

## **Basal opioid receptor activity, neutral antagonists, and therapeutic opportunities**

Sadee W, Wang D, and Bilsky E

Life Sciences 2005 Feb 11;76(13):1427-37

**Abstract:** The mu opioid receptor (MOR, OPRM)--the principal receptor involved in narcotic addiction--has been shown to display basal (spontaneous, constitutive) signaling activity. Interaction with other signaling proteins, such as calmodulin, regulates basal MOR activity. Providing a mechanism for long-lasting regulation, basal MOR activity potentially plays a key role in addiction, in combination with gene regulation and synaptic remodeling. Recent results support a link to physical dependence--one of the main manifestations of addiction to drugs of abuse. The prototypical opioid antagonists, naloxone and naltrexone, were shown to act as inverse agonists in the morphine-dependent state (i.e., they suppress basal MOR signaling) and thereby appear to elicit or contribute to precipitated withdrawal. This affords the opportunity to explore therapeutic applications for neutral antagonists (blocking agonists at MOR without affecting basal activity) with reduced adverse effects. Neutral antagonists are promising drug candidates in the treatment of addiction and overdose, and of peripheral adverse effects of narcotic analgesics.

---