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Ultra-low-dose naltrexone suppresses rewarding effects of opiates and aversive effects of opiate withdrawal in rats.

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Abstract

RATIONALE: Ultra-low-dose opioid antagonists enhance opiate analgesia and attenuate tolerance and withdrawal.

OBJECTIVES: To determine whether ultra-low-dose naltrexone (NTX) coadministration alters the rewarding effects of opiates or the aversive effects of opiate withdrawal.

METHODS: We used the conditioned place preference (CPP) and conditioned place aversion (CPA) paradigms to assess whether ultra-low-dose NTX alters the acute rewarding effects of oxycodone or morphine, or the aversive aspect of withdrawal from either drug. To assess the dose response for ultra-low-dose NTX, a range of NTX doses (0.03-30 ng/kg) was tested in the oxycodone CPP experiment. In order to avoid tolerance or sensitization effects, we used single conditioning sessions and female rats, as females are more sensitive to the conditioning effects of these drugs.

RESULTS: Ultra-low-dose NTX (5 ng/kg) blocked the CPP to morphine (5 mg/kg) and the CPA to withdrawal from chronic morphine (5 mg/kg, for 7 days). Coadministration of ultra-low-dose NTX (30 pg/kg) also blocked the CPA to withdrawal from chronic oxycodone administration (3 mg/kg, for 7 days). The effects of NTX on the CPP to oxycodone (3 mg/kg) revealed a biphasic dose response. The two lowest doses (0.03 and 0.3 ng/kg) blocked the CPP, the middle dose (3 ng/kg) was ineffective, and oxycodone combined with the highest dose (30 ng/kg) produced a trend toward a CPP.

CONCLUSIONS: Ultra-low-dose NTX coadministration blocks the acute rewarding effects of analgesic doses of oxycodone or morphine as well as the anhedonia of withdrawal from chronic administration.

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