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Resveratrol regulates N-methyl-D-aspartate receptor expression and suppresses neuroinflammation in morphine-tolerant rats.

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Abstract

BACKGROUND: In the present study, we examined the effects and mechanisms of the Chinese herb resveratrol on attenuation of morphine tolerance in rats.

METHODS: Male Wistar rats were implanted with 2 intrathecal catheters; one catheter was connected to a mini-osmotic pump, used for either morphine (15 μg/h) or saline (1 μL/h) infusion for 5 days. On day 5, resveratrol (7.5, 15, 30, or 60 μg), dimethyl sulfoxide (5 μL), or saline (5 μL) was injected via the other catheter immediately after the discontinued morphine infusion. Three hours later, intrathecal morphine (15 μg in 5 μL saline) was given. All rats received the nociceptive tail-flick test every 30 minutes for 120 minutes after the morphine challenge.

RESULTS: Long-term morphine infusion induced antinociceptive tolerance and up-regulated N-methyl-D-aspartate receptor (NMDAR) subunit NR1 and NR2B expression in the synaptosome fraction of the tolerant spinal cord dorsal horn. Resveratrol pretreatment provided a significant antinociceptive effect of morphine in morphine-tolerant rats, and it was associated with reversal of the up-regulated NR1 and NR2B subunits in the synaptosome fraction of morphine-tolerant rat spinal cords. NR1/NR2B-specific antagonist ifenprodil treatment produced a similar effect as that of resveratrol. Furthermore, an increase of postsynaptic density-95/NR1/NR2B complex immunoprecipitation in morphine-tolerant rat spinal cord was also inhibited by resveratrol pretreatment. Moreover, chronic morphine infusion activated glial cells with an increase of proinflammatory cytokine tumor necrosis factor-α, interleukin-1β, and interleukin-6 mRNA expression in morphine-tolerant rat spinal cords and these effects were suppressed by resveratrol pretreatment before the morphine challenge.

CONCLUSIONS: Resveratrol attenuates morphine tolerance by inhibiting neuroinflammation and down-regulating NMDAR NR1 and NR2B subunit expression. Resveratrol regulates the NMDAR expression, which might be involved in a loss of scaffolding postsynaptic density-95 protein.

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