Mu-opioid receptor (MOR) is a GPCR representing the main target of opioid analgesics and it is expressed also in glial cells, which contribute to pain integration and sensitization: in fact, glia is activated at multiple sites along the pain pathway to produce pro-inflammatory mediators, as TNF-alpha, which drive pain amplification and nociceptors’ hyperexcitability, thus contributing to the development of chronic pain.

For these reasons, MOR-induced signaling within glia may significantly affect both nociception and opioids efficacy; Toll-like receptor 4 (TLR4) is another glial key activator as its induction in glial cells significantly contributes to their activation and initial release of pro-inflammatory cytokines. Whether TNF-alpha release or TLR4 activation within glial cells may influence MOR-induced signaling or not is still to be fully characterized. Therefore, the aim of this research has been to investigate which intracellular signaling pathways are activated by opioid agonists in human glial cells exposed to TNF-alpha or LPS (Lipopolysaccharide from E.Coli - TLR4 agonist). We found that opioid agonists trigger different signaling pathways in un-stimulated glial cells. Surprisingly, MOR-induced signaling is dramatically hampered upon exposure of glial cells to TNF-alpha or LPS, albeit the strong up-regulation of MOR surface receptor number by such stimuli. These findings show that prolonged exposure of glia to inflammatory agents significantly affects MOR-mediated intracellular signaling, which under these conditions seems to be no longer related to the receptor expression levels.