Morphine tolerance does not develop in mice treated with endothelin-A receptor antagonists.

Brain Res 1064(1-2):126-35, 2005.

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Long-term use of morphine leads to development of antinociceptive tolerance. We provide evidence that central endothelin (ET) mechanisms are involved in development of morphine tolerance. In the present study, we investigated the effect of ET(A) receptor antagonists, BQ123 and BMS182874, on morphine antinociception and tolerance in mice. Mechanism of interaction of ET(A) receptor antagonists with morphine was investigated. BQ123 (3 microg, i.c.v.) and BMS182874 (50 microg, i.c.v.) significantly enhanced antinociceptive effect of morphine ($P < 0.05$), through an opioid-mediated effect. Treatment with a single dose of BQ123 (3 microg, i.c.v.) reversed tolerance to morphine antinociception in morphine-tolerant mice. BQ123 or BMS182874 did not affect naloxone binding in the brain. Therefore, ET(A) receptor antagonists did not bind directly to opioid receptors. [35S]GTPgammaS binding was stimulated by morphine and ET-1 in non-tolerant mice. Morphine- and ET-1-induced GTP stimulation was significantly lower ($P < 0.05$) in morphine-tolerant group (33% and 42%, respectively) compared to control group. BQ123 and BMS182874 did not activate binding in non-tolerant mice. BQ123 and BMS182874 significantly increased G protein activation in morphine-tolerant mice (96% and 86%, respectively; $P < 0.05$). These results provide evidence that uncoupling of G protein occurs in morphine-tolerant mice, and ET(A) antagonists promote coupling of G protein to its receptors, thereby restoring antinociceptive effect. These findings indicate that ET(A) receptor antagonists potentiate morphine antinociception and reverse antinociceptive tolerance in mice, through their ability to couple G proteins to opioid receptors.