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Implication of β_1- and β_2-adrenergic receptors in the antinociceptive effect of tricyclic antidepressants

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Abstract

Tricyclic antidepressants have been shown to be useful for the treatment of pain of varying etiology. Monoaminergic systems seem to be implicated in this phenomenon. In this study, the influence of the selective β_1- (CGP 20712A) and β_2- (ICI 118551) adrenergic blockers on the antinociceptive effect of desipramine and nortriptyline was studied in mice using physical and chemical nociceptive tests that implicate different levels of sensory-motor integration in the central nervous system (CNS). An activity test was performed to detect ''false positive'' or ''false negative'' results. Results obtained show that both CGP 20712A and ICI 118551 are able to antagonize the antinociceptive effect of these antidepressants in physical tests (hot-plate and tail-flick). However, in chemical tests (acetic acid and formalin), the analgesic effect of the antidepressants used was only antagonized by CGP 20712A. These results suggest that the analgesic effect of desipramine and nortriptyline is mediated by β-adrenoceptors. The β-adrenoceptor involved depends on the type of nociceptive stimulus: β_1 and β_2 are both implicated when the stimulus is physical, but only β_1 is involved when the stimulus is chemical.

Keywords: Antidepressants; β-Adrenoceptors; Analgesia; Mice

1. Introduction

Tricyclic antidepressants have been proved to increase pain thresholds both in men (Onghena and Van Houdenhove, 1992) and animals (Rigal et al., 1983). Although in some cases their analgesic and antidepressant effects may operate simultaneously to alleviate pain (Blummer et al., 1980), several clinical (for review see Magni, 1991) and experimental (Casas et al., 1993) reports seem to demonstrate that these two effects may be independent.

The hypothesis formulated about the mechanisms of action of the analgesic effect of tricyclic antidepressants implies both monoaminergic and opioid mechanisms (Eschalier et al., 1994; Valverde et al., 1994).

The involvement of monoamines, mainly serotonin and noradrenaline, in the physiological control of nociception has been well established (Basbaum and Fields, 1984). Tricyclic antidepressants are able to inhibit the reuptake of these two monoamines in the synapse (Carlsson et al., 1969), with the secondary amines such as nortriptyline or desipramine being more effective in the inhibition of noradrenaline reuptake (Sulser and Mobley, 1980).

In relation to noradrenaline, several studies have focused on the role that α-adrenergic receptors play in analgesia (Bernard et al., 1991; Paalzow, 1982; Kitahata, 1989; Ansuategui et al., 1989), but little information exists about the participation of β-adrenergic receptors in nociception. However, several reports suggest that this receptor may play a role in pain control and analgesia. The beta-adrenergic receptors participate in the mechanism of action of anti-depressants, an hypothesis that was first proposed by Vetulani et al. (1976). This receptor has been located in

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areas directly related to pain pathways (Patterson and Hanley, 1987). Moreover, Dennis et al. (1980) demonstrated that β-adrenergic antagonists counteract the analgesic effect of morphine, and it has been shown that administration of β-adrenergic agonists induce antinociception (Gardella et al., 1970; Bentley et al., 1983).

In previous reports, we have demonstrated that two selective β-adrenergic receptor agonists (salbutamol and clenbuterol) induce a clear analgesic effect in the hot-plate test in mice (Brochet et al., 1986). Besides in a previous experiment, we demonstrated that penbutolol, a β-adrenergic blocker, is able to antagonize the analgesic effect of desipramine (Micó et al., 1992).

Our aim in this paper is to establish the subtypes of β-adrenergic receptors implicated in the analgesic effect of two antidepressants with experimental (Danysz et al., 1986) and clinical (Max et al., 1992) analgesic activity. We have performed a study to find out if CGP 20712A, a selective β_1-adrenoceptor blocking agent, and/or ICI 118551, a selective β_2-adrenergic antagonist (Henry et al., 1990), can antagonize the analgesic effect of desipramine and nortriptyline, two tricyclic antidepressants with potent and selective properties to inhibit noradrenaline reuptake (Sulser and Mobley, 1980). Since the mechanisms of the antidepressant-induced analgesic effect may be different, depending on the pain tests used (Gibert-Rahola et al., 1991), we carried out the experiments using several nociceptive tests that implicate different sensory-motor integration. In addition, the effect of these two antagonists on the decrease in motor activity produced by desipramine and nortriptyline has also been studied.

2. Methods

2.1. Animals

Albino male mice of the OF1 strain (20–25 g), obtained from the Central Animal Service of the University of Cádiz, were maintained on a 12-h light–dark schedule (light on at 8 a.m.) with ad libitum food and water and a constant temperature (21°C). Animals were housed 24 h before starting the experiments. We paid attention to the ethical guidelines for investigation of experimental pain in conscious animals (Zimmerman, 1983) and our experimental protocol was approved by the Local Committee for Animal Experimentation of the School of Medicine of the University of Cádiz (Licence number 079604).

2.2. Pain models

2.2.1. Thermal stimulus pain models

Hot plate test (Woolfe and MacDonald, 1944)

Mice were placed on a hot plate (Digital DS-37 Socrel model), which was thermostatically maintained at 55°C. The reaction time of each animal (either paw licking or jumping) was measured as the pain response. When none of these responses occurred within 30 s of exposure (cut off), the test was concluded in order to avoid damage to the animal.

Tail flick test (D'Amour and Smith, 1941)

Mice were exposed to an overhead lamp (100 W) of the LI 7106 tail-flick model, which had a photoelectric sensor for automatic arrest and a digital time counter. This test was carried out on three different points of the mouse tail by focusing a lightbeam on each point, with 1 min intervals between each exposure. Determinations were done at those three different points and the average of them was considered as the pain latency. When the animals did not respond after 10 s of exposure (cut off), the test was concluded in order to avoid damaging the animal's tissue.

2.2.2. Chemical stimulus pain models

Acetic acid test (Koster et al., 1959)

A 0.8% acetic acid solution was injected (i.p.) into the animals. After a 6-min period, the animal was placed in a plexiglass chamber for observation and the number of contortions was recorded during a 2-min period.

Formalin test (Dubuisson and Dennis, 1977)

A 20-μl volume of a 1% formalin–saline solution was injected (s.c.) into the dorsal surface of the mouse's hind paw. Immediately after injection, the mouse was placed in a plexiglass chamber for observation. The amount of time the animal spent licking the injected paw was recorded over a 2-min period and immediately after formalin injection.

2.3. Motor activity measurement

A S.M.A.R.T. (Spontaneous Motor Activity Recording and Tracking) apparatus provided by LETICA Scientific Instruments was used. Each animal was placed in a plexiglass chamber (20×20×15 cm). After 30 min, the apparatus began to record the total activity of each animal over a 10-min period. Motor activity was assessed following the arbitrary units established by the S.M.A.R.T.

2.4. Drugs

CGP20712A ((±)-1-[2-(3-carbamoyl-4-hydroxyphenoxyl)-ethylamino]-3-[4(1-methyl-4-trifluoromethyl-2-imidazolyl)-phenoxy]-2-propanolol methane sulphonate, Ciba-Geigy Pharmaceuticals Division) and ICI 118551 (erythro-(±)-1-(7-methylindan-4-yloxyl-3-isopropylamin)butan-2-ol hydrochloride, RBI), at doses capable of blocking the β_1- and β_2-adrenoceptors, respectively (1 mg/kg and 30 μg/kg, respectively) or their vehicle [saline, 0.9% (SS)],

were s.c. injected 40 min before starting the different tests. Desipramine hydrochloride, DMI, (Sigma); nortriptyline hydrochloride, NOR, (Sigma), or their vehicle, SS, were i.p. injected 30 min before starting the different tests. In previous experiments (data not shown), we obtained a dose–effect curve in every test for each antidepressant in order to choose the lowest effective dose that would subsequently be associated with the β-blockers in each test. The doses selected were the following: tail-flick test: 20 mg/kg of DMI and 20 mg/kg of NOR; hot-plate test: 40 mg/kg of DMI and 4 mg/kg of NOR; acetic acid test: 2 mg/kg of DMI and 2 mg/kg of NOR; formalin test: 4 mg/kg of DMI and 2 mg/kg of NOR; activity test: 40 mg/kg of DMI and 5 mg/kg of NOR. The injection volume was 0.25 ml/25 g.

The treatments were administered under blind conditions, and 10 animals were used per group.

2.5. Statistical analysis

The results are expressed as the mean±S.E. value. Differences between groups were analyzed using a Student-Newman-Keuls test, following the significant main effect of treatments by ANOVA. A p-value of <0.05 was considered to be significant.

3. Results

The results obtained show DMI and NOR have an antinociceptive effect when measured by chemical and physical tests. The β_1- and β_2-selective adrenergic blockers show no intrinsic antinociceptive activity in this test. The effects of the antidepressants were antagonized by the selective adrenergic blockers, CGP 20712A (for β_1) and/or ICI 118551 (for β_2), depending on the test used.

3.1. Tail-flick test

Both antidepressants (at doses of 20 mg/kg) induced a significant antinociceptive effect. The tail-flick latency in animals treated with DMI was 6.50±0.27 s and with NOR was 7.19±0.20 s, with the latency being 4.37±0.18 s in control, saline-treated, animals. In this test, the antinociceptive effect of DMI and NOR was significantly antagonized by pretreatment with either β_1 or β_2 blockers (Fig. 1).

3.2. Hot-plate test

In this test, NOR (4 mg/kg) and DMI (40 mg/kg) administration significantly increased the latency time for forelimb licking. For NOR- and DMI-treated animals, the values (in seconds) were 10.04±0.56 and 14.33±1.41, respectively, with the latency for control animals being 6.83±0.92. Pretreatment with either β_1 or β_2 blockers

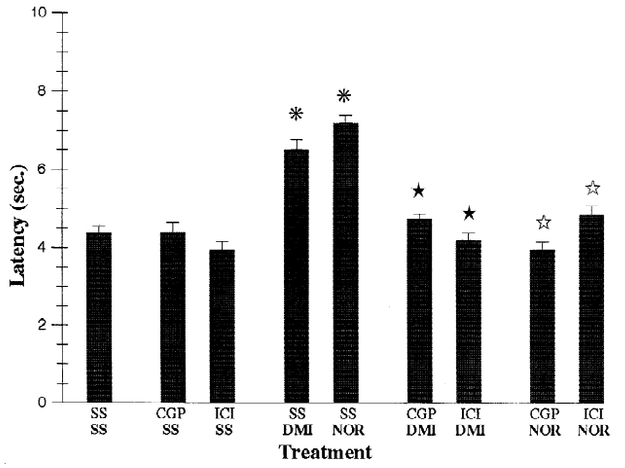

Fig. 1. Effect of the association of 20 mg/kg of desipramine (DMI) or 20 mg/kg of nortriptyline (NOR) to 1 mg/kg of CGP 20712A or 30 μg/kg of ICI 118551 in the tail-flick test. *$p<0.05$ vs. SS–SS; ★$p<0.05$ vs SS–DMI; ☆$p<0.05$ vs. SS–NOR.

significantly antagonized the effect of both DMI and NOR (Fig. 2).

3.3. Acetic acid test

Both DMI and NOR (at doses of 2 mg/kg) had a significant antinociceptive effect. The value for the DMI-treated group was 4.80±0.66 writhings, for the NOR-treated group, the value was 4.20±0.41 writhings, and for control animals, it was 10.00±0.47 writhings. Pretreatment with the β_1 blocker (CGP 20712A), but not with the β_2 blocker (ICI 118551), antagonized the antinociceptive effect of both DMI and NOR (Fig. 3).

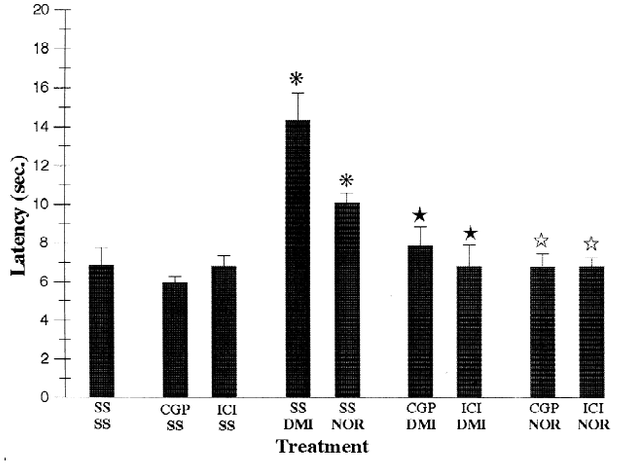

Fig. 2. Effect of the association of 40 mg/kg of desipramine (DMI) or 4 mg/kg of nortriptyline (NOR) to 1 mg/kg of CGP 20712A or 30 μg/kg of ICI 118551 in the hot-plate test. *$p<0.05$ vs. SS–SS; ★$p<0.05$ vs. SS–DMI; ☆$p<0.05$ vs. SS–NOR. SS: saline; SS-SS: two injections of saline.

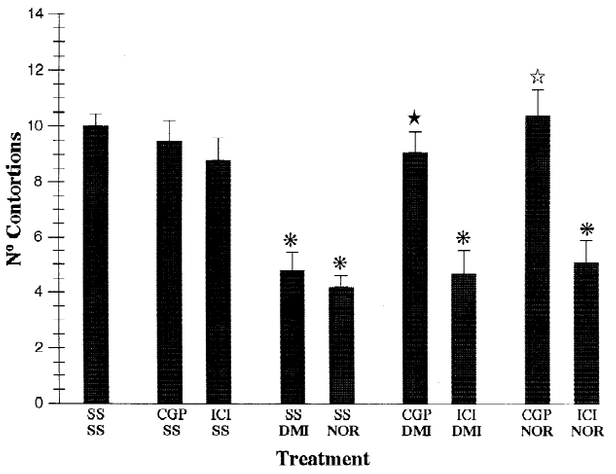

Fig. 3. Effect of the association of 2 mg/kg of desipramine (DMI) or 2 mg/kg of nortriptyline (NOR) to 1 mg/kg of CGP 20712A or 30 μg/kg of ICI 118551 in the acetic acid test. *$p<0.05$ vs. SS–SS; ★$p<0.05$ vs. SS–DMI; ☆$p<0.05$ vs. SS–NOR.

Table 1
Effect of the association of 40 mg/kg of desipramine (DMI) or 5 mg/kg of nortriptyline (NOR) to 1 mg/kg CGP 20712A or 30 μg/kg of ICI 118551 in the activity test.

Treatment	Arbitrary units
Saline–saline	11.6±3.28
CGP–saline	9.82±3.55
ICI–saline	22.6±6.92
Saline–nortriptyline	0.85±0.67*
Saline–desipramine	0.75±0.32*
CGP–nortriptyline	0.20±0.20*
CGP–desipramine	0.12±0.12*
ICI–nortriptyline	0.11±0.11*
ICI–desipramine	0.45±0.34*

*$p<0.05$ vs. SS–SS.

3.4. Formalin test

DMI (4 mg/kg) and NOR (2 mg/kg) administration significantly decreased the time for limb licking, 43.40±5.98 and 41.38±8.28 s, respectively. The latency for the control group was 64.90±3.91 s. The effects of DMI and NOR were antagonized by pretreatment with β_1, but not by β_2 blocker pretreatment (Fig. 4).

3.5. Activity test

DMI (40 mg/kg) and NOR (4 mg/kg) decreased spontaneous motor activity. For DMI- and NOR-treated groups, the values (in arbitrary units) were 0.75±0.32 and 0.85±0.67, respectively; the value for control animals was 11.60±3.28. Pretreatment with β_1 and β_2 blockers did not antagonize the effect on activity induced by either DMI or NOR (Table 1).

4. Discussion

This study has demonstrated that desipramine and nortriptyline, two selective inhibitors of noradrenaline reuptake, induce antinociceptive activity when measured using several nociceptive methods that implicate different sensory-motor integration. Our results are in agreement with other studies as they show that these two antidepressants elicit an acute antinociceptive effect in the four nociceptive tests used (Fasmer et al., 1984; Ibba et al., 1987; Valverde et al., 1994).

The first conclusion to be drawn from these data is that the β_1-adrenergic receptor always participates in the analgesic effect of desipramine and nortriptyline, whereas the β_2-adrenergic receptor may or may not be involved,

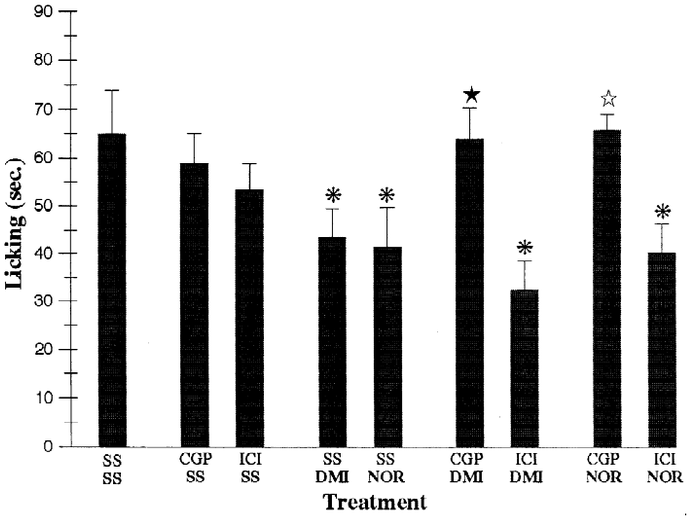

Fig. 4. Effect of the association of 4 mg/kg of desipramine (DMI) or 2 mg/kg of nortriptyline (NOR) to 1 mg/kg of CGP 20712A or 30 μg/kg of ICI 118551 in the formalin test. *$p<0.05$ vs. SS–SS; ★$p<0.05$ vs. SS–DMI; ☆$p<0.05$ vs. SS–NOR.

depending on the type of noxious stimulus. Indeed, both CGP 20712A, a selective β_1-adrenoceptor antagonist, and ICI 118551, a selective β_2-adrenoceptor antagonist, inhibited the analgesic effect of desipramine and nortriptyline in the two physical tests, while in chemical tests, only the β_1 antagonist inhibited the analgesic effect of these two antidepressants.

Although antidepressants elicit an analgesic effect in a great variety of nociceptive tests, it seems that noradrenergic antidepressants, such as desipramine and maprotiline, are more effective in doing so when using chemical tests than when using thermal tests (Ardid et al., 1992). However, given the wide variety of antidepressants and their relative potencies to inhibit noradrenaline reuptake, as well as the existence of different thermal and chemical nociceptive tests, this aspect needs to be investigated further.

In general, it has not yet been demonstrated what makes one test different from another with respect to assessing drug effects. Some reports postulate that two factors are implicated in the case of adrenergic agents (Dennis et al., 1980): (i) The physical and temporal properties of the noxious stimulus and (ii) the pattern of the required motor response. In this sense, we have tested the antidepressants in four nociceptive tests with different noxious stimuli and which trigger different responses. The contrasts between these tests might then reflect the differential processing of noxious stimuli with different physical and/or temporal properties and with different motor responses. Unfortunately, the modulation of these responses by β-adrenergic receptors is still unknown.

Our results show that the analgesic effects of DMI and NOR in physical tests, which implies central integration, were totally inhibited by the selective β_1-adrenoceptor antagonist, CGP 20712A, as well as by the selective β_2-adrenoceptor antagonist, ICI 118551. These results may suggest a difference in the synaptic location of these receptors. Indeed, the existence of presynaptic β-adrenergic receptors within the superficial layers of the dorsal horn has been proved, however, whether these presynaptic receptors belong to the β_1, β_2 or both types has not yet been determined (Hamon et al., 1991). Moreover, the anatomical distribution of β_1- and β_2-adrenergic receptors, as determined by in situ hybridization, seems to be different (Nicholas et al., 1993).

On the other hand, when the analgesic effect of the antidepressant was tested in chemical tests, which implies peripheral as well as central components, the effect was only inhibited by the β_1-antagonist, CGP 20712A. This suggests that, in these models, other mechanisms could be implicated. Thus, Ansuategui et al. (1989) showed, using the formalin test, that the antinociceptive effect of clomipramine was antagonized by phentolamine, a non-specific α_1- and α_2-noradrenergic antagonist, and by prazosin, a selective α_1-antagonist, but not by yohimbine, an α_2-antagonist. Moreover, Gray et al. (1990) showed that the analgesic effect of oxaprotiline was antagonized by naloxone.

It has been extensively demonstrated that the analgesic effect of noradrenalin is exerted mainly at the spinal level and, hence, the analgesic effect of noradrenergic antidepressants is probably mediated through α-adrenergic receptors (Reddy and Yaksh, 1980; Yaksh, 1985), however, the possible involvement of β-adrenergic receptors cannot be ruled out. In fact, several lines of evidence suggest that the β-adrenergic receptors could be implicated in modulating pain processes. Thus, the presence of β-adrenoceptors in the CNS has been convincingly demonstrated through several methods and the distribution of β_1- and β_2-receptor subtypes has also been determined in various brain regions (Palacios and Kuhar, 1982; Pazos et al., 1985). Although some of these CNS areas are directly related to pain control, their functional significance in this aspect is still largely unknown. Moreover, the presence of β-adrenergic receptors on sensory nerve terminals has been well documented. In fact, neonatal rats treated with capsaicin, a sensory toxin, showed a selective loss in [^{3}H] Dihydroalprenolol (DHA) sites from the dorsal horn laminae (Patterson and Hanley, 1987), which are known to receive capsaicin-sensitive fiber input (Nagy and Hunt, 1983). The regional distribution of the capsaicin-sensitive sites correlates well with the known pattern of sensory afferent substance P-immunoreactivity nerve endings (Nagy et al., 1983). These observations lead to a crucial question: What is the physiological role of the β-receptors located on the unmyelinated primary afferent fibers that enter the dorsal horn (Hamon et al., 1991). This question remains unanswered.

The analgesic mechanism of antidepressants has been widely discussed (Feinmann, 1985; Eschalier et al., 1994). The majority of investigations carried out on this topic have focused on the participation of opioids and their receptors (Eschalier et al., 1981; Valverde et al., 1994) or serotonin and its different receptors (Eschalier et al., 1981). However, little information exists about the participation of the noradrenergic system. We have shown previously (Valverde et al., 1994) that the antinociceptive effect induced by tricyclic antidepressants in the formalin test is antagonized by the administration of α-methyl-*p*-tyrosine, a tyrosine hydroxylase inhibitor that decreases noradrenaline synthesis. Focussing on the implication of β-adrenergic receptors, we demonstrated, in a previous study, that the analgesic effect of desipramine in the hot-plate test could be inhibited by penbutolol (Micó et al., 1992) and that two β-adrenergic agonists have analgesic properties in the hot-plate test (Brochet et al., 1986).

Other reports also found a relationship between analgesia and β-adrenergic receptors. In relation to chemical tests, in the acetic acid-induced writhing, the implication of both α- and β-adrenoceptors has been well documented (Bentley et al., 1983; Bentley and Starr, 1986). In the acetic acid test, several β-adrenergic agonists induced

potent antinociceptive activity. However, the type of receptor implicated has not yet been elucidated. Bentley and Starr (1986) suggested that there exists an ''analgesic β-adrenoceptor''.

On the other hand, β-adrenergic receptors are closely related to two other neural systems that are directly implicated in pain modulation, i.e. serotonergic (Green et al., 1984) and opioid (Berkenbosch et al., 1981), which, in turn, participate in the mechanism of action of antidepressants. Thus, the importance of these relationships cannot be ruled out when the participation of β-adrenergic receptors in the analgesic effect of the antidepressants is considered.

In conclusion, since the possible role of β-adrenergic receptors, in specific brain structures and peripheral terminals, in the control of antinociceptive response is at present largely unknown, the exact significance of the antagonism by β_1- and β_2-antagonists in physical tests and the lack of effect of β_2-antagonists in chemical tests on the analgesia induced by the antidepressant cannot be assessed with sufficient accuracy. It is unlikely, however, that sedation would be a critical factor in the ability of antidepressants to induce analgesia, since our results on activity test showed an absence of effect of the β_1- or β_2-adrenergic antagonists on the reduction of motor activity induced by these antidepressants. This suggests that changes in motor activity could not account for the modification of pain thresholds. Other reports have come to the same conclusion, at least as far as the hot-plate and writhing tests are concerned (Ardid et al., 1992).

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