

**Inverse agonists and neutral antagonists at mu opioid receptor (MOR): possible role of basal receptor signaling in narcotic dependence.**

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**Abstract:** The mu opioid receptor, MOR, displays spontaneous agonist-independent (basal) G protein coupling in vitro. To determine whether basal MOR signaling contributes to narcotic dependence, antagonists were tested for intrinsic effects on basal MOR signaling in vitro and in vivo, before and after morphine pretreatment. Intrinsic effects of MOR ligands were tested by measuring GTPgammaS binding to cell membranes and cAMP levels in intact cells. beta-CNA, C-CAM, BNTX, and nalmefene were identified as inverse agonists (suppressing basal MOR signaling). Naloxone and naltrexone were neutral antagonists (not affecting basal signaling) in untreated cells, whereas inverse agonistic effects became apparent only after morphine pretreatment. In contrast, 6alpha- and 6beta-naltrexol and -naloxol, and 6beta-naltrexamine were neutral antagonists regardless of morphine pretreatment. In an acute and chronic mouse model of morphine-induced dependence, 6beta-naltrexol caused significantly reduced withdrawal jumping compared to naloxone and naltrexone, at doses effective in blocking morphine antinociception. This supports the hypothesis that naloxone-induced withdrawal symptoms result at least in part from suppression of basal signaling activity of MOR in morphine-dependent animals. Neutral antagonists have promise in treatment of narcotic addiction.