BMC Pharmacology

Meeting abstract

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

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from 15th Scientific Symposium of the Austrian Pharmacological Society (APHAR) Joint meeting with the Hungarian Society of Experimental and Clinical Pharmacology (MFT) and the Slovenian Pharmacological Society (SDF)
Graz, Austria. 19-21 November 2009

Published: 12 November 2009

BMC Pharmacology 2009, **9**(Suppl 2):A48 doi:10.1186/1471-2210-9-S2-A48

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S2/A48

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-Ala^2-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-TIPPψ 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 (150-200 g) were treated with subcutaneous (s.c) morphine twice daily for four days with increasing doses (50, 100, 200, 200 μmol/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-TIPPψ and naltrindole, respectively.

Results

The repeated treatment with morphine resulted in approximately three to six-fold shift of the ED_{50} 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.

Conclusion

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.

Acknowledgements

This work was supported by the Hungarian grants OTKA K-60999 and ETT-441/2006, and a Bolyai Fellowship of the Hungarian Academy of Sciences and Faculty of General Medicine, Semmelweis University.