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Tramadol antinociception is potentiated by clonidine through α_2-adrenergic and I_2-imidazoline but not by endothelin ET(A) receptors in mice.

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Abstract

Tramadol is a centrally acting analgesic that acts via μ-opioid agonism and by blocking the neuronal uptake of norepinephrine and serotonin. Clonidine potentiates the antinociceptive effects of tramadol; however the receptors involved in this potentiation have not been studied. Endothelin ET(A) receptor antagonists potentiate antinociceptive effects of morphine and oxycodone; however the effects of endothelin ET(A) receptor antagonists on tramadol antinociception have not been evaluated. This study was conducted to determine the effect of clonidine on tramadol antinociception; the role of opioid, α_2-adrenergic and I_2-imidazoline receptors in clonidine potentiation of tramadol antinociception; and the effect of endothelin ET(A) receptor antagonists in modulating tramadol antinociception. Antinociceptive (tail-flick and hot-plate) latencies were measured in male Swiss Webster mice treated with tramadol; clonidine plus tramadol; or antagonists plus tramadol. Mice were pretreated with naloxone (opioid antagonist), yohimbine (α_2-adrenoceptor antagonist), idazoxan (α_2-adrenoceptor/I_2-imidazoline antagonist), BMS182874 or BQ123 (endothelin ET(A) receptor antagonists) to study the involvement of these receptors. Tramadol produced a dose dependent increase in antinociceptive latencies. Tramadol antinociception was partially blocked by naloxone but not by yohimbine or idazoxan. Clonidine potentiated tramadol antinociception; potentiation was blocked by naloxone, yohimbine and idazoxan. Idazoxan produced a more pronounced blockade of potentiation than yohimbine. BMS182874 or BQ123 had no effect on tramadol antinociception, indicating that endothelin ET(A) receptors are not involved in tramadol antinociception in mice. Results demonstrate the involvement of opioid but not α_2-adrenergic/I_2-imidazoline receptors in tramadol antinociception and that opioid, α_2-adrenergic and I_2-imidazoline receptors are involved in clonidine potentiation of tramadol antinociception.

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