



Potentialiation of morphine analgesia by BQ123, an endothelin antagonist.

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Several neurotransmitter mechanisms have been proposed to play a role in the actions of morphine. The present study is the first to provide evidence that central endothelin (ET) mechanisms are involved in the modulation of pharmacological actions of morphine. The effect of intracerebroventricular (i.c.v.) administration of endothelin-A (ET(A)) antagonist, BQ123, on morphine-induced analgesia, hyperthermia, and catalepsy was determined in the rat. Morphine produced a significant increase in tail-flick latency as compared to control group. Pretreatment with BQ123 significantly potentiated the effect and duration of morphine (2 and 8 mg/kg, s.c.)-induced analgesia as compared to vehicle-pretreated control rats. The hyperthermic effect of morphine was not only significantly greater in BQ123-pretreated rats but also lasted for more than 6 h. ET antagonist, BQ123, did not affect the pharmacological effect of morphine on cataleptic behavior. These studies demonstrate that BQ123, a specific ET(A) receptor antagonist, significantly potentiated morphine-induced analgesia and hyperthermia in rats without affecting morphine-induced cataleptic behavior. [(3)H]-Naloxone binding was carried out to determine the possibility of BQ123 acting on opiate receptors. It was found that morphine could displace [(3)H]-naloxone but BQ123 did not affect [(3)H]-naloxone binding even at 1,000 nM concentration. Therefore, it can be concluded that BQ123 does not act on opioid receptors. This is the first report suggesting that an ET(A) antagonist, BQ123, significantly potentiates the analgesic effect of morphine, possibly through a nonopioid mechanism.