ-receptor activation leads to a modulation of ion channel TRPV1.

μ-receptors and TRPV1 are co-localized in sensory neurons. Opioids restrain capsaicin and heat induced TRPV1 activity, mediated by μ-receptor activation and inhibitory G proteins. This effect was also confirmed under inflammatory conditions. TRPV1 protein expression increases under inflammatory conditions while the number of mRNA transcripts does not change. The functional relevance of the interaction between μ-receptors and TRPV1 interaction could be confirmed *in vivo*: Behavioral experiments show, that capsaicin-induced thermal hyperalgesia is attenuated by local administration of a not systemically effective dose of an opioid.

In opposite to opioid mediated TRPV1 inhibition, TRPV1 is sensitized to capsaicin after longer opioid administration followed by opioid withdrawal. The opioid mediated TRPV1 sensitization is to be due to an increased protein kinase A (PKA) activity, which is triggered by a compensatory cAMP upregulation after opioid withdrawal. In our cell system, mainly adenylylcyclases AC3 and AC5 contribute to the improved conversion from ATP to cAMP and the following increase in PKA activity.

The interaction between μ-receptors and TRPV1 represents a new molecular mechanism, which characterizes the analgesic characteristics of opioids during inflammatory pain.