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Spinal interaction between μ and δ opioid receptors in naive and morphine-tolerant rats

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Background

The role of δ opioid receptors in opioid antinociception and tolerance development is still unclear. In the spinal cord of morphine-tolerant mice δ receptor ligands given intrathecally (i.t.) differently influenced the antinociceptive effect of the μ agonist D-Ala²-methyl-glycinol (DAMGO). The δ_1 agonist D-Pen^{2,5}-enkephalin (DPDPE) inhibited, the δ_2 agonist deltorphin II did not alter, and the δ antagonist cha-TIPP ψ potentiated the effect of DAMGO. We hypothesized that during the development of morphine tolerance the formation of μ - δ heterodimers may contribute to the spinal μ opioid tolerance. Delta ligands may affect the dimer formation differently. Those, like DPDPE may facilitate the dimer formation, hence inhibit the antinociceptive effect of DAMGO by causing virtual μ receptor down-regulation. Ligands that do not affect the dimer formation do not influence antinociception but ligands with the presumed capability of disconnecting the dimers may decrease the spinal tolerance to DAMGO. The δ ligand profile in morphine-tolerant rats, were also studied.

Methods

Male Wistar rats (150–200g) were treated with subcutaneous (s.c) morphine twice daily for four days with increasing doses (50, 100, 200, 200 μ mol/kg). On the fifth day the antinociceptive effect (rat tail flick test) of DAMGO was measured alone and combined with a fixed dose of δ ligands given i.t.: DPDPE, Ile^{3,5}-deltorphin II, cha-TIPP ψ and naltrindole, respectively.

Results

The repeated treatment with morphine resulted in approximately three to six-fold shift of the ED₅₀ value of DAMGO compared to that of naive rats. Both in naive control and morphine-tolerant rats all ligands except naltrindole potentiated the antinociceptive effect of i.t. DAMGO (two to five-fold). In the tolerant rats the potentiation restored the potency of DAMGO to the control level.

Conclusions

Delta ligands behave differently in rats than in mice. One possible explanation could be a higher basal density of the μ - δ heterodimers in rats. The inhibitory action of naltrindole on the antinociceptive effect of DAMGO could be explained by its relatively low μ/δ selectivity as well as by the different effect on the μ - δ heterodimer. The difference in the DPDPE effect in morphine-tolerant rats and mice requires further clarification.

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