

In vivo characterization of 6B-naltrexone, an opioid ligand with less inverse agonist activity compared with naltrexone and naloxone in opioid-dependent mice

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Abstract: The mu-opioid receptor displays basal signaling activity, which seems to be enhanced by exposure to opioid agonists. This study assesses the in vivo pharmacology of the putative "neutral" antagonist 6beta-naltrexol in comparison to other ligands with varying efficacy, such as naloxone, an inverse agonist in the opioid-dependent state. ICR mice were used to generate full antagonist dose-response curves for naloxone, naltrexone, nalbuphine, and 6beta-naltrexol in blocking acute antinociceptive effects of morphine and precipitating opioid withdrawal in models of physical dependence. 6beta-Naltrexol was roughly equipotent to naloxone and between 4.5- and 10-fold less potent than naltrexone in blocking morphine-induced antinociception and locomotor activity, showing that 6beta-naltrexol enters the central nervous system. In contrast to naloxone and naltrexone, 6beta-naltrexol precipitated only minimal withdrawal at high doses in an acute dependence model and was approximately 77- and 30-fold less potent than naltrexone and naloxone, respectively, in precipitating withdrawal in a chronic dependence model. 6beta-Naltrexol reduced the inverse agonist effects of naloxone in vitro and in vivo, as expected for a neutral antagonist. Therefore, the pharmacological effects of 6beta-naltrexol differ markedly from those of naloxone and naltrexone in the opioid-dependent state. A reduction of withdrawal effects associated with neutral mu-opioid receptor antagonists may offer advantages in treating opioid overdose and addiction.