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Blockade of peripheral σ_1-receptors increases morphine-induced antinociception.

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Antecedents

Several studies showed that the intracerebroventricular administration of σ_1-receptor antisense oligodeoxynucleotides and of haloperidol, a non-selective σ_1-receptor antagonist, enhances morphine antinociception against heat-induced pain. Together, these studies suggest the presence of a tonically active anti-opioid σ_1 system in the central nervous system (CNS). Morphine also produces antinociception through peripheral opioid receptors. However, it is unknown whether the blockade of σ_1-receptor outside the CNS is able to increase the peripherally-mediated opioid antinociception. Therefore, our aim was to study the local antinociceptive effect of morphine when injected into the hind paw alone and associated to several selective σ_1-receptor antagonists. Moreover, we compared the peripheral antinociception induced by morphine in wild-type and σ_1-receptor knockout (σ_1-KO) mice.

Methods

Experiments were performed in CD-1 wild-type (WT) and σ_1-KO mice weighing 25-30 g. Non-punctate nociceptive mechanical stimuli (450 g pressure) were applied alternatively to both hind-paws with a rounded tip cone-shaped paw-presser Analgesimeter (Ugo Basile, Italia) until the mouse showed a struggling behavior or 50 s had passed (cut-off time). The antinociceptive effect of intraplantar (i.pl.) administration of morphine and morphine co-administered i.pl. with several selective σ_1-receptor antagonists [BD-1063 (12.5-200 µg/20µl), BD-1047 (50 µg/20µl), NE-100 (50 µg/20µl), S1RA (100 µg/20µl)], was tested 5 minutes after injection into the right hind paw. The density of µ opioid receptors was measured with [^{3}H]DAMGO (15 nM) binding assays in hind-paw skin from WT and σ_1-KO mice.

Results

Morphine (50, 100 and 200 µg, i.pl.) produced no antinociception in WT mice (struggle response latencies were: 1.66 ± 0.17, 1.29 ± 0.10 and 1.58 ± 0.20 s, respectively); however, it produced a dose-dependent antinociceptive effect in σ_1-KO mice (14.5 ± 1.12, 26.42 ± 3.49 and 48.69 ± 3.93 s; respectively). This effect was locally-mediated because antinociception was observed in the injected paw but not in the non-injected paw of σ_1-KO mice (1.12 ± 0.08, 1.5 ± 0.22 and 1.13 ± 0.09 s). Statistically significant differences between the values obtained in the injected and non-injected hind paws in σ_1-KO mice. [^{3}H]DAMGO binding characteristics were the same in hind-paw skin from WT (0.030 ± 0.002 pmol/mg of protein) and σ_1-KO mice (0.0296 ± 0.001 pmol/mg of protein), which indicates that there were no differences in the peripheral µ-opioid receptors between both types of mice. In wild-type mice the antinociceptive effect of morphine (100 µg, i.pl.) was potentiated by co-administration with all the σ_1-receptor antagonists evaluated. In contrast, none of the σ_1-receptor antagonists modified morphine-induced antinociception in σ_1-KO mice. Statistical analysis was carried out using two-way ANOVA followed by the Bonferroni test. The differences between values were considered to be significant when the value of p was below 0.05.

Conclusion

These results suggest that blockade of peripheral σ_1 receptors increase the peripherally-mediated antinociceptive effect of morphine.

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