Discoveries of Distinction

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In Vivo Characterization of the Opioid Antagonist Nalmefene in Mice

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Our lab is exploring the structure activity of opioid neutral antagonists as well as inverse agonists, and has tested a number of structurally similar ligands for their activity in opioid naïve and opioid-exposed systems. This has led to the characterization of two putative neutral antagonists, 6β-naltrexol and 6β-naloxol. These compounds differ from naltrexone and naloxone by the reduction of the ketone group at the six-position of the parent compound to a hydroxyl moiety. The current study assessed the antagonist properties of nalmefene which substitutes the ketone with a methylene group, maintaining the double bond and its influence on the overall structure of the molecule. Similar to naloxone and naltrexone, nalmefene was shown to precipitate withdrawal symptoms in patients either acutely or chronically treated with opioid antagonists. Severity of withdrawal is likely to be related to both the displacement of the agonist from the receptor and the potential inverse agonist effects of the “antagonist.” Inverse agonists are thought to stabilize G-protein coupled receptors into an inactive state, suppressing basal or constitutive activity. Our study exhibited that similar to naloxone and naltrexone, nalmefene acts as an inverse agonist in opioid exposed symptoms. This information helps better characterize the preclinical efficacy of nalmefene and will aid in the development of novel opioid antagonists for use in opioid-exposed/dependent subjects.

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