



Endothelin ETA receptor blockade potentiates morphine analgesia but does not affect gastrointestinal transit in mice.

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Development of analgesic tolerance and constipation remain a major clinical concern during long-term administration of morphine in pain management. Central endothelin mechanisms are involved in morphine analgesia and tolerance. The present study was conducted to investigate the effect of intracerebroventricular (i.c.v.) and peripheral administration of endothelin ET(A) receptor antagonist, BMS182874, and endothelin ET(B) receptor agonist, IRL1620, on morphine analgesia and changes in gastrointestinal transit in male Swiss Webster mice. Results indicate that morphine (6 mg/kg, s.c.) produced a significant increase in tail flick latency compared to control group. Pretreatment with BMS182874 (50 microg, i.c.v.) significantly enhanced morphine-induced analgesia, while IRL1620 (30 microg, i.c.v.) pretreatment did not affect tail-flick latency values. Changes in gastrointestinal transit were measured by percent of distance traveled by charcoal in the small intestine of gastrointestinal tract. Percent distance traveled in morphine (6 mg/kg, s.c.) treated mice (48.45+/-5.65%) was significantly lower ($P<0.05$) compared to control group (85.07+/-1.82%). Administration of BMS182874 centrally (50 mug, i.c.v.) or peripherally (10 mg/kg, i.p.) did not affect morphine-induced inhibition of gastrointestinal transit. Pretreatment with IRL1620 (30 microg, i.c.v., or 10 mg/kg, i.v.) also did not affect morphine-induced inhibition of gastrointestinal transit. This study demonstrates that endothelin ET(A) receptor antagonists delivered to the CNS enhance morphine analgesia without affecting gastrointestinal transit.