



A novel combination of opiates and endothelin antagonists to manage pain without any tolerance development.

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Gulati A, Bhalla S, Matwyszyn G.

Several neurotransmitter mechanisms have been proposed as playing a role in the development of morphine tolerance. We provide evidence for the first time that endothelin antagonists can restore morphine analgesia in morphine-tolerant rats and prevent the development of tolerance to morphine. Studies were carried out in rats and mice treated with implanted placebo or implanted morphine pellet. The maximal tail-flick latency in morphine pellet + vehicle-treated rats (7.54 seconds) was significantly lower when compared with placebo pellet + vehicle-treated rats (10 seconds), indicating that tolerance developed to the analgesic effect of morphine. BQ123 potentiated tail-flick latency by 30.0% in placebo-tolerant rats and 94.5% in morphine-tolerant rats compared with respective controls. BMS182874 potentiated tail-flick latency by 30.2% in placebo-tolerant rats and 66.7% in morphine-tolerant rats. The enhanced analgesic effect of morphine after treatment with endothelin antagonists could be blocked by naloxone, indicating an opiate-mediated effect; but naloxone binding to brain membranes was not affected by BQ123. Guanosine triphosphate binding was stimulated by morphine and endothelin-1 in non-tolerant mice and not in morphine-tolerant mice; however, guanosine triphosphate binding was stimulated by BQ123 in morphine-tolerant mice and was unaffected in non-tolerant mice. These results suggest that uncoupling of G-protein occurs in morphine tolerance and endothelin antagonist restores the coupling of G-protein to its receptors. A combination use of endothelin antagonist and opiates could provide a novel approach in improving analgesia and eliminating tolerance.