THE ANTINOCICEPTIVE EFFECT OF TRAMADOL IN THE FORMALIN TEST IS MEDIATED BY THE SEROTONERGIC COMPONENT

Oliva P., 3° anno di corso del Dottorato di Ricerca in Scienze Farmacologiche e Fisiopatologia Respiratoria, XV ciclo. Durata del Dottorato in anni: 4. Sede di servizio: Dipartimento di Medicina Sperimentale, Sezione di Farmacologia "L. Donatelli", Facoltà di Medicina e Chirurgia, Seconda Università degli Studi di Napoli, via Costantinopoli, 16-80138 Napoli.

Background: Tramadol (1 *RS*, 2 *RS*)-2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, a racemic mixture of two enantiomers, has affinity for μ-opioid receptors (Raffa et al., 1992) and inhibits neuronal reuptake of serotonin (5-HT) and norepinephrine (Driessen et al., 1993). However, the mechanism of action of tramadol remains unclear because its binding affinity for opioid receptors appears to be too low to account for the antinociceptive effect via this system (Rhoda et al., 1993), and the noradrenergic and serotonergic involvement is still not completely understood. The aim of this study was to investigate the neurotransmissions involved in the antinociceptive effect of tramadol in the formalin test, which is an animal model of acute and tonic pain. A subcutaneous injection of formalin (50 μl; 1.25%) produces a biphasic nociceptive response: phase 1 (0-10 min-acute pain) and phase 2 (21-60 min - tonic pain). Nociceptive activity is reduced greatly during the 10 min between these two phases.
Methods: We used the following experimental protocol: (±)-tramadol, (+)-tramadol, (-)-tramadol or morphine (control) were injected i.p. 15 min before formalin. The antagonists of opioid and 5- HT_2 receptors (naloxone and ketanserin, respectively) and the inhibitors of 5-HT and norepinephrine reuptake (fluoxetine and maprotiline, respectively) were injected i.p. 15 min after formalin administration. Doses were: (±)-tramadol and its enantiomers 0.5, 1, 2 and 4 mg/kg; morphine 1 mg/kg; naloxone 2 mg/kg; ketanserin 0.5 mg/kg; fluoxetine 5 mg/kg and maprotiline 5 mg/kg. A vehicle/control consisting of saline 0.3 ml was also used in all experiments.
Results: With respect to animals treated with formalin alone, (±)-tramadol and its enantiomers significantly reduced the duration of nociceptive behaviours (lifting, licking, favouring, shaking, and flinching of the formalin-treated paw), during phase 2. This effect was prevented by the 5-HT_2 receptor antagonist ketanserin, but not by naloxone which, on the contrary, was able to prevent the antinociceptive effect of morphine. Naloxone and ketanserin did not affect the duration of nociceptive behaviour in animals not treated with tramadol. Fluoxetine (a selective 5- hydroxytryptamine (5-HT) reuptake inhibitor), but not maprotiline (a selective norepinephrine reuptake inhibitor), potentiated the antinociceptive effect of (±)-tramadol.
Conclusions: In conclusion, we demonstrate that the serotonergic pathway is responsible for the antinociceptive effect of tramadol in phase 2 of the formalin test, and that this effect is mediated by 5-HT_2 receptors.

References

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