



Endothelin receptor antagonists restore morphine analgesia in morphine tolerant rats.

Peptides 24(4):553-61, 2003.

Bhalla S, Matwyshyn G, Gulati A.

Several neurotransmitter mechanisms have been proposed to play a role in the development of morphine tolerance. The present study provides evidence for the first time that endothelin (ET) antagonists can restore morphine analgesia in morphine tolerant rats. Tolerance to morphine was induced by subcutaneous implantation of six morphine pellets during a 7-day period. The degree of tolerance to morphine was measured by determining analgesic response (tail-flick latency) and hyperthermic response to morphine sulfate (8 mg/kg, subcutaneously (s.c.)) in placebo and morphine pellet implanted rats. The maximal tail-flick latency in morphine pellet-vehicle treated rats (7.54 s) was significantly lower ($P < 0.05$) when compared to placebo pellet-vehicle treated rats (10s), indicating that tolerance developed to the analgesic effect of morphine. In separate sets of experiments, ET antagonists, BQ123 (10 microg, intracerebroventricularly (i.c.v.)) and BMS182874 (50 microg, i.c.v.) were administered in placebo and morphine tolerant rats. BQ123 was injected twice daily for 7 days and once on day 8. BMS182874 was administered only on day 8. Morphine (8 mg/kg, s.c.) was administered 30min after BQ123 or BMS182874 administration. It was found that both BQ123 and BMS182874 potentiated morphine analgesia in placebo and morphine tolerant rats. BQ123 potentiated tail-flick latency by 30.0% in placebo tolerant rats and 94.5% in morphine tolerant rats compared to respective controls. BMS182874 potentiated tail-flick latency by 30.2% in placebo tolerant rats and 66.7% in morphine tolerant rats. Morphine-induced hyperthermic effect was also potentiated by BQ123 and BMS182874. The duration of analgesic action was also prolonged by BQ123 and BMS182874. The effect of BMS182874 was less as compared to BQ123. BQ123 and BMS182874 are selective ET(A) receptor antagonists. Therefore, it is concluded that ET(A) receptor antagonists restore morphine analgesia in morphine tolerant rats.