Interactions of mu-, kappa, and Nociceptin Receptors after Opioid Exposure in HEK 293 Cells

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Buprenorphine is used in maintenance therapy for heroin addicts. It is a µ-opioid (MOP) receptor partial agonist and a potent κ-opioid (KOP) receptor antagonist as well as a nociceptin/opioid receptor-like 1 (NOP) receptor agonist. In this study, we established an in vitro cell model overexpressing human MOP, KOP, and NOP receptors individually or simultaneously in human embryonic kidney (HEK) 293 cells, and compared the effects of U-69593, DAMGO, nociceptin, and buprenorphine on adenylate cyclase (AC) activity in these cells (KOP, KOP+MOP, KOP+NOP, and KOP+MOP+NOP). Saturation radioligand binding assay using [³H]-diprenorphine was performed to verify surface expression of KOP receptor. After acute exposure, U-69593 inhibited AC activity in all four stable clones, showing that KOP receptor was successfully expressed. Acute application of DAMGO and nociceptin could elicit AC activity inhibition in cells expressing MOP and NOP receptors, respectively. Buprenorphine, when applied acutely, was able to inhibit AC activity to about 90% of the E_{max} in cell expressing MOP, NOP and KOP receptors simultaneously, which is more efficacious than the other three stable clones. Chronic exposure to buprenorphine induced AC superactivation in cells coexpressing KOP and NOP receptors, and the level of AC superactivation was further elevated in KOP+MOP+NOP-expressing cells. The study demonstrated that MOP receptor might act as an enhancer in AC superactivation in HEK 293 cells coexpressing KOP, MOP and NOP receptors during long-term exposure to buprenorphine.