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Curcumin attenuates opioid tolerance and dependence by inhibiting Ca2+/calmodulin-dependent protein kinase II α activity.

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Abstract

Chronic use of opioid analgesics has been hindered by the development of opioid addiction and tolerance. We have reported that curcumin, a natural flavonoid from the rhizome of Curcuma longa, attenuated opioid tolerance, although the underlying mechanism remains unclear. In this study, we tested the hypothesis that curcumin may inhibit Ca(2+)/calmodulin-dependent protein kinase II α (CaMKIIα), a protein kinase that has been previously proposed to be critical for opioid tolerance and dependence. In this study, we used state-of-the-art polymeric formulation technology to produce poly(lactic-co-glycolic acid) (PLGA)-curcumin nanoparticles (nanocurcumin) to overcome the drug's poor solubility and bioavailability, which has made it extremely difficult for studying in vivo pharmacological actions of curcumin. We found that PLGA-curcumin nanoparticles reduced the dose requirement by 11- to 33-fold. Pretreatment with PLGA-curcumin (by mouth) prevented the development of opioid tolerance and dependence in a dose-dependent manner, with ED50 values of 3.9 and 3.2 mg/kg, respectively. PLGA-curcumin dose-dependently attenuated already-established opioid tolerance (ED50 = 12.6 mg/kg p.o.) and dependence (ED50 = 3.1 mg/kg p.o.). Curcumin or PLGA-curcumin did not produce antinociception by itself or affect morphine (1-10 mg/kg) antinociception. Moreover, we found that the behavioral effects of curcumin on opioid tolerance and dependence correlated with its inhibition of morphine-induced CaMKIIα activation in the brain. These results suggest that curcumin may attenuate opioid tolerance and dependence by suppressing CaMKIIα activity.

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