



Involvement of endothelin in morphine tolerance in neuroblastoma (SH-SY5Y) cells.

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Bhalla S, Ciaccio N, Wang ZJ, Gulati A.

Long-term use of morphine in pain management leads to adverse effects, such as development of antinociceptive tolerance. We have previously shown the involvement of central endothelin (ET) mechanisms in morphine analgesia and development of tolerance in vivo. The present study was conducted to investigate the in vitro mechanism of interaction of the ET(A) receptor antagonist, BMS182874, and morphine during acute and chronic morphine tolerance in SH-SY5Y cells. SH-SY5Y cells were exposed to acute and chronic treatment with vehicle, morphine, ET-1, BMS182874, or morphine plus BMS182874. Activation of G-protein-coupled receptors in SH-SY5Y cells was determined using [³⁵S]GTPγS binding assays. Acute morphine treatment produced a concentration-dependent increase in GTP binding. Median effective concentration (EC₅₀) values were significantly decreased after acute morphine treatment, suggesting sensitization of opioid receptors. Chronic morphine treatment produced a lower maximal response of GTP binding compared with both control (vehicle treated) and acute morphine treatment, indicating uncoupling of G-proteins. Acute and chronic exposure of cells to ET-1 did not affect changes in ET-1-induced GTP binding. BMS182874 treatment alone (acute or chronic) did not produce G-protein activation. However, in cells chronically cotreated with 10 μM morphine and 1 μM BMS182874, morphine-induced GTP stimulation was significantly higher than control (vehicle treated). The EC₅₀ value after control treatment was 414 nM, and was significantly increased in chronically morphine-treated cells (>1000 nM). However, the EC₅₀ value in cells receiving a chronic treatment of BMS182874 and 63 nM morphine was significantly reduced compared with control (vehicle treated) and chronic morphine treatment. ET(A) antagonists significantly enhance the coupling of G-protein to opioid receptors. Therefore, we propose that restoration of morphine antinociception by ET(A) antagonists in morphine-tolerant animals is likely via a G-protein mediated mechanism.