Abstract: The issue of tolerance to continuous or repeated administration of opioids should be addressed. The ability of ketamine to improve opioid tolerance has been reported in clinical studies, and its mechanism of tolerance may involve improved desensitization of μ-opioid receptors (MORs). We measured changes in MOR activity and intracellular signaling induced by repeated fentanyl and morphine administration and investigated the effects of ketamine on these changes with human embryonic kidney 293 cells expressing MOR using the CellKey™, cADDis cyclic adenosine monophosphate and PathHunter® β-arrestin recruitment assays. Repeated administration of fentanyl or morphine suppressed the second MOR responses. Administration of ketamine before a second application of opioids within clinical concentrations improved acute desensitization and enhanced β-arrestin recruitment elicited by fentanyl but not by morphine. The effects of ketamine on fentanyl were suppressed by co-treatment with an inhibitor of G protein-coupled receptor kinase (GRK). Ketamine may potentially reduce fentanyl tolerance but not that of morphine through modulation of GRK-mediated pathways, possibly changing the conformational changes of β-arrestin to MOR.

Keywords: μ-opioid receptor; desensitization; tolerance; fentanyl; morphine; ketamine; G protein receptor kinase; β-arrestin