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## Effects of ?-opioid receptor agonists in assays of acute pain-stimulated and pain-depressed behavior in male rats: role of ?-agonist efficacy and noxious stimulus

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**Abstract:** Pain is associated with stimulation of some behaviors and depression of others, and ?-opioid receptor agonists are among the most widely used analgesics. This study used parallel assays of pain-stimulated and pain-depressed behavior in male Sprague-Dawley rats to compare antinociception profiles for six ?-agonists that varied in efficacy at ?-opioid receptors (from highest to lowest: methadone, fentanyl, morphine, hydrocodone, buprenorphine, and nalbuphine). Intraperitoneal injection of diluted lactic acid served as an acute noxious stimulus to either stimulate stretching or depress operant responding maintained by electrical stimulation in an intracranial self-stimulation (ICSS). All ?-agonists blocked both stimulation of stretching and depression of ICSS produced by 1.8% lactic acid. The high-efficacy agonists methadone and fentanyl were more potent at blocking acid-induced depression of ICSS than acid-stimulated stretching, whereas lower-efficacy agonists displayed similar potency across assays. All ?-agonists except morphine also facilitated ICSS in the absence of the noxious stimulus at doses similar to those that blocked acid-induced depression of ICSS. The potency of the low-efficacy ?-agonist nalbuphine, but not the high-efficacy ?-agonist methadone, to block acid-induced depression of ICSS was significantly reduced by increasing the intensity of the noxious stimulus to 5.6% acid. These results demonstrate sensitivity of acid-induced depression of ICSS to a range of clinically effective ?-opioid analgesics and reveal distinctions between opioids based on efficacy at the ?-receptor. These results also support the use of parallel assays of pain-stimulated and -depressed behaviors to evaluate analgesic efficacy of candidate drugs.