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Determination of adrenergic and imidazoline receptor involvement in augmentation of morphine and oxycodone analgesia by clonidine and BMS182874.

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Abstract

BACKGROUND: Numerous agents have been demonstrated to potentiate morphine analgesia, including clonidine (alpha(2)-adrenergic and I(1)-imidazoline receptor agonist) and BMS182874 (endothelin-A, ET(A,) receptor antagonist). ET has been shown to affect pharmacological actions of clonidine. The present study was conducted to determine whether alpha(2)-adrenergic and/or I(1)-imidazoline receptors are involved in the augmentation of morphine and oxycodone analgesia by clonidine and BMS182874.

METHODS: Analgesic tail flick latencies were measured in rats at various time intervals, and were converted to AUC(0)-->(360 min).

RESULTS: It was found that clonidine produced mild analgesia, while BMS182874 did not have any analgesic effect. Clonidine (p = 0.015) and BMS182874 (p = 0.009) enhanced the analgesic action of morphine and oxycodone. Clonidine- or BMS182874-induced increases in the analgesic effect of morphine were not inhibited by idazoxan (I(1)-imidazoline receptor antagonist), while increases in the analgesic effect of oxycodone were blocked by idazoxan. Yohimbine (alpha(2)-adrenergic receptor antagonist) blocked the clonidine-induced potentiation of analgesic effect of morphine (p = 0.036) and oxycodone (p = 0.0167), while yohimbine did not affect BMS182874-induced potentiation of the analgesic effect of morphine or oxycodone.

CONCLUSIONS: This is the first report showing that clonidine and BMS182874 augment oxycodone analgesia. Results suggest that alpha(2)-adrenergic receptors are involved in clonidine-induced, but not in the BMS182874-induced, potentiation of the analgesic effects of morphine or oxycodone, and that I(1)-imidazoline receptors are involved in the potentiation of oxycodone analgesia, but not morphine analgesia, by clonidine and BMS182874.

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