Evaluation of Selective NK\textsubscript{1} Receptor Antagonist CI-1021 in Animal Models of Inflammatory and Neuropathic Pain

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ABSTRACT

CI-1021 ([(2-benzofuran)-CH\textsubscript{2}OCO]-((R)-\alpha-\text{MeTrp}-(S)-NHCH(CH\textsubscript{3})Ph}) is a selective and competitive neurokinin-1 (NK\textsubscript{1}) receptor antagonist. This study examines its activity in animal models of inflammatory and neuropathic pain. In mice, CI-1021 (1–30 mg/kg, s.c.) dose dependently blocked the development of the late phase of the formalin response with a minimum effective dose (MED) of 3 mg/kg. Two chemically unrelated NK\textsubscript{1} receptor antagonists, CP-99,994 (3–30 mg/kg) and SR 140333 (1–100 mg/kg), also dose dependently blocked the late phase, with respective MEDs of 3 and 10 mg/kg. PD 156982, a NK\textsubscript{1} receptor antagonist with poor central nervous system penetration, failed to have any effect. However, when administered i.c.v., it selectively blocked the late phase of the formalin response. Chronic constrictive injury (CCI) to a sciatic nerve in the rat induced spontaneous pain, thermal and mechanical hyperalgesia, and cold, dynamic, and static allodynia. CI-1021 (10–100 mg/kg) and morphine (3 mg/kg) blocked all the responses except dynamic allodynia. Carbamazepine (100 mg/kg) was weakly effective against all the responses. Once daily administration of morphine (3 mg/kg, s.c.) in CCI rats led to the development of tolerance within 6 days. Similar administration of CI-1021 (100 mg/kg, s.c.) for up to 10 days did not induce tolerance. Moreover, the morphine tolerance failed to cross-generalize to CI-1021. CI-1021 blocked the CCI-induced hypersensitivity in the guinea pig, with a MED of 0.1 mg/kg, p.o. CI-1021 (10–100 mg/kg, s.c.) did not show sedative/ataxic action in the rat rota-rod test. It is suggested that NK\textsubscript{1} receptor antagonists possess a superior side effect profile to carbamazepine and morphine and may have a therapeutic use for the treatment of inflammatory and neuropathic pain.

The tachykinin neuropeptides, substance P and neurokinin A, are colocalized in capsaicin-sensitive high threshold nociceptive sensory afferents. They are released by a wide variety of noxious stimuli from these neurones. Substance P is the preferred endogenous ligand for the neurokinin-1 (NK\textsubscript{1}) receptor (Maggi et al., 1993). This receptor type is widely distributed in specific regions of the central nervous system (CNS; Kiyama et al., 1993). In the spinal cord, NK\textsubscript{1} binding sites are distributed throughout the dorsal (particularly laminae I and II) and ventral horn (Yashpal et al., 1990). For some time, the potential role of substance P as a mediator of pain has received a major interest. The main reason for this has been the discovery of nonpeptide, highly selective NK\textsubscript{1} receptor antagonists with the ability to penetrate the CNS. Several studies have reported that such compounds are active in animal models of inflammatory (Levine et al., 1984; Yamamoto et al., 1993; Seguin et al., 1995) and neuropathic (Coudoré-Civiale et al., 1998; Cumberbatch et al., 1998) pain. Several distinct behavioral signs considered to be representative of pain can be observed in animals after tissue or nerve injury. However, most studies to date have examined effects of NK\textsubscript{1} receptor antagonists in these models on only few of these signs. Therefore, the full profile of these compounds in animal models of pain remains unclear.

CI-1021 (previously, PD 154075) is a selective NK\textsubscript{1} receptor antagonist. It possesses nanomolar affinity for human and guinea pig NK\textsubscript{1} receptors. However, it has approximately 300 times lower affinity for the rodent NK\textsubscript{1} receptor (Singh et al., 1997). We have previously reported that CI-1021 is active in rat models of surgical (Gonzalez et al., 1998) and neuropathic (Field et al., 1998) pain. This study further characterizes the role of NK\textsubscript{1} receptors in inflammatory and neuropathic pain states by addressing several issues. First, we evaluate and compare the profile of chemically different classes of NK\textsubscript{1} receptor antagonists in a model of inflammatory pain and also examine their site of action. Second, we assess the activity of CI-1021 against a wide range of behavioral signs induced by nerve injury and compare it with other compounds currently used in the clinic (carbamazepine, morphine). Third, our study addresses the possible development of tolerance to the antiallodynic action of CI-1021.

ABBREVIATIONS: NK\textsubscript{1}, neurokinin-1; CCI, chronic constriction injury; MED, minimum effective dose; PEG200, polyethylene glycol 200; PHN, postherpetic neuralgia; PWL, paw withdrawal latency; CI-1021, [(2-benzofuran)-CH\textsubscript{2}OCO]-((R)-\alpha-\text{MeTrp}-(S)-NHCH(CH\textsubscript{3})Ph); CNS, central nervous system.
Materials and Methods

Animals

Male Sprague-Dawley rats (70–90 g) and male BKTO mice (20–25 g) were obtained from Bantin and Kingman, (Hull, UK) and used in the rota-rod and formalin tests. Male Sprague-Dawley rats (180–220 g) were also obtained from Charles River (Margate, UK) and used for the chronic constriction injury (CCI) model. Male Dunkin Hartley guinea pigs (200–250 g) were obtained from Harlan Olac (Blackthorn, UK). Rats, guinea pigs, and mice were housed, respectively, in groups of 6, 4 to 6, and 10 to 12 under a 12-h light/dark cycle (lights on at 7:00 AM) with food and water ad libitum.

Surgery

The CCI was induced in rats as previously described (Bennett and Xie, 1988). Briefly, rats were anesthetized with 60 mg/kg i.p. sodium pentobarbital (Sagatal; Rhone Merieux, distributed in the UK by National Vet. Suppl. Ltd., Stoke-on-Trent, UK). Guinea pigs were anesthetized with Hypnorm (1 ml/kg, i.m., containing 0.315 mg fentanyl citrate and 10 mg fluanisone/ml; Janssen, distributed in the UK by National Vet. Suppl. Ltd.) plus diazepam (2.5 mg/kg, i.p.). The common left sciatic nerve was exposed at the level of the middle of the thigh by blunt dissection through biceps femoris and proximal to the sciatic trifurcation. Four ligatures (4.0 braided silk) were tied loosely around it with about 1-mm spacing. The muscle was closed in layers and two wound clips were applied to close the skin incision. The wound was then covered with topical antibiotics (rat) or iodine and chloramine-T powder (guinea pig).

Behavioral Tests

Formalin Test. Mice were habituated to perspex observation chambers (24 cm × 24 cm × 24 cm) for at least 15 min before testing. Formalin-induced hind paw licking and biting was initiated by a 20-μl s.c. injection of a 5% formalin solution into the plantar surface of the left hind paw. Immediately after the formalin injection, licking/biting of the injected hind paw was scored in 5-min bins for 60 min. The results are expressed as mean combined licking/biting time for the early phase (0–10 min) and late phase (10–45 min).

Spontaneous Pain. CCI rats were individually placed in perspex observation chambers (24 cm × 24 cm × 24 cm). A mirror was placed behind the box to aid observation, and animals were habituated for 5 min. Spontaneous pain was scored for 5 min as described previously by Choi et al. (1994). The test consisted of noting the cumulative duration that the rat holds its ipsilateral paw off the floor. The paw lifts associated with locomotion or body repositioning were not counted. It has been suggested that the foot lifts off a neutral temperature surface, in the absence of any overt external stimuli, are a form of the paw withdrawal reflex that is associated with spontaneous pain, and are correlative of ongoing pain (Choi et al., 1994).

Thermal Hyperalgesia. Thermal hyperalgesia was assessed using the rat plantar test (Ugo Basile, Comerio, Italy) following a modified method of Hargreaves et al. (1988). The test was started after the rat was habituated to the apparatus that consisted of three individual perspex boxes on a glass table. A mobile radiant heat source was located under the table and focused onto the desired paw; paw withdrawal latencies (PWLs) were recorded. PWLs weere taken three times for both hind paws of each animal, the mean of which represented baselines for right and left hind paws. The apparatus was calibrated to give a PWL of approximately 10 s.

Static Alldynia. Rats were placed into wire mesh-bottomed cages allowing access to the underside of their paws. They were habituated to this environment before the start of the experiment. Static allodynia was tested by touching the plantar surface of hind paws with von Frey hairs (Stoelting, Wood Dale, IL) in ascending order of force (0.7, 1.2, 1.5, 2, 3.6, 5.5, 8.5, 11.8, 15.1, and 29 g) for up to 6 s. When a withdrawal response was established, the paw was retested, starting with the next descending von Frey hair until no response occurred. The highest force of 29 g lifted the paw as well as elicited a response, and represented the cut off point. The lowest amount of force required to elicit a response was recorded as the paw withdrawal threshold in grams.

Mechanical Hyperalgesia. The plantar surface of the hind paws was touched with the point of a safety pin. The duration of the normal pinprick-evoked hindpaw withdrawal was too short to time with a stopwatch and was arbitrarily assigned a duration of 0.5 s. The hyperalgesic response seen ipsilateral to the nerve injury was much longer and easy to time. We defined a withdrawal as being abnormally prolonged if it lasted at least 2 s. A cut-off of 15 s was applied to long withdrawals, many of which lasted for over 1 min.

Cold Alldynia. Rats were placed into wire mesh bottom cages (allowing access to the underside of their paws). The cage was then placed 10 mm deep into a water bath kept at 10°C. This allowed immersion of the paws only, without struggle or evidence of stress. The immersion lasted for a maximum of 15 s. The withdrawal latency was measured. This temperature is considered to be non-noxious and normal rats do not exhibit paw withdrawal over a 15-s period.

Dynamic Alldynia. Dynamic allodynia was assessed by lightly stroking the plantar surface of both hind paws with a cotton bud (Field et al., 1999a,b). Latency to paw withdrawal was noted. Two to three measurements were taken at each time point. If no paw withdrawal was shown within 15 s, the procedure was terminated and animals were assigned this withdrawal time. Thus, 15 s effectively represents no withdrawal. A withdrawal response was often accompanied with repeated flinching or licking of the paw. Animals were only selected for drug study if they exhibited a withdrawal time of 8 s or under.

Weight Bearing. Guinea pigs with CCI were tested for hypersensitivity in the weight-bearing test, using an “Incapacitance tester” (Linton Instruments, Norfolk, UK). Briefly, the animal was placed in the apparatus, and the weight load exerted by the hind paws was noted. The duration of the measurement was adjusted to 4 s. Three measurements were taken at 60-s intervals and the mean was calculated.

Rota-Rod. Male Sprague-Dawley rats (70–90 g) were trained to stay on an accelerating rota-rod (Ugo Basile) for 2 min. On the next day, animals were retested after s.c. administration of CI-1021 (10–100 mg/kg) or diazepam (10 mg/kg) 0.5 h before the test.

Chronic Administration of CI-1021. Two groups of CCI rats were subjected to daily dosing of CI-1021 (100 mg/kg, s.c.) or vehicle (polyethylene glycol 200 (PEG200), 1 ml/kg) over 12 days from postoperative day 10. Each animal was tested for static allodynia using Von Frey hairs before and 30 min after drug administration to assess the possible development of tolerance. Two separate groups of CCI rats were subjected to daily dosing with morphine (3 mg/kg, s.c.) or saline (1 ml/kg) over 6 days from day 10. They were also tested every day before and 30 min after treatments for static allodynia for development of tolerance. On day 7, the morphine chronically treated animals received CI-1021 (100 mg/kg, s.c.) and static allodynia was reassessed 30 min after to assess the possible cross-generalization of opiate tolerance to CI-1021.

Drugs Used

CI-1021 ([2-benzofuran]-CH2OCO)R-o-Me-Trp-(S)-NHCH2Ph was synthesized at Parke-Davis Neuroscience Research Center (Cambridge, UK). CP-99,994 and SR 140333 were synthesized at Gödecke AG, Freiburg. CI-1021 was dissolved in PEG200 (Sigma, UK) for s.c. administration, or in Gelucire 44/14 (Gateffosse, France) for oral administration. CI-1021 was administered under brief isoflurane anesthesia in guinea pigs. PD 156942 was synthesized at Parke-Davis Neuroscience Research Center. It was dissolved in PEG200 for s.c. administration and in 20% hydroxypropyl-β-cyclodextrin for i.c.v. administration (Singh et al., 1990). CP-99,994 and SR 140333 were dissolved, respectively, in saline and distilled water containing 1% Tween 80. All drugs were administered 30 min before injection of formalin, except SR 140333, which was administered 1 h before injection of formalin.
before formalin. Morphine sulfate was obtained from Savory and Moore (Cambridge, UK) and dissolved in 0.9% w/v NaCl. Carbamazepine was obtained from Sigma and suspended in 1% carboxymethyl-cellulose containing 0.1% Tween 80. Both carbamazepine and morphine were administered s.c. All compounds were administered in a dosing volume of 10 ml/kg for mice and 1 ml/kg for rats and guinea pigs except formalin, which was administered in a volume of 20 μl. PD 156942 was administered i.c.v. in a volume of 5 μl. The control group received in all cases the relevant vehicle.

**Results**

**Effect of NK₁ Receptor Antagonists in the Mouse Formalin Test.** The administration of formalin into the hind paw of mice induced a typical biphasic licking/biting response with an early and a late phase. The s.c. administration of CI-1021 had no effect on the early or the late phase of the formalin response. However, it dose dependently (1–30 mg/kg, s.c.) blocked the development of the late phase with a minimum effective dose (MED) of 3 mg/kg (Table 1). Similar administration of CP-99,994 (3–30 mg/kg) and SR 140333 (1–100 mg/kg) also dose dependently reduced the late phase, with respective MEDs of 3 and 10 mg/kg (Table 1). SR 140333 had no effect on the early phase of the formalin response, consistent with CI-1021 (Table 1). However, CP 99,994 did have a modest action on the early phase at the highest dose (30 mg/kg) tested (Table 1). PD 156982 (1–30 mg/kg, s.c.) failed to have any effect on either phase after systemic administration (Table 1). However, after i.c.v. administration (30 μg) it selectively blocked the late phase of the formalin test (Table 1).

**Statistics**

Data obtained for the formalin test, spontaneous pain, thermal hyperalgesia, mechanical hyperalgesia, cold allodynia, and rotarod were subjected to a one-way ANOVA followed when significant by Dunnett’s test. Data obtained for static allodynia were analyzed using a Kruskall-Wallis ANOVA for nonparametric data, followed when significant by Mann-Whitney’s U test. All comparisons were analyzed separately for each time point. The difference in weight bearing between the ipsilateral and contralateral paws was calculated and it was then subjected to a one-way ANOVA followed by Dunnett’s test for each time point studied.

**Effects of CI-1021, Carbamazepine, and Morphine in the CCI Rat**

**CI-1021.** CI-1021 dose dependently (10–100 mg/kg, s.c.) blocked spontaneous pain 30 min after administration with a MED of 30 mg/kg (5.60 ± 1.80, 2.60* ± 1.20, and 1.80* ± 0.70 s for 10, 30, and 100 mg/kg, respectively, versus 9.40 ± 2.40 s for vehicle group, *P < .05 Dunnett’s test, n = 6–10). It also dose dependently blocked thermal hyperalgesia (Fig. 1A), mechanical hyperalgesia (Fig. 2A), and static allodynia (Fig. 3A) induced by CCI, with MEDs of 30, 30, and 10 mg/kg, respectively. These actions of CI-1021 were maximum 30 min after administration. The dose of 100 mg/kg completely blocked thermal hyperalgesia and static allodynia at this time point. The effects disappeared by 2 h. Cold allodynia induced by the CCI was significantly reduced by 100 mg/kg CI-1021 (Fig. 4A). This effect remained significant for up to 3 h. However, CI-1021 (30–100 mg/kg, s.c.) failed to have any effect on the maintenance of dynamic allodynia (3.30 ± 0.36 and 3.22 ± 0.49 s for 30 and 100 mg/kg, respectively, versus 2.88 ± 0.39 s for vehicle group, n = 7–15).

**Carbamazepine.** Carbamazepine (50–100 mg/kg, s.c.) at the highest dose significantly reduced thermal hyperalgesia induced by the CCI at 2.5 and 3.5 h after administration (Fig. 1B). However, unlike CI-1021, it did not produce a total blockade of this hyperalgesic response. The 100-mg/kg dose of carbamazepine also reduced mechanical hyperalgesia and cold allodynia induced by CCI (Figs. 2B and 4B). Unlike CI-1021, carbamazepine was weakly active against static allodynia (Fig. 3B) and inactive against spontaneous pain (8.60 ± 1.70 s for 100 mg/kg versus 10.55 ± 1.44 s for vehicle group, n = 6–10). Carbamazepine (50–100 mg/kg, s.c.) blocked dynamic allodynia only at the highest dose (100 mg/kg). The effect was small in magnitude and significant only 30 min after administration (2.63 ± 0.46 and 6.00* ± 1.49 s for 50 and 100 mg/kg, respectively, versus 2.38 ± 0.41 s for vehicle group, *P < .05 Dunnett’s test, n = 7–15).

**Morphine.** Morphine completely blocked thermal hyperalgesia at doses of 1 and 3 mg/kg at 30 min after administration (Fig. 1C). The effect of 1 mg/kg disappeared shortly after 30 min, but that of 3 mg/kg remained significant for up to 3.5 h (Fig. 1C). At these doses, morphine also blocked mechanical hyperalgesia and static allodynia, with a MED of 1 mg/kg (Figs. 2C and 3C). The 3-mg/kg dose of morphine blocked cold allodynia induced by CCI. The effect remained significant for up to 3 h (Fig. 4C). This dose of morphine also reduced spontaneous pain when administered 30 min before the test (5.4 ± 2.6 and 4.33* ± 1.28 s for 1 and 3 mg/kg, respectively, versus 10.55 ± 1.44 s for vehicle group, *P < .05 Dunnett’s test, n = 6–10). Morphine (1–3 mg/kg, s.c.) failed to have a significant effect on the maintenance of dynamic allodynia (3.70 ± 0.72 and 6.50 ± 1.83 s for 1 and 3 mg/kg, respectively, versus 4.25 ± 0.92 s for vehicle group, *P < .05 Dunnett’s test, n = 6–10).
Lack of Development of Tolerance to the Antiallodynic Action of CI-1021.

In the rat, morphine (3 mg/kg, s.c.) blocked static allodynia on days 1 to 3 of chronic treatment (Fig. 5A). At these time points, morphine also significantly increased the withdrawal threshold on the contralateral paw, thus showing not only antihyperalgesic but also antinociceptive action. On the 4th day of treatment, morphine still showed significant antiallodynic effect, although smaller in magnitude and without producing antinociceptive action. However, on the 6th day of administration, morphine failed to show significant antiallodynic effect, indicating development of tolerance (Fig. 5A). In contrast, CI-1021 (100 mg/kg, s.c.) blocked static allodynia for up to 12 days without showing development of tolerance (Fig. 5B). CI-1021 also produced total blockade of static allodynia in the animals that received morphine for 6 days (Fig. 5A).

Effect of CI-1021 on CCI-Induced Hypersensitivity in the Guinea Pig Measured Using Weight-Bearing Test.

The sciatic nerve ligation in the guinea pig led to the reduction in the weight load on the paw ipsilateral to the ligation, whereas the weight load on the contralateral paw increased. The difference in weight load between paws changed from 0 to 40 to 50 g. The difference in weight load was evident from postoperative day 6 to 8 and was maintained for up to 3 weeks. Morphine (3 mg/kg, s.c.) blocked this hypersensitivity induced by CCI. The effect was only significant 2 h after administration (Fig. 6). Oral administration of CI-1021 blocked the CCI-induced hypersensitivity, with a MED of 0.1 mg/kg. The effect was significant for up to 2 h after administration (Fig. 6).

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Fig. 1. Effect of CI-1021 (A), carbamazepine (B), or morphine (C) on thermal hyperalgesia in the rat CCI pain model. Thermal hyperalgesia was assessed on postoperative days 26 to 28 by determining PWLs using the plantar test. Baseline (BL) measurements were taken before treatment. Animals then received a single s.c. injection of CI-1021 (10–100 mg/kg), carbamazepine (50–100 mg/kg), or morphine (1–3 mg/kg), and PWLs were reassessed at various times after treatment. Results are expressed as mean ± S.E. *P < .05, **P < .01 significantly different from ipsilateral paw of vehicle-treated animals (ANOVA followed by Dunnett’s test; n = 8–12).

Fig. 2. Effect of CI-1021 (A), carbamazepine (B), or morphine (C) on mechanical hyperalgesia in the rat CCI model. Mechanical hyperalgesia was assessed on postoperative days 29 to 36 by determining withdrawal duration to the pinprick test. Baseline (BL) measurements were taken before treatment. Animals then received a single s.c. injection of CI-1021 (10–100 mg/kg), carbamazepine (50–100 mg/kg), or morphine (1–3 mg/kg), and withdrawal durations were reassessed at various times after treatment. Results are expressed as mean ± S.E. *P < .05, **P < .01 significantly different from ipsilateral paw of vehicle-treated animals (ANOVA followed by Dunnett’s test; n = 7–15).
Effect of CI-1021 in the Rat Rota-Rod Test. Vehicle (PEG200)-treated animals spent 119 ± 6 s on the accelerating rota-rod. CI-1021 (10–100 mg/kg), administered s.c. 30 min before the test, did not affect rota-rod performance and thus failed to show a significant sedative/ataxic action [values expressed as mean (s) ± S.E. are 102.1 ± 12.7, 100.6 ± 12.3, and 108.6 ± 7.46 for 10, 30, and 100 mg/kg, respectively; n = 8 per group).

Discussion

The results of this study indicate that CI-1021 possesses antihyperalgesic and antiallodynic actions in animal models of inflammatory and neuropathic pain. These effects appear to be mediated via an interaction at the NK₁ receptor. Two lines of evidence support this conclusion. First, the three compounds examined in the formalin test are chemically unrelated; the only property they are known to share is their affinity for the NK₁ receptor. Thus, their similar profile in the formalin test implies that this action is likely to involve the NK₁ receptor. It is worth noting that unlike CI-1021 and CP 99,994, SR 140333 does not show species differences but possesses high affinity for the human, rat, and guinea pig NK₁ receptors (Emonds-Alt et al., 1993). However, in this study it was no more potent than the other two compounds in the formalin test. This may be related to its relatively poor CNS penetration (Jung et al., 1994). Second, 2 orders of magnitude lower doses in guinea pigs compared with rats were required to block CCI-induced hypersensitivity. This is consistent with the much higher affinity of CI-1021 for the guinea pig NK₁ receptor (Singh et al., 1997). Previous studies
have shown that PD 156982 is a functional NK\textsubscript{1} receptor antagonist in vivo but has poor CNS penetration (Field et al., 1998). Its ability to block the late formalin response after central but not systemic administration indicates the importance of the central NK\textsubscript{1} receptor in inflammatory pain. This is consistent with a previous report suggesting that the actions of CI-1021 in a neuropathic pain model are centrally mediated (Field et al., 1998).

Neuropathic pain is often present as a combination of several heterogeneous symptoms. A selective nerve damage in animals also leads to induction of multiple signs that appear to be indicative of pain. For example, rats with CCI show hyperalgesia and allodynia provoked by thermal and mechanical stimuli. These animals also show what has been termed spontaneous pain. The results of this study show that neither CI-1021, carbamazepine, nor morphine completely blocked all of these responses. These data are consistent with the suggestion that different mechanisms may be involved in the mediation of these responses.

Mechanical allodynia is a prominent feature of inflammatory, neuropathic, and postoperative pain syndromes. The results of this study support previous reports that two distinct types of mechanical allodynia can be detected in animal models of neuropathic pain (Field et al., 1999a,b). They have been termed static and dynamic allodynia after the type of stimulus that leads to their induction. Both types of allodynia are also present in patients suffering from neuropathic pain (Ochoa and Yarnitsky, 1993). It has been suggested that static allodynia is signaled by A\textsubscript{\delta} fibers, whereas dynamic allodynia is signaled by A\textsubscript{\beta/capsaicin-insensitive A\textsubscript{\delta}} primary sensory neurons (Ochoa and Yarnitsky, 1993). The failure of morphine to block dynamic allodynia suggests our previous studies showing that this is also the case in the diabetic and Chung models of neuropathic pain (Field et al., 1999a,b). Moreover, these observations are consistent with electrophysiological observations that morphine can block small (C- and A\textsubscript{\delta}) but not large diameter (A\textsubscript{\beta}-) fiber-evoked responses into the dorsal horn (Le Bars et al., 1979; Dickenson and Sullivan, 1986). The A-fibers that appear to signal dynamic allodynia (Koltzenburg et al., 1992; Gracely et al., 1993) do not contain substance P. This may explain the failure of CI-1021 to block this type of allodynia. It has been shown that chronic inflammation can induce synthesis of substance P in A\textsubscript{\beta}-fibers (Neumann et al., 1996). The failure of CI-1021 to block dynamic allodynia in this study suggests that this is unlikely to be the case after nerve injury.

The results presented here indicate that unlike morphine, repeated administration does not lead to the development of tolerance to the antiallodynic action of CI-1021. However, it remains to be seen whether administration for a longer period leads to tolerance. This study further shows that opiate tolerance does not cross-generalize to the NK\textsubscript{1} receptor antagonist. It remains to be seen whether NK\textsubscript{1} receptor antagonists can block development of opiate tolerance and also reduce abuse liability. The other difference between CI-1021 and morphine is that the NK\textsubscript{1} receptor antagonist did not block the first phase of the formalin response or affect the contralateral paw in the CCI model. This would suggest that neither CI-1021, carbamazepine, nor morphine completely blocked all of these responses. These data are consistent with the suggestion that different mechanisms may be involved in the mediation of these responses.

Mechanical allodynia is a prominent feature of inflammatory, neuropathic, and postoperative pain syndromes.
adequately block NK₁ receptors. More recently, it has been reported that L-754,030 failed to block pain induced by postherpetic neuralgia (PHN; Block et al., 1998). It is known that PHN can lead to destruction of peptidergic C-fiber function. A lack of effect of an NK₁ receptor antagonist in PHN patients with loss of substance P function is not surprising. The results of this study show that CI-1021, morphine, and carbamazepine have differential effects on various behavioral responses induced by CCI. The potency of CI-1021 in the experimental pain model reflects its receptor affinity in that it is 100 times more potent in the guinea pig than in the rat. The limited antiallodynic action of morphine and carbamazepine may explain the inconsistent efficacy of these compounds observed against neuropathic pain (Arner and Meyerzon, 1988; Leijon and Boivie, 1989; McQuay et al., 1995). The failure of CI-1021 to block dynamic allodynia suggests that NK₁ receptor antagonists may not be effective against α-Fiber-signalized responses. These results taken together with clinical studies indicate that a mechanistic approach may represent a better way for designing future clinical studies with NK₁ receptor antagonists. Thus, in addition to using visual analog scale as a measure of overall pain relief, effects on individual (e.g., spontaneous pain, hyperalgesia, and allodynia) components of pain will provide invaluable information for discovering novel treatments. Chronic pain syndromes consist of a wide range of symptoms likely to be mediated by multiple mechanisms. Therefore, blockade of just one of these mechanisms may not provide full pain relief in every patient. A better approach may be a combination therapy involving two compounds with independent mechanisms of action. Mechanical hypersensitivity can be the most debilitating symptom in some patients suffering from neuropathic pain. It remains to be seen whether a combination of CI-1021 with a compound that blocks dynamic allodynia, which is insensitive to the NK₁ receptor antagonist, proves to be a superior treatment of neuropathic pain.

References

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