Conclusions

Fluorescence Cross-Correlation Spectroscopy (FCCS) studies in live cells show that prolonged treatment with morphine potentiates heterodimer formation between the mu-opioid receptor (MOP) and the serotonin receptor 1A (5-HT_1A) (Fig. 1). Hypothetically, altered cellular signaling due to MOP and 5-HT_1A receptor heterodimer formation may contribute to neuropathic changes that, at the mechanistic level, may lead to sensitization of pronociceptive pathways. Combined treatment with morphine and serotonin receptor agonists; morphine and serotonin or morphine and buspirone, diminished MOP and 5-HT_1A receptor heterodimer formation (Fig. 1). Our study suggests that interactions between the MOP and the 5-HT_1A receptors may potentially be a target for the development of new therapeutic strategies for the treatment of chronic pain. Similar results have been seen in animal studies, where 5-HT_1A agonists reversed opioid-induced hyperalgesia/tolerance [1,2].

Aim of Investigation

The usefulness of long-term opioid treatment of chronic pain is seriously hampered by the development of opioid-induced hyperalgesia and tolerance. In animal studies serotonin (5-HT_1A) receptor agonists can prevent and reverse opioid-induced hyperalgesia/tolerance, although the underlying cellular and molecular mechanisms are still not well understood. In this study, we investigated in live cell interactions between the mu-opioid (MOP) and serotonin (5-HT_1A) receptors and assessed the effect of morphine on these interactions. Our aim is to understand whether these two signaling pathways are integrated at the cellular level via direct binding between the MOP and 5-HT_1A receptors and to quantitatively characterize the effect of morphine and serotonin on these receptor-receptor interactions.

Results

Our study in live HEK293 cells shows that MOP and 5-HT_1A receptors do not form heterodimers under normal physiological conditions (Fig. 1). Prolonged (18 h) treatment with morphine (750 nM) facilitates MOP hetero-dimerization with 5-HT_1A. Combined treatment with MOP and 5-HT_1A agonists (750 nM morphine and 1 μM serotonin or 750 nM morphine and 1 μM buspirone, 18 h treatment) abolishes hetero-dimerization of these receptors (Fig. 1). Similarly to morphine, prolonged (18 h) treatment with tianeptine (750 nM), recently shown to act as the MOP agonist, facilitated the formation of hetero-dimers (Fig. 1).

Acknowledgments/Disclosures

Funding by FP7-Heath-2013-Innovation-1 GLORIA-020291 "Understanding chronic pain and new drugs development: from mice to real patients on glial-opioid receptor interface" is gratefully acknowledged.