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Effects of clomipramine and desipramine on a C-fiber reflex in rats

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Abstract

A C-fiber nociceptive reflex evoked by electrical stimulation within the territory of the sural nerve, was recorded from the ipsilateral biceps femoris muscle in urethane anesthetized rats. Intravenously administered clomipramine and desipramine produced a dose-dependent depression of the C-fiber reflex. High doses of intrathecal desipramine also inhibited the C-fiber reflex, while similar intrathecal doses of clomipramine produced only a modest inhibition of the response. Intracerebroventricular administration of clomipramine decreased dose-dependently the C-fiber reflex whereas intracerebroventricular desipramine increased this reflex. These findings suggest that tricyclic antidepressants with noradrenergic selectivity, as desipramine, inhibit the spinal processing of C inputs by acting directly at the spinal cord level, while those with serotonergic spectra, as clomipramine, depress the C-fiber-evoked spinal reflex by acting at a supraspinal modulatory site. © 1997 Elsevier Science B.V.

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1. Introduction

Tricyclic antidepressants are currently employed for achieving analgesia in a variety of chronic pain syndromes (Eschalier, 1990; Magni, 1991; Onghena and Van Houdenhove, 1992). The antinociceptive efficacy of tricyclic antidepressants, which appears to depend on the ability of these molecules to inhibit monoamine reuptake in the central nervous system, has also been studied in experimental animals. In fact, several studies have shown that tricyclic antidepressants with different monoaminergic spectrum exert antinociceptive actions in thermal (Eschalier et al., 1988; Lund et al., 1989; Tura and Tura, 1990; Ventafridda et al., 1990), chemical (Michael-Titus and Costentin, 1987; Takahashi and Paz, 1987; Fasmer et al., 1989; Sierralta et al., 1995b), mechanical (Reichenberg et al., 1985; Ardid et al., 1992) and electrical (Rigal et al., 1983; Danysz et al., 1986) tests. There is evidence supporting that the antinociceptive effects of tricyclic antidepressants are independent of their antidepressant efficacy (for review see Eschalier et al., 1994): (a) it has been reported that a lower dose of tricyclic antidepressants is required for inducing clinical analgesia, as compared to that required to ameliorate a depressive syndrome; (b) tricyclic antidepressant-induced analgesia could be produced in patients with no depressive syndrome associated to a painful state; (c) antinociceptive effects of tricyclic antidepressants have been shown in animals.

Central sites for the antinociceptive effects of tricyclic antidepressants have been suggested, on the basis that they could display antinociceptive activity in rodents when administered intrathecally (Kehl and Wilcox, 1984; Hwang and Wilcox, 1987; Lund et al., 1990) and intracerebroventricularly (Spiegel et al., 1983; Sierralta et al., 1995a), but not after intraplantar injection in rats submitted to carrageenan-induced hyperalgesia (Ardid et al., 1991). However, it remains unclear if efficacy of spinal or supraspinal administration of tricyclic antidepressants is associated with the monoamine selectivity of these drugs.

In the present experiments we studied whether intravenous, intrathecal and intracerebroventricular administration of tricyclic antidepressants, with preferential serotonergic or noradrenergic spectrum, could depress the C-fiber-evoked reflex response in intact anesthetized rats. As recently reported, this reflex response is a useful tool for pharmacological studies of mechanisms involved in noci-

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ception, since it can be strongly modulated by peripheral and central factors which influence the spinal processing of nociceptive transmission (Strimbu-Gozariu et al., 1993; Falinower et al., 1994; Guirimand et al., 1994, 1995).

2. Materials and methods

The experiments were carried out on Sprague–Dawley rats weighing 250–300 g and anesthetized with urethane (1 g/kg, i.p.). The left femoral vein was cannulated for subsequent intravenous administration of tricyclic antidepressants. Intrathecal administration of tricyclic antidepressants was performed by direct percutaneous injection into the subarachnoid space (Mestre et al., 1994), while intracerebroventricular injection was carried out by approaching the lateral ventricle at stereotaxic coordinates A: 5.8, L: 1.6, V: 3.5, in mm (Pellegrino and Cushman, 1967).

2.1. C-fiber-evoked nociceptive reflex

The flexor reflex was elicited in the right hindlimb as described previously (Strimbu-Gozariu et al., 1993; Falinower et al., 1994). Rectangular electric pulses of sufficient strength for threshold activation of C-fibers (3–7 mA strength, 2 ms duration) were initially employed, applied every 10 s to the sural nerve receptive field by means of two stainless steel needles inserted into the skin of toes 4 and 5. The C-fiber-evoked reflex activity was recorded from the ipsilateral biceps femoris muscle via another pair of stainless steel needles. Once a threshold C-fiber response was obtained, the stimulus strength was increased by a 3-fold factor. After amplification, the electromyographic (EMG) responses were fed to a computerized system for on-line digitization. The digitized EMG responses were full-wave rectified and the C-fiber-evoked responses were integrated within a time-window from 150 until 450 ms after the stimulus.

2.2. Drugs administration

In a first series of experiments, the effects of intravenous administration of either 1.5, 3.0 and 6.0 mg/kg of clomipramine (a preferential serotonergic reuptake inhibitor) or 4.5, 9.0 and 18.0 mg/kg of desipramine (a preferential noradrenergic reuptake inhibitor) were assessed. In a second series of studies, the effects of intrathecal administration of 4.0, 8.0, 16.0 and 32.0 μg/rat of clomipramine and 8.0, 16.0 and 32.0 μg/rat of desipramine were investigated. In the last run of experiments, the effects of intracerebroventricular administration of 5.0, 10.0 and 25.0 μg/rat of both tricyclic antidepressants were studied. The doses used in the experiments utilizing systemic tricyclic antidepressants administration were equivalent to those employed to induce analgesia in humans (Reichenberg et al., 1985; De Felipe et al., 1986; Sacerdote et al., 1987). On the other hand, intrathecal doses of tricyclic antidepressants were selected from the literature, the maximal dose being slightly lower than which may induce motor perturbations (Dirksen et al., 1994).

Recording of the mean of 30 C-fiber responses before tricyclic antidepressant administration served as control. Drug-induced effects were expressed as the percentage change with respect to the mean of 30 successive control responses, and the scores were plotted against time to allow the study of the time-course of the effects on the C-fiber reflex. To appreciate the global effects of tricyclic antidepressants in the C-reflex paradigm, an estimated area under the curve (AUC) was calculated by the algebraic sum of the scores over the total period of testing that followed drug administration.

2.3. Statistical analyses

Results were expressed as means ± S.E.M. and analyzed by an analysis of variance followed by a Student's *t*-test for independent samples to compare different treatments. Three values of t with a probability of less than 0.05 were considered to indicate statistically significant difference between means: $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$.

3. Results

3.1. Effects of intravenous clomipramine and desipramine administration

Intravenous administration of clomipramine produced a significant depression of the C-fiber-evoked response. The maximum inhibition of the C-reflex was 50 ± 9% following 6.0 mg/kg. The doses of 1.5 and 3.0 mg/kg produced an inhibition of 22 ± 3 and 36 ± 7%, respectively (Fig. 1A). The intravenous administration of desipramine also significantly inhibited the reflex activity. The maximum depressive effect (43 ± 5%) was obtained with 18 mg/kg, whereas 4.5 and 9.0 mg/kg of the drug induced a response decrease of 11 ± 7 and 32 ± 4%, respectively (Fig. 2A). Results expressed as summed scores over the total period of drug testing (65 min) showed that the inhibitory effect on the reflex response was dose-dependent for both clomipramine (Fig. 1B) and desipramine (Fig. 2B).

3.2. Effects of intrathecal clomipramine and desipramine administration

The intrathecal administration of clomipramine produced no clear inhibitory effects on the C-fiber reflex. Clomipramine in amounts of 4.0, 8.0 and 16.0 μg/rat did not modify the C-fiber reflex, while the highest dose (32.0 μg/rat) produced only a modest depression of the reflex

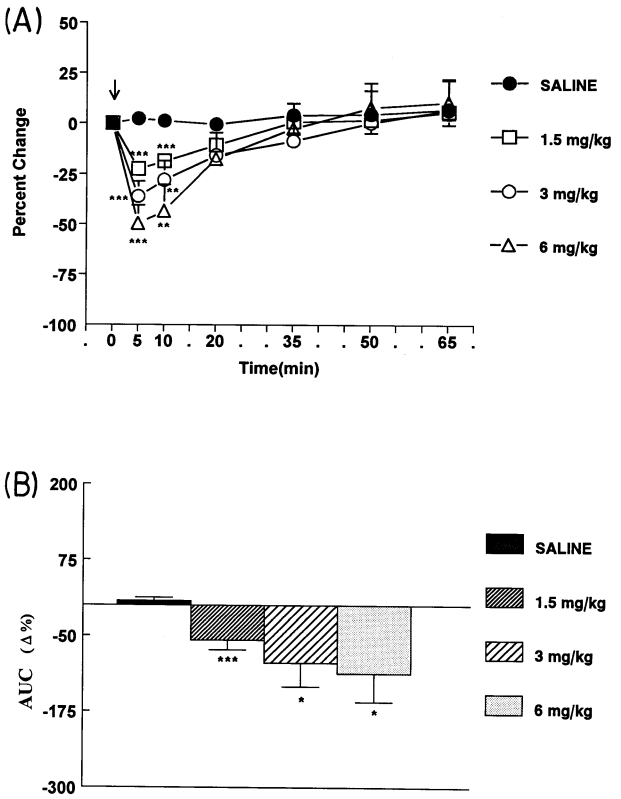

Fig. 1. Effect of intravenous clomipramine administration on the C-fiber-evoked reflex. (A) Time-course of the inhibition of the C-reflex response (in percentage) after clomipramine. The arrow indicates the time of clomipramine injection. (B) Effect of clomipramine on the C-reflex activity, revealed by estimated areas under the curves (AUC). Each value indicates the mean percentage change as compared to the control. Values are means ± S.E.M. Stars represent a significant change in the C-reflex, when the values were compared to their respective values of the saline series. * $P < 0.05$; ** $P < 0.01$; and *** $P < 0.001$ (non-paired Student's *t*-test).

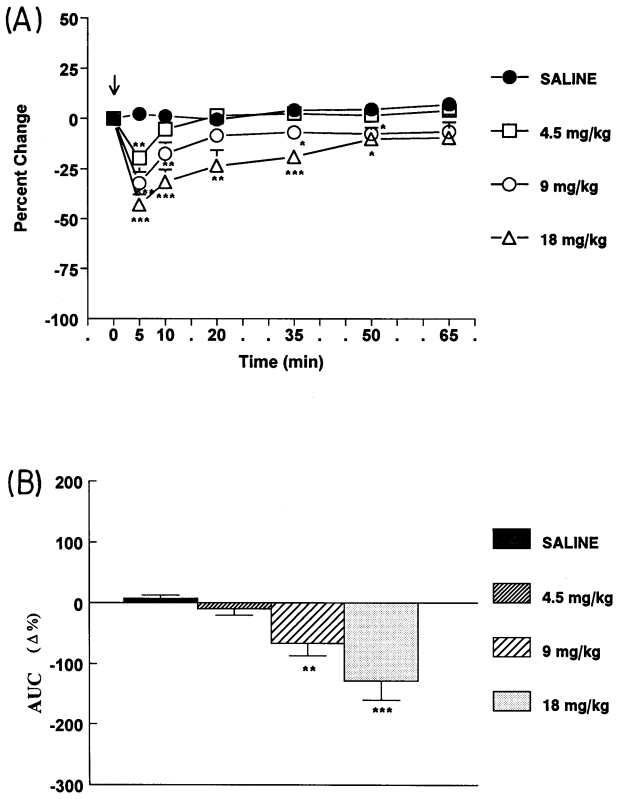

Fig. 2. Effect of intravenous desipramine administration on the C-fiber-evoked reflex. For all further explanations refer to Fig. 1.

response (Fig. 3A). Desipramine intrathecally administered was only active at the highest dose employed (32.0 μg/rat), its inhibitory effect peaking (32 ± 5%) at 5 min after injection (Fig. 4A). Results expressed as summed scores over the total period of drug testing showed that the effect was not dose-dependent neither for clomipramine (Fig. 3B) nor for desipramine (Fig. 4B).

3.3. Effects of intracerebroventricular clomipramine and desipramine administration

Fig. 5A shows that intracerebroventricular administration of clomipramine depressed the C-fiber reflex at all doses utilized. 5.0 μg/rat of clomipramine induced a slight but significant inhibition of the reflex amounting 22 ± 6%, while 10.0 μg/rat decreased the C-fiber response by 66 ± 15%. The dose of 25.0 μg/rat induced a strong depression of 91 ± 7%. The inhibitory effect of clomipramine on the reflex response was clearly dose-dependent (Fig. 5B). By contrast, desipramine induced an

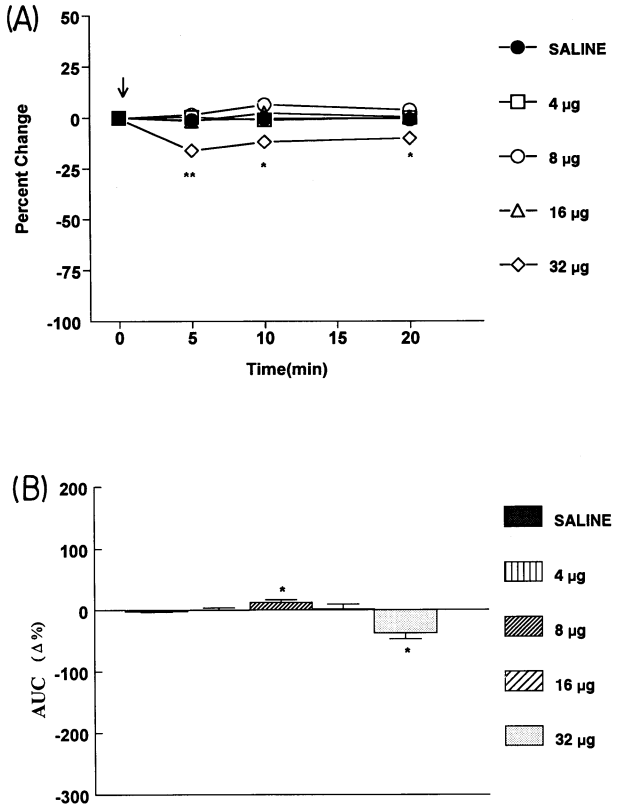

Fig. 3. Effect of intrathecal clomipramine administration on the C-fiber-evoked reflex. For all further explanations refer to Fig. 1.

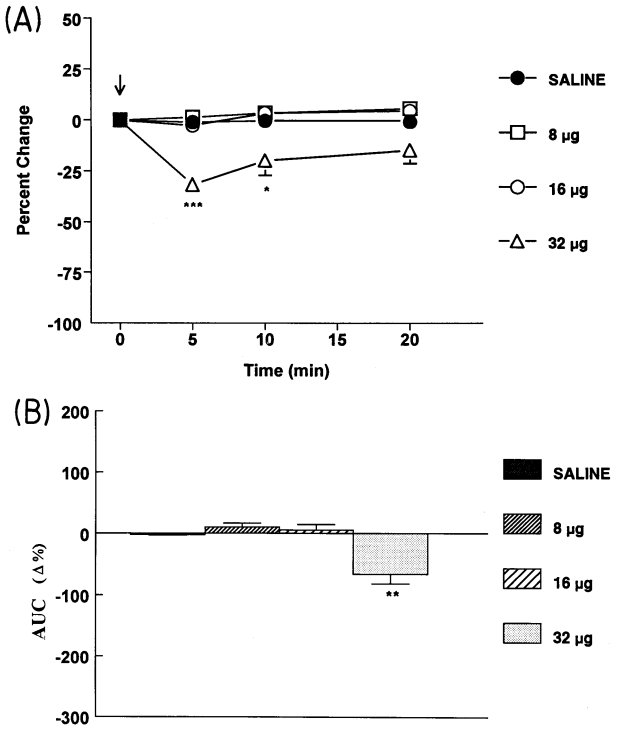

Fig. 4. Effect of intrathecal desipramine administration on the C-fiber-evoked reflex. For all further explanations refer to Fig. 1.

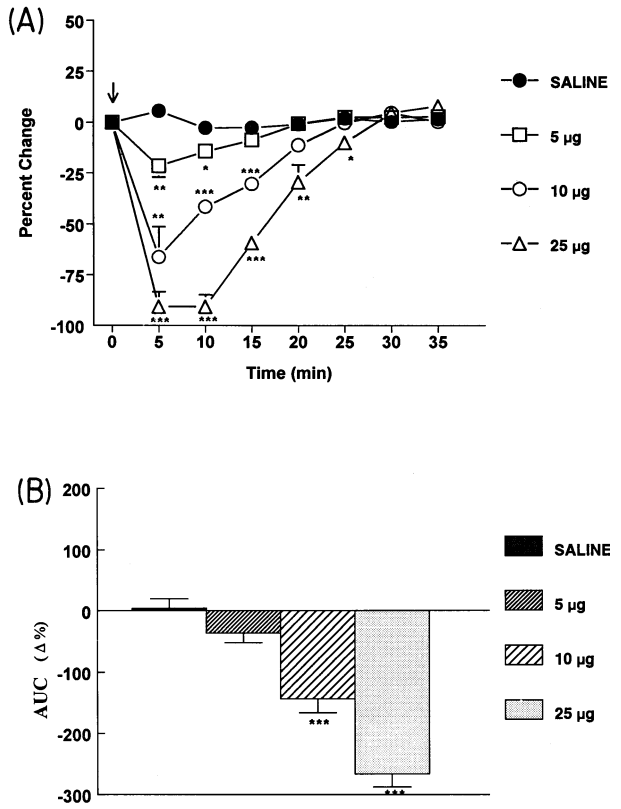

Fig. 5. Effect of intracerebroventricular clomipramine administration on the C-fiber-evoked reflex. For all further explanations refer to Fig. 1.

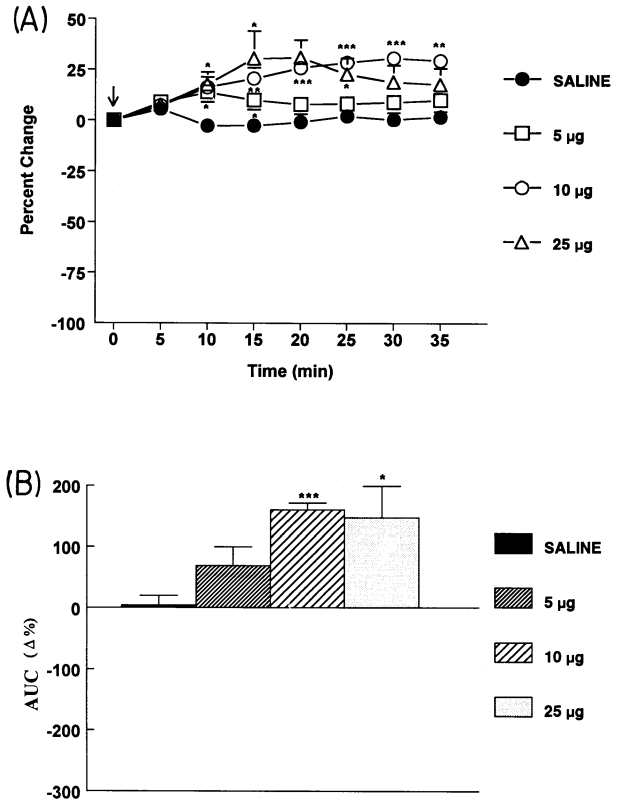

Fig. 6. Effect of intracerebroventricular desipramine administration on the C-fiber-evoked reflex. (A) Time-course of the increase of the C-reflex response (in percentage) after desipramine. The arrow indicates the time of desipramine injection. (B) Facilitatory effect of desipramine on the C-reflex activity, revealed by estimated areas under the curves (AUC). Each value indicates the mean percentage change as compared to the control. Values are means ± S.E.M. Stars represent a significant change in the C-reflex, when the values were compared to their respective values of the saline series. $^{*}P < 0.05$; $^{**}P < 0.01$; and $^{***}P < 0.001$ (non-paired Student's *t*-test).

increase of the C-fiber-evoked reflex activity. This facilitation amounted to 31% with doses of 10.0 and 25.0 µg/rat, while a smaller facilitation (14 ± 5%) was obtained with 5.0 µg/rat of desipramine (Fig. 6A). The effects induced by intracerebroventricular desipramine administration, expressed as summed scores over the total period of drug testing, are represented in Fig. 6B.

4. Discussion

As discussed elsewhere, electric stimulation of the sural nerve receptive field evokes a two-component reflex in the ipsilateral hindlimb flexor muscle, the fast and slow components being elicited by activation of myelinated and unmyelinated afferent fibers, respectively (Strimbu-Gozariu et al., 1993). The slow component is known as the C-fiber-evoked reflex, and involve activation of convergent neurons of the spinal cord.

The present results show that intravenous administration of tricyclic antidepressants resulted in a dose-dependent

decrease of the C-fiber reflex, indicating that these substances can depress the spinal nociceptive transmission. These results are in agreement with previous reports showing that systemic administration of tricyclic antidepressants in rats and mice induces antinociception against pain generated by different kinds of stimuli (Eschalier et al., 1988, 1992; Danysz et al., 1986; Michael-Titus and Costentin, 1987; Ardid et al., 1992). The doses employed in the present experiments were very close to those used for achieving analgesia in humans and far below the doses utilized in other experimental studies (Reichenberg et al., 1985; De Felipe et al., 1986; Sacerdote et al., 1987). This suggests that the antinociceptive mechanisms that participate in the C-fiber reflex depression reported here are relevant for tricyclic antidepressants-induced clinical analgesia.

The serotonin reuptake inhibition has been considered for many years as the principal mechanism underlying the antinociceptive effect of antidepressants drugs (Messing and Lytle, 1977; Loldrup et al., 1989; Imahita and Shimizu, 1992); but recent data have shown that noradrenaline reuptake inhibitors also exert important antinociceptive effects (Onghena and Van Houdenhove, 1992; Ardid et al., 1992). In the present study, both clomipramine and desipramine significantly depressed the C-fiber reflex after intravenous administration, although a 3-fold dose of desipramine was required to produce a similar inhibitory effect than clomipramine. Clinical studies have pointed out that oral administration of some new non-tricyclic serotonergic antidepressants exert modest (Sjaastad, 1983; Sindrup et al., 1990, 1992) or even no antinociceptive effects (Davidoff et al., 1987; Frank et al., 1988, Max et al., 1992). This is probably due to the fact that these studies have been carried out in patients with chronic pain, which is known to be rather refractory to analgesic drug medication. By contrast, recent data suggest that noradrenergic antidepressants are able to relieve pain in the same chronic pathologies (Max et al., 1992; Sindrup, 1994).

Experimental series utilizing intrathecal administration of tricyclic antidepressants revealed that only the higher dose employed of both clomipramine and desipramine (32.0 μg/rat) produced a depression of the C-fiber-evoked reflex. It can be noted, however, that the inhibitory effect of desipramine on the C-reflex was twice larger than that of clomipramine, in spite of the fact that the dose employed was the same for the two drugs. These observations are in agreement with previous reports showing that intrathecally administered desipramine has been reported to induce antinociceptive activity in mice (Hwang and Wilcox, 1987), while other tricyclic antidepressants with less noradrenergic selectivity failed in producing antinociception. In fact, amitryptiline (Larsen and Christensen, 1982; Botney and Fields, 1983; Taiwo et al., 1985), citalopram (Larsen and Christensen, 1982; Larsen and Arnt, 1984; Hwang and Wilcox, 1987), clomipramine (Ardid et al., 1991), fluoxetine and nortryptiline (Hwang and Wilcox, 1987), were all found to be inefficacious against experimentally-induced pain when administered to rats and mice by intrathecal route. In accordance with the present results it has been reported that a single oral dose of desipramine (noradrenergic selectivity), but not fluvoxamine (serotonergic selectivity) and moclobemide (dopaminergic selectivity), increased threshold for eliciting the R_{III} spinal reflex in healthy volunteers, a human nociceptive reflex quite similar to the rat C reflex. In turn, fluvoxamine changed the subjective perception of pain but not the evoked R_{III} reflex, suggesting a lack of spinal effect (Coquoz et al., 1991). Collectively, all these data suggest that blockade of noradrenaline uptake in the spinal cord seems to be more relevant for modulating C-input processing than blockade of serotonin uptake, at least in conditions of acute painful stimulation. Such an effect of tricyclic antidepressants with noradrenergic spectrum is consistent with the inhibitory action of iontophoretical administration of noradrenaline on nociceptive neurons of the spinal cord (Carlton et al., 1991), as well as with the antinociceptive activity of intrathecally administered α_2-adrenoreceptor agonists (Carlton et al., 1989; Fleetwood-Walker, 1992).

Intracerebroventricular administration of clomipramine produced a marked, dose-dependent inhibition of the C reflex response, the reflex being almost completely depressed after administration of the higher dose utilized. Comparable results have been described by other authors for tricyclic antidepressants with serotonergic profile. Spiegel et al. (1983) showed antinociception in the mouse writhing test after intracerebroventricular amitriptyline injection. Besides, it has been demonstrated that microinjection of zimelidine (serotonin uptake inhibitor) into the nucleus raphe magnus, a nucleus that is known to provide serotonergic innervation to the spinal cord (Sorkin et al., 1990), induces antinociceptive activity in the rat tail-flick test (Llewelyn et al., 1984). These observations suggest a supraspinal site of action for serotonin reuptake inhibitors, where these drugs may activate raphe-spinal serotonergic fibers. As it is known, the nucleus raphe magnus receives serotonergic innervation from the periaqueductal gray matter (Beitz, 1982), the ventral posterior lateral nucleus of the thalamus (Sorkin et al., 1992), as well as from other brain regions (Le Bars, 1988). Besides, administration of the 5-HT receptor antagonist LSD reduces the spontaneous activity of raphe neurons (Aghajanian et al., 1970), indicating that serotonergic innervation to these cells is excitatory. Recent studies of Ardid et al. (1995) showing that the antinociceptive effect of i.v. clomipramine is prevented by lesion of the dorsolateral funiculus of the spinal cord, give further support to the notion that tricyclic antidepressants with serotonergic profile induce antinociception by triggering supraspinal descending mechanism that ultimately inhibits noxious input at the spinal cord level.

By contrast, intracerebroventricular injection of desipramine resulted in facilitation of the C reflex. Increases

of the C-fiber response observed after i.c.v. desipramine exclude a supraspinal action to explain the antinociceptive effect of noradrenergic antidepressants, and strengthen the hypothesis of a spinal modulatory site for tricyclic antidepressants with noradrenergic selectivity. This is consistent with observations indicating that spinally projecting neurons located in the nucleus raphe magnus, which are known to participate in pain control in the spinal cord, are tonically inhibited by activation of noradrenergic neurons situated in the caudal part of the A5 catecholamine nucleus (Proudfit, 1988). In fact, there is evidence demonstrating that electrolytic lesion of the caudal part of the A5 group produces antinociception (Sagen and Proudfit, 1986), and that the microinjection of noradrenergic antagonists into the nucleus raphe magnus also induces antinociception (Hammond et al., 1980; Sagen and Proudfit, 1985). Thus, inhibition of the noradrenaline reuptake by i.c.v. desipramine could result in hyperalgesia by enhancing the inhibitory influences of the catecholaminergic terminals projecting to raphe magnus neurons, thereby resulting in decreased activity of the raphe-spinal system involved in pain control. It is interesting to remark that in the present experiments desipramine resulted in facilitation of the C-reflex response at lower i.c.v. doses than those used i.t. for inducing reflex inhibition, raising the question of how i.v. desipramine (the combination of the spinal and supraspinal effects of the drug) may result in a significant inhibitory effect on the reflex. A possible explanation for this result could be that reflex facilitation by i.c.v. desipramine is probably mediated through decreased activity of serotonergic bulbospinal pathways, as discussed above, while reflex inhibition by i.t. desipramine is possibly the result of increased noradrenergic control at the spinal cord level, both effects of desipramine being not necessarily additive. Whether the supraspinal facilitatory effect of desipramine on the C-reflex activity is involved in the lower antinociceptive efficacy displayed by this drug when administered i.v., as compared with clomipramine, remains unclear.

The fact that tricyclic antidepressants act mainly by increasing the availability of endogenous biogenic amines, which interact with several subtypes of receptors, makes it difficult to interpret the present results in terms of activation of a particular set of neurotransmitter receptors. In this regard, it is known that the main adrenoceptor underlying antinociception at the spinal cord level is the α_2 subtype (Howe et al., 1983; Takano and Yaksh, 1992), suggesting that the antinociceptive activity of tricyclic antidepressants with noradrenergic profile would be blocked by α_2-adrenoceptor antagonists. In turn, serotonergic excitation of brainstem neurons, the hypothesized primary action for the antinociceptive effect of tricyclic antidepressants with serotonergic profile, appears to be mediated by the 5-HT_2 receptor subtype (Davies et al., 1988), while 5-HT_{1B} and 5-HT_3 receptors seem to be involved in pain inhibition at the spinal cord (Cesselin et al., 1994). Thus, mechanistic interpretation of the monoamine receptor subtypes implicated in the antinociceptive effects of tricyclic antidepressants becomes very difficult, and further investigation employing intrathecal and intracerebroventricular administration of highly selective neurotransmitter receptor antagonists is required to elucidate these aspects.

In summary, the present results indicate that tricyclic antidepressants can depress C-fiber afferent processing at the spinal cord in anesthetized rats. In addition, they provide support to the hypothesis of a spinal level for antinociceptive actions of tricyclic antidepressants with noradrenergic spectra, and to a supraspinal mechanism for tricyclic antidepressants with serotonergic selectivity. Further studies are needed for a better understanding of the antinociceptive mechanisms of action of antidepressant drugs according to their spectra, especially in conditions of chronic pain, where neuronal plastic changes associated with persistent injury are known to modify the therapeutic potential of analgesic drugs.

Acknowledgements

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