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Evidence for an involvement of tachykinins in allodynia in streptozocin-induced diabetic rats

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Abstract

A better knowledge of the pathophysiology of chronic pain could help to improve the treatment of patients with such syndrome. The aim of the present work was to elucidate the possible involvement of spinal substance P and neurokinin A in the mechanical and thermal allodynia observed in streptozocin-induced diabetic rats. A tachykinin NK_1 receptor antagonist, RP-67,580 ((3aR,7aR) -7,7-diphenyl-2-(1-imino-2(2-methoxy phenyl)-ethyl) perhydroisoindol-4-one hydrochloride), a tachykinin NK_2 receptor antagonist, SR-48,968 ((*S*)-*N*-methyl (4-(acetylamino-4phenylpiperidino)-2-(3, 4-dichlorophenyl) butyl) benzamide) and their respective enantiomers were intrathecally administered 4 weeks after the induction of diabetes. Mechanical and thermal allodynia were evaluated before and up to 60 min after injection. The tachykinin receptor antagonists at the highest doses (10 and 25 μg) significantly reduced allodynia, their enantiomers being inactive. Both of these data suggest the involvement of substance P and neurokinin A in the neuropathy-induced allodynia and offer a novel hypothesis to treat chronic pain due to diabetes.

Keywords: Diabetic, rat; Allodynia, tactile; Allodynia, thermal; Tachykinin receptor antagonist

1. Introduction

It has been shown that streptozocin-induced diabetic rats develop not only progressive hyperalgesia to mechanical (Ahlgren et Levine, 1993; Coudoré-Civiale et al., 1998; Courteix et al., 1993), thermal (Courteix et al., 1993; Lee and McCarty, 1992) or chemical stimuli (Calcutt et al., 1995; Courteix et al., 1993; Malmberg et al., 1993), but also, allodynia to mechanical (Calcutt et al., 1996) or thermal (Courteix et al., 1993) stimuli. These symptoms are similar to those generally observed in diabetic patients with painful peripheral neuropathy (Malmberg et al., 1993). On the other hand, the treatment of these troubles is not based on knowledge of the pathophysiology of diabetic neuropathy pain. We assume that a better knowledge of this pathophysiology could lead to new pharmacological approaches.

Some data seem to suggest an involvement of the substance P-ergic system in these troubles (Coudoré-Civiale et al., 1998). An up-regulation of substance P binding sites in the spinal cord of diabetic rats has been shown (Kamei et al., 1990). The sensitization of dorsal horn neurones during chronic pain is induced by enhanced activity of C-fibres that release glutamate and substance P (Field et al., 1998). However, Garrett et al. (1997) and Malcangio and Tomlison (1998) failed to observe any increase of the release of substance P in the spinal cord. In a previous work, Courteix et al. (1993) have shown a reduction of mechanical hyperalgesia after subcutaneous injection of a tachykinin NK_1 receptor antagonist in diabetic rats and, in the same way, we have shown a reduc-

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tion of mechanical hyperalgesia after intrathecal administrations of tachykinin NK_1 and NK_2 receptor antagonists in diabetic and mononeuropathic rats, which suggests a maintained stimulation of the substance P-ergic system during neuropathic pain, whether of metabolic or of compressive etiology (Coudoré-Civiale et al., 1998). However, the pharmacological sensitivity of diabetes-induced allodynia to tachykinin receptor antagonists has never been investigated. Only lidocaine (Kastrup et al.,1987) and aldose–reductase inhibitors (Calcutt et al., 1996) have been shown effective on diabetes-induced allodynia.

The aim of this study was, firstly, to follow the development of mechanical allodynia in diabetic rats and, secondly, to appreciate the sensitivity of mechanical and thermal allodynia to non-peptide tachykinin NK_1 and NK_2 receptor antagonists. Their effect was compared to that of their respective enantiomer to eliminate a possible non-specific effect like a Ca^{2+}-channel inhibitory effect, described for RP-67,580 and its enantiomer RP-68,651 (Rupniak et al., 1993).

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (Charles River, France) initially weighing 175–200 g were housed five per cage under standard laboratory conditions and allowed food and water ad libitum as outlined in the 'NIH Guide for the Care and Use of Laboratory Animals' (National Institute of Health Publication, No. 85-23, Revised 1985). Great care was taken, particularly with regard to housing conditions, to avoid or minimize discomfort to the animals. The animals were kept on solid floored cages with a deep layer of sawdust to accommodate the excess of urination and cages were changed daily.

2.2. Induction of diabetes

Animals were intraperitoneally injected with streptozocin (75 mg/kg) (Zanosar®, Upjohn, France) dissolved in distilled water.

Diabetes was confirmed 1 week later by measurement of tail blood glucose levels with Ames Dextrostix and a reflectance colorimeter (Ames Division, Miles Laboratories, France). Blood samples were obtained from the tail by pinprick and only animals with a final blood glucose level > 14 mM were included in this study. Control (normal) rats received only distilled water.

2.3. Pain behaviour testing

2.3.1. Assessement of mechanical allodynia

Rats were individually placed on an elevated plastic mesh (1 cm^2 perforations) in a clear plastic cage and were adapted to the testing environment for at least 15 min. Von Frey hairs (Semmes–Weinstein monofilaments, Stoelting IL, USA) with calibrated bending forces (1.479, 2.041, 3.63, 5.495, 8.511, 11.749, 15.136 and 28.84 g) were used to deliver punctuate mechanical stimuli of varying intensity. The von Frey hairs were applied to the plantar surface of each hindpaw, from below the mesh floor. Each stimulus was applied for a duration of approximately 1 s with an interstimulus interval of approximately 5 s. Care was taken to stimulate random locations on the plantar surface. Withdrawal responses evoked by each monofilament were obtained from five consecutive trials. Voluntary movement, associated with the locomotion, was not counted as a withdrawal response. Only robust and immediate withdrawal responses from the stimulus were considered. Mechanical allodynia was defined as a significant decrease in withdrawal thresholds to von Frey hair application. The 28.84-g hair was selected as the upper limit cut-off for testing.

2.3.2. Assessement of thermal allodynia

The tail of the rats was immersed in a water bath maintained at 42°C (a temperature that is normally innocuous in normal rats (Courteix et al., 1993)) until tail withdrawal or signs of struggle were observed (cut-off time: 15 s). A shortened duration of immersion indicates allodynia.

2.4. Drugs

The following antagonists and their respective enantiomer were used (generous gifts from companies): RP-67,580 ((3aR,7aR) -7,7-diphenyl-2-(1-imino-2(2-methoxy phenyl)-ethyl) perhydroisoindol-4-one hydrochloride) (molecular weight: 438.57 g), a potent and selective non-

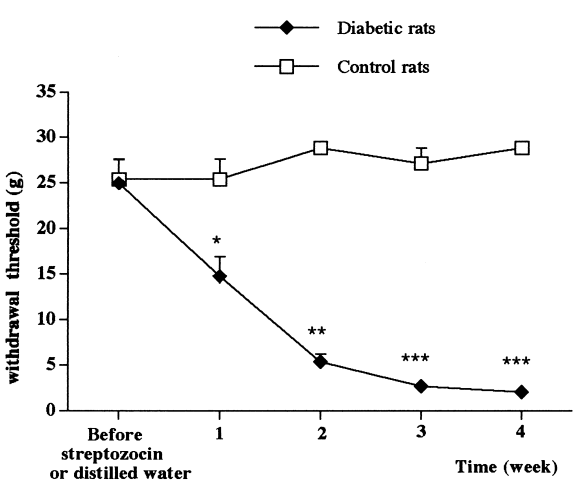

Fig. 1. Time-course of von Frey hair (VFH) thresholds in diabetic and normal rats ($n = 8$), determined before streptozocin or distilled water injection (0) and once a week during 4 weeks after streptozocin injection. Vertical bars represent the standard error of the mean. $n = 8$ animals for each treatment group. $^{*}P < 0.05$; $^{**}0.01 < P < 0.05$; $^{***}P < 0.001$ vs. pre-injection value.

peptide tachykinin NK_1 receptor antagonist (Garret et al., 1992) and its enantiomer: RP-68,651 (Rhône–Poulenc Rorer, France) were dissolved in an aqueous solution (1%) of methane sulfonic acid; SR-48, 968 ((*S*)-*N*-methyl (4-(acetylamino-4phenylpiperidino)-2-(3, 4-dichlorophenyl) butyl) benzamide) (molecular weight: 552 g), a competitive and highly selective non-peptide tachykinin NK_2 receptor antagonist (Emonds-Alt et al., 1992; Maggi et al., 1993) and its enantiomer: SR-48, 965 (Sanofi, France) were dissolved in distilled water.

Drugs or vehicle were intrathecally injected in a volume of 10 μl in the subarachnoid space between (L_5–L_6) according to the method described by Mestre et al. (1994).

2.5. Experimental design

2.5.1. Assessment of allodynia

Thresholds to tactile stimulus were assessed before and once a week for 4 weeks after streptozocin (diabetic rats) or distilled water (control rats) injection. Thermal allodynia was only assessed at the fourth week of diabetes.

2.5.2. Pharmacological experiments

Four weeks after streptozocin injection, allodynic diabetic rats (i.e. rats in which an aversive reaction is observed after the application of a non-painful tactile or thermal stimulus) were submitted to the test before the injection of:

- RP-67,580 (0.1, 1, 10 and 25 μg) or RP-68,651 (10 and 25 μg), and
- SR-48,968 (0.1, 1, 10 and 25 μg) or SR-48,965 (10 and 25 μg).

The doses of the drugs were chosen according to the literature data (Chapman and Dickenson, 1993; Picard et

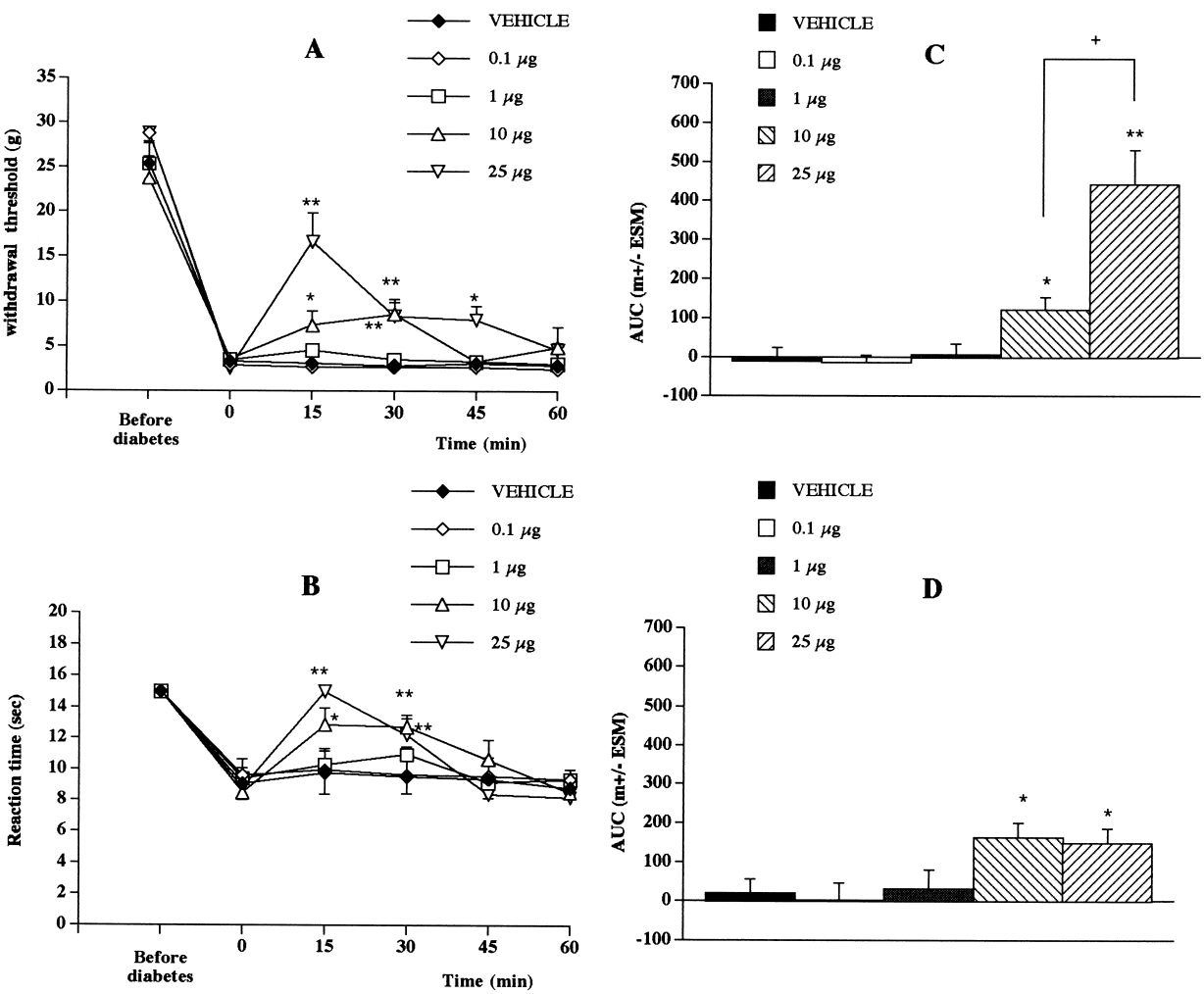

Fig. 2. Effect of various doses of i.t.-administered RP-67,580, a non-peptide NK_1 receptor antagonist in diabetic rats submitted to a mechanical ((A) von Frey hair) or a thermal ((B) tail immersion) innocuous stimulus. Withdrawal thresholds or reaction time, determined before (0) and after drug injection, are expressed as grams (g) or as seconds (s), respectively. $^{*}P < 0.05$ vs. predrug value. (C and D) Results are expressed A.U.C. for mechanical and thermal allodynia, respectively. $^{*}P < 0.05$ vs. values obtained after vehicle; $^{+}P < 0.05$ vs. values obtained after different doses (Student's *t*-test in unpaired series). Vertical bars represent the standard error of the mean. $n = 8$ animals for each treatment group.

al., 1993; Yashpal et al., 1996). The von Frey hair thresholds and tail immersion duration were measured each 15 min for 60 min following the injections.

All the experiments were performed blind, using the method of equal blocks ($n = 8$ rats per treatment) to avoid uncontrollable environmental or chronobiological influence and to allow to compare, in the same laps of time, the effect of the different treatments tested. A block corresponds to a group of n animals, each being treated in the same time lapse by either the vehicle or the different drugs or doses of drugs tested (n animals for n treatment). Such a method avoid any period effect due to uncontrollable environment and/or chronobiological influence, and therefore, allows to compare the effects of the different treatments tested with more accuracy.

2.6. Statistical analysis

The paw withdrawal thresholds (g) and the reaction times for tail withdrawal (s) (tail immersion test) were expressed as mean ± S.E.M. To analyse the time-course of the mechanical allodynia, differences between groups were assessed using the Mann–Whitney U-test.

The mean area under the time course curves (A.U.C.) (to neutralize the pre-drug values variations, individual values used for calculation are: postdrug value−predrug value) was calculated by the trapezoidal rule using the program Siphar/Win (1-2b, SIMED, Créteil, France). A Student's t-test was performed to compare the effect of each treatment expressed as A.U.C.

The significance level was set at $P < 0.05$.

3. Results

3.1. Time-course of mechanical allodynia

Prior to the injection of streptozocin or distilled water, the mean withdrawal thresholds to von Frey hair application were 24.99 ± 2.54 g.

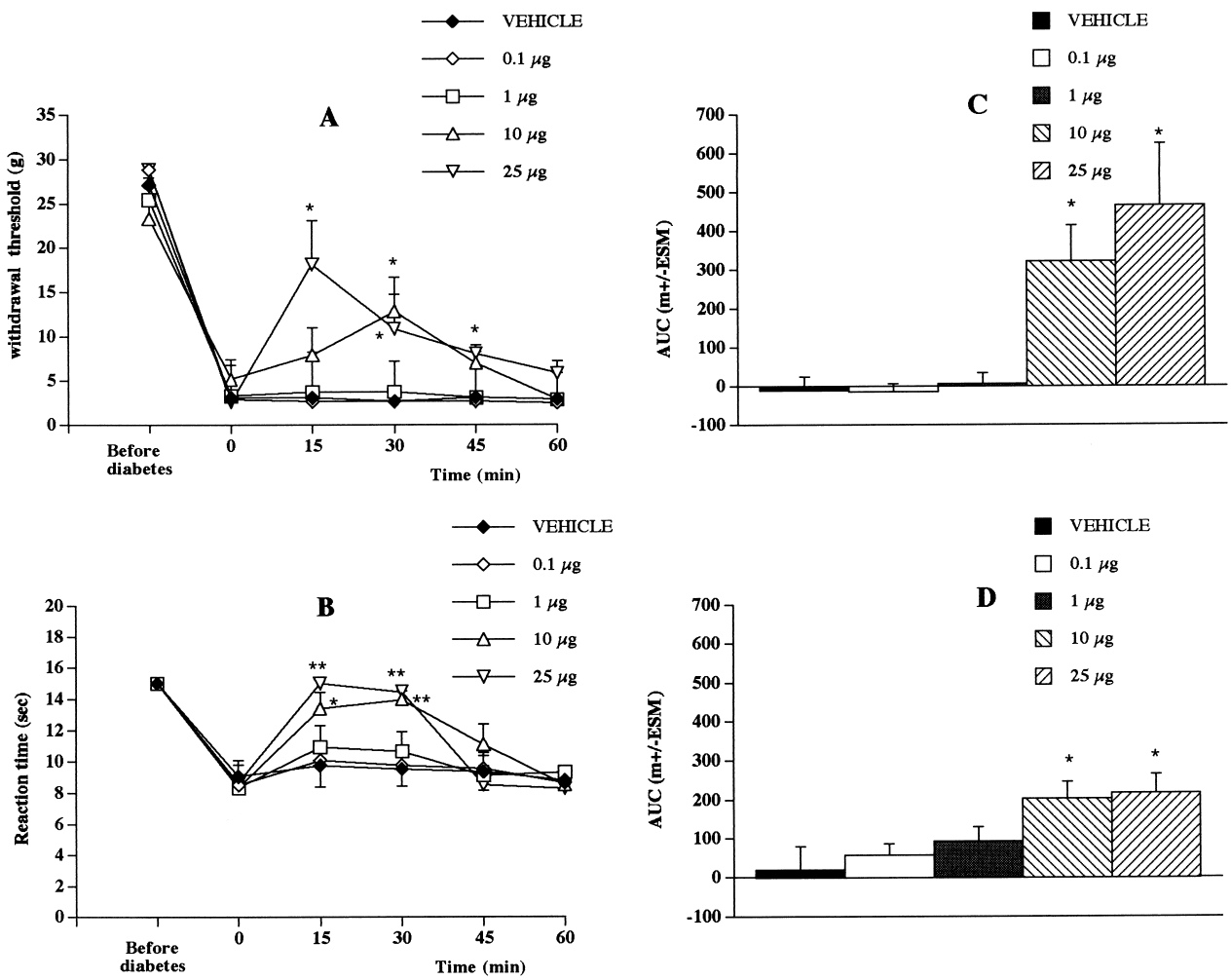

Fig. 3. Effect of various doses of i.t.-administered SR-48,968, a non-peptide NK_2 receptor antagonist, in diabetic rats submitted to a mechanical ((A) von Frey hair) or a thermal ((B) tail immersion) innocuous stimulus. Withdrawal thresholds or reaction time, determined before (0) and after drug injection, are expressed as grams (g) or as seconds (s), respectively. $^{*}P < 0.05$ vs. predrug value. (C and D) Results are expressed as A.U.C. for mechanical and thermal allodynia, respectively. $^{*}P < 0.05$ vs. scores obtained with vehicle. Vertical bars represent the standard error of the mean. $n = 8$ animals for each treatment group.

In control rats, the responses to von Frey hair application remained stable during the 4 weeks of experiment. In diabetic rats, the withdrawal thresholds were significantly lower than the pre-injection values, from the first week following the injection of streptozocin (14.75 ± 2.18 g, $P < 0.05$), and they progressively decreased until the week 4 (2.041 ± 0 g; $P < 0.0001$) (Fig. 1).

3.2. Thermal allodynia in diabetic rats (data not shown):

Streptozocin induced a significant reduction in the reaction time vs. control group ($P < 0.01$) on the fourth week of diabetes (8.83 ± 1.00 vs. 15 ± 0 s).

3.3. Effect of tachykinin NK_1 and NK_2 receptor antagonists

3.3.1. Tachykinin NK_1 receptor antagonist

The two highest doses of RP-67,580 (10 and 25 μg) dose-dependently and significantly increased the von Frey hair withdrawal thresholds for 15–45 min according to the dose. The maximal effect was observed 15 and 30 min after injections and corresponded to von Frey hair withdrawal thresholds of 16.65 ± 3.23 ($P < 0.01$) and 8.56 ± 1.73 g ($P < 0.01$) for 25 and 10 μg, respectively (Fig. 2A). However, the highest dose failed to reverse the mechanical allodynia. As shown in Fig. 2C, the global effect of RP-67,580 at 10 and 25 μg, as assessed by A.U.C.s, was significantly higher than that of vehicle or of the other doses.

Similarly, in the tail immersion test (Fig. 2B), RP-67,580 was only effective for the doses of 10 and 25 μg: the maximal scores obtained (at 15 min) were 12.9 ± 1.1 ($P < 0.05$) and 15 ± 0 s ($P < 0.01$), respectively. The effect observed with the highest dose corresponds to a total reversion of thermal allodynia. Comparing the A.U.C.s, the global effect of the dose of 10 μg was not statistically different from that of the dose of 25 μg (Fig. 2D).

The enantiomer RP-68,651 (10 and 25 μg) was inactive on both the von Frey hair and the tail immersion tests (data not shown).

3.3.2. Tachykinin NK_2 receptor antagonist

SR-48,968 was ineffective at doses of 0.1 and 1 μg but significantly increased the von Frey hair withdrawal thresholds at the highest doses (Fig. 3A). The maximal thresholds were obtained 30 and 15 min after injection for 10 (12.81 ± 3.79 g, $P < 0.05$) and 25 μg (18.14 ± 4.95 g, $P < 0.05$), respectively. However, mechanical allodynia was not suppressed by the dose of 25 μg. Expressed as A.U.C.s (Fig. 3C), the effect of 25 μg was not statistically different from that of 10 μg.

The tail immersion duration (Fig. 3B) was also significantly increased after 10 (maximal effect: 13.99 ± 0.53 s, $P < 0.01$) and 25 μg (maximal effect: 15 ± 0 s, $P < 0.01$) of SR-48,968. The dose of 25 μg induced a total suppression of thermal allodynia. The global effect expressed as A.U.C.s was not statistically different for 10 vs. 25 μg.

The enantiomer SR 48965 was inactive on the two tests (data not shown).

4. Discussion

Allodynia following the cutaneous application of mechanical, warm or cool stimuli were previously observed after a chronic constrictive injury of the sciatic nerve in rats (Bennett, 1994). In our study, we showed that streptozocin-induced diabetic male rats presented a marked tactile allodynia when submitted to light touch to plantar hindpaw while normal rats were insensitive to this stimulus. It was notable within the first week of diabetes and remained for up to 4 weeks with worsening of the trouble from the second week. The maximal decrease of withdrawal thresholds was 87% vs. baseline values. A similar time-course of tactile allodynia using the von Frey hairs was described by Calcutt et al. (1996) in female diabetic rats. Thermal allodynia to warm stimulus (42°, innocuous stimulus) was also observed at the fourth week of diabetes as previously described (Courteix et al., 1993).

Mechanisms of these troubles are complex and remain to be more elucidated, and so we investigated in this work the possible role of substance P and neurokinin A released by the Aδ and C fibres, and possibly, by the low threshold, wide diameter Aβ fibres. These Aβ fibres are known to be activated by an innocuous stimulation, which induces a noxious response in neuropathic conditions (Devor, 1996). However, previous studies have shown that the Aβ fibres, which normally respond to tactile stimuli, exhibit electrophysiological properties, such as conduction velocity, not altered in diabetic neuropathy (Ahlgren et al., 1992). In the same way, there were no spontaneous discharges or change in the sensitivity of C fibres to von Frey filaments under the same experimental conditions (Ahlgren et al., 1992, 1997). On the other hand, axonal dystrophy was reported at the peripheral nerve terminals in the interosseus muscle of diabetic rats (Jirmanova, 1993). Morphological evidence of nerve fibre disruption in the spinal roots of diabetic rats was also shown (Tamura and Parry, 1994). In addition, the Aβ fibres are known to be able to more express different neuropeptides, notably, substance P, following peripheral nerve injury (Willis and Coggeshall, 1991; Hökfelt et al., 1994). More recently, Field et al. (1998) have shown that a sensitization of the dorsal horn neurones during chronic pain was induced by an enhanced activity of C-fibres that release substance P and glutamate. Nevertheless, the role of substance P is still unclear in diabetic neuropathy. It has been reported that substance P-like immunoreactivity was decreased in the sciatic nerve and spinal cord (Kamei et al., 1990; Brewster et al., 1994), and that there was an up-regulation of the

substance P binding sites in the spinal cord of diabetic rats (Kamei et al., 1991). On the other hand, Kamei et al. (1991) have shown that K^+ can evoke an excessive release of substance P-like immunoreactivity from the spinal cord in diabetic rats. In addition, no loss of myelinated or unmyelinated fibres or evidence of regenerative clusters were observed in the sciatic nerve of diabetic rats (Sharma and Thomas, 1974), suggesting that tactile allodynia in this model was not related to a nerve degeneration or regeneration per se. However, Leem et al. (1993) have proposed that changes in the sensory properties in the rat foot may be involved in tactile allodynia in rats with experimental peripheral neuropathy. Taken together, as suggested by Calcutt et al. (1996), all these factors might induce tactile allodynia in diabetic rats by a process of degeneration and regeneration at the nerve endings.

In this study, we demonstrated the involvement of substance P and neurokinin A. Effectively, the blockade of spinal tachykinin NK_1 and NK_2 receptors was able to reduce and suppress both mechanical and thermal allodynia, respectively, in diabetic animals. Furthermore, the maximal effect obtained with the highest dose (25 μg) of the tachykinin NK_1 and the NK_2 receptor antagonists corresponds to a total reversion of the thermal allodynia while the mechanical allodynia was only reduced with the same dosage, suggesting a differential involvement of the two tachykinins, according to the applied stimulus. The implication of NK_1 acting tachykinins in allodynia was also observed by Ma and Woolf (1995), who have reported that the tachykinin NK_1 receptor antagonist RP 67580 prevented both the threshold decrease and the enhancement of the normally absent touch-evoked response of spinal flexor motoneurones in decerebrate-spinal rats, suggesting that the induction of the mechanical allodynia by cutaneous afferences depends on NK_1 receptor activation. In a model of inflammation, Neumann et al. (1996) have shown that RP-67,580 significantly attenuated the degree of progressive allodynia elicited by a tactile stimulation of the inflammed hindpaw. In the same way, Field et al. (1998) reported that CI 1021, a central selective tachykinin NK_1 receptor antagonist, dose-dependently blocked the hypersensitivity induced by activation of central NK_1 receptors in diabetic rats. Taken together, all these results suggest that the tachykinin NK1 receptors may be involved in allodynia.

Concerning the involvement of the NK_2 receptors, it was known that some afferent fibres contained substance P alone, whereas others contained both substance P and neurokinin A, which may co-exist with other peptides such as calcitonin gene-related peptide (Weihe, 1990), and also, with excitatory amino acids (Duggan and Weihe, 1991). Neurokinin A could play in a cooperative way an inducing role in central sensitization like substance P and the activation of AMPA receptors seem to act on NMDA receptors-mediated transmission. Nevertheless, other works are needed to better define these mechanisms.

To conclude, diabetic rats develop alterations of tactile perception characterised by a rapid onset and a tendency to worsen as a function of duration of diabetes. These changes concomitant with thermal allodynia and hyperalgesia confirm the interest of this animal model of metabolic neuropathic pain in reproducing clinical symptoms observed in human diabetes (Watkins, 1990). The anti-allodynic effect of tachykinin NK_1 and NK_2 receptor antagonists suggests the involvement of substance P and neurokinin A in allodynia with a lower degree than in hyperalgesia (Coudoré-Civiale et al., 1998). These results offer new data for the understanding of the pathophysiology of diabetes-induced pain, which could help to a different therapeutic stategy of diabetic patients with painful neuropathy.

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