

Effects of Analgesics on Delayed Postherpetic Pain in Mice

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Background: Postherpetic neuralgia is pain that persists long after the disappearance of the cutaneous lesions of herpes zoster. However, the mechanisms of this delayed pain are unclear. Herpes simplex virus infection induces cutaneous lesions and pain-related responses in mice. The authors examined whether such responses would persist after the disappearance of the cutaneous lesions and whether some analgesics would be effective against them.

Methods: Female BALB/c mice were inoculated with herpes simplex virus type 1 on the unilateral hind paw. Pain-related responses of hind paw were determined using von Frey filaments. Beginning 5 days after inoculation, mice were given perorally the antiherpes agent acyclovir five times a day for 7 days. Effects of morphine (3–5 mg/kg subcutaneously), gabapentin (30–100 mg/kg perorally), mexiletine (10–30 mg/kg intraperitoneally), and diclofenac (30 mg/kg intraperitoneally) on pain-related responses were examined on days 25–35 after inoculation.

Results: Viral inoculation induced cutaneous lesions and pain-related responses beginning on day 5 after inoculation. Acyclovir treatment healed all skin lesions by day 15 after inoculation. Approximately half of the mice given acyclovir showed pain-related responses at least until day 40 after inoculation. Morphine, gabapentin, and mexiletine dose-dependently inhibited pain-related responses, but diclofenac had no effects.

Conclusions: The authors show a mouse model of delayed postherpetic pain. This may be useful for manifesting the mechanisms of postherpetic neuralgia and the factors contributing to the transition from acute herpetic pain to delayed postherpetic pain. This may also be useful for the development of new analgesics against postherpetic neuralgia.

HERPES zoster is caused by the reactivation of latent varicella-zoster virus in the sensory ganglia and is characterized by neurocutaneous symptoms, such as dermatitic rash and severe pain. Although herpes zoster usually resolves in 2–4 weeks, some patients experience pain for a long time even after the healing of herpes zoster.¹ Patients with postherpetic neuralgia (PHN) report various types of pain, including a continuous burning or aching pain, a periodic piercing pain, and allodynia elicited by tactile stimulation.² Although tricyclic

antidepressants, anticonvulsants, local anesthetics, and topical agents (e.g., capsaicin and aspirin) are prescribed for PHN patients, these medications do not always reduce the established PHN. The pathophysiologic mechanisms of PHN are not well-understood.

Varicella-zoster virus infection has been reported to cause allodynia and hyperalgesia in rats.³ However, because of high species specificity of this herpes virus, the mode of infection in animals is different from that in humans. In fact, there may be no chickenpox and acute pain in that rat model. Therefore, it is unclear whether the mechanisms of pain-related responses of infected rats are similar to those of postherpetic pain in humans. It is impossible to examine the effects of management of acute pain on the incidence rate of PHN in that model.

Inoculation with herpes simplex virus type 1 (HSV-1) results in extensive infection of primary sensory neurons in rats,⁴ but it causes hypoalgesia rather than nociceptive hypersensitivity, without skin lesions.^{4,5} However, when mice are inoculated transdermally with HSV-1, herpes zoster-like skin lesions develop unilaterally in the same dermatome several days later.^{6,7} In addition, they show aversive responses to innocuous tactile and noxious mechanical stimulation (designated as allodynia and hyperalgesia, respectively).⁷ Even if the mice are given no stimulation, they lick and flinch the affected hind paw. The pain-related responses (allodynia, hyperalgesia, and licking) and eruption become apparent on the same day and last at least several days.⁷ Unfortunately, when they are given no anti-herpes virus agents, approximately half show motor paralysis and die in a few weeks.⁶ Therefore, to develop a mouse model of PHN in the current experiments, we administered an anti-herpes virus agent to mice with acute herpetic pain and examined whether mice showed pain-related responses to innocuous and noxious mechanical stimuli even after the disappearance of cutaneous lesions. We then examined the effects of several analgesics on the pain-related responses long after recovery from the cutaneous lesions.

Materials and Methods

Animals

Female BALB/c mice weighing 18–20 g (6 weeks old at the start of experiments; Japan SLC, Shizuoka, Japan) were used. They were housed six per cage under controlled temperature ($22 \pm 1^\circ\text{C}$) and humidity ($55 \pm 10\%$). The room was lighted from 7:00 AM to 7:00 PM and during the behavioral test. Food and water were freely available. HSV-1 inoculation and behavioral experiments

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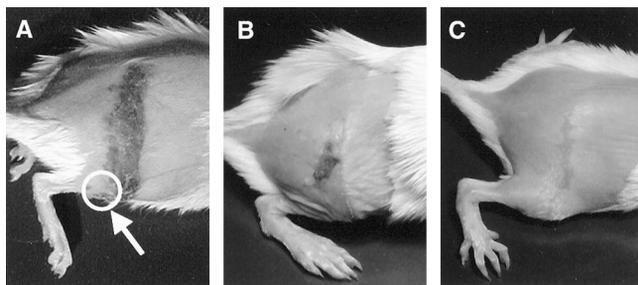


Fig. 1. The recovery stage of herpes zoster-like cutaneous lesions of mice infected with herpes virus. Mice were inoculated with herpes simplex virus type 1 (1×10^6 plaque-forming units) on the shin of the right hind paw (circle and arrow). (A) Score 10, severe herpes zoster-like skin lesions; (B) score 5, presence of scabs flaking off from cutaneous lesions; (C) complete recovery of the lesions.

were performed in the infection room of the Molecular Genetics Research Center, Toyama Medical and Pharmaceutical University (Toyama, Japan). The animal experiments were conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals approved by the Committee for Animal Experiments at Toyama Medical and Pharmaceutical University. Behavioral nociceptive tests were performed according to ethical standards for investigations of experimental pain in animals.⁸

Virus Infection

The mice were inoculated with HSV-1 as described previously.⁷ Briefly, 3 days after depilation, the shin skin of the right hind paw (5×5 mm) was scarified without anesthesia using 27-gauge needles and $10 \mu\text{l}$ suspension containing 1×10^6 plaque-forming units of HSV-1 (7401H strain; supplied by K. S.) was applied to the scarified area. The contralateral hind paw was without inoculation.

At the development stage of skin lesions (until day 9 after inoculation), they were scored as follows: 0 = no lesions; 2 = one or two vesicles on the back; 4 = many vesicles on the back, the surrounding inoculated area, or both; 6 = mild herpes zoster-like lesions; 8 = apparent zoster-like lesions, paw inflammation, or both; 10 = severe zoster-like lesions.⁷ At the recovery stage of skin lesions (from day 10 after inoculation), they were scored as follows: 10 = severe herpes zoster-like lesions; 5 = the presence of scabs flaking off from cutaneous lesions; 0 = complete recovery of the lesions (fig. 1).

Behavioral Test

Pain-related responses of the hind paw were assessed using von Frey filaments, as described previously.⁷ After at least a 15-min acclimation period, von Frey filaments with a bending force of 0.17 or 1.20 g were pressed perpendicularly against the plantar skin and held for 3–5 s with it slightly buckled. The stimulation of the same intensity was applied six times to each hind paw at

intervals of several seconds. All normal mice tested responded at least three times to six-time stimulation with the filament of 1.20 g strength and had no responses to the filament of 0.17 g strength. The responses to these stimuli were ranked as follows: 0 = no response; 1 = moving away from the von Frey filament; 2 = immediate flinching or licking of the hind paw.

Drugs

Acyclovir (GlaxoSmithKline, Tokyo, Japan) was dissolved in water and administered perorally five times daily (09:00, 12:00, 15:00, 18:00, and 21:00 h) from day 5 to day 11 after inoculation. Morphine hydrochloride (Sankyo, Tokyo, Japan) was dissolved in physiologic saline and administered subcutaneously. Diclofenac sodium (Research Biochemical International, Natick, MA) and mexiletine (Sigma, St. Louis, MO) were dissolved in physiologic saline and administered intraperitoneally. Gabapentin, synthesized by us,⁹ was dissolved in water and administered perorally. The dosage of salts is given in terms of the weight of salt.

Determination of Herpes Simplex Virus Type 1 DNA

The thymidine kinase gene of HSV-1 was determined with polymerase chain reaction, as described previously.⁷ The sequences of primers used were as follows: sense, 5'-ataccgacgatatgacacct-3'; antisense, 5'-ttattgccgtcatagcgcgg-3'. The plasmid containing HSV-1 thymidine kinase gene was used as a standard.

Statistical Analysis

Unless otherwise mentioned, the means of data are presented together with standard errors of the means. Data on the time course of analgesic effects were analyzed with the Friedman repeated-measures analysis of variance on ranks with the Dunnett *post hoc* test. Statistical differences between groups were analyzed with the Mann-Whitney U test or Kruskal-Wallis analysis of variance on ranks. A value of $P < 0.05$ was considered significant.

Results

Acute Herpetic Pain

Herpes simplex virus type 1 inoculation on the hind paw produced herpes zoster-like skin lesions in the same dermatome (fig. 1A) and induced allodynia (responses to 0.17-g von Frey filament) and hyperalgesia (responses to 1.20-g von Frey filament) in the affected hind paw in all mice examined. These pain-related responses became apparent on day 5 after inoculation and then gradually increased over a few days. The responses of the contralateral hind paw were unaffected by HSV-1 inoculation.

Table 1. Effects of Acyclovir Treatment on Pathologic Parameters in Mice Inoculated with Herpes Simplex Virus type 1

Agent* (mg/kg)	n	Mortality Rate† (%)	Pain-related Response Score‡		Skin Lesion Score‡	Body Weight‡ (g)
			0.17 g VF	1.20 g VF		
Water	6	50	0.56 ± 0.07	1.69 ± 0.13	9.0 ± 0.7	18.0 ± 0.5
Acyclovir						
5	5	40	0.47 ± 0.13	1.64 ± 0.13	8.3 ± 1.7	17.4 ± 0.4
10	6	0	0.50 ± 0.10	1.61 ± 0.16	8.7 ± 0.8	17.8 ± 0.5
20	6	0	0.50 ± 0.10	1.74 ± 0.11	6.7 ± 1.1	18.2 ± 0.4

The values except mortality represent mean ± standard error of the mean.

* Acyclovir was administered orally 5 times daily from day 5 to day 11 after inoculation. † Results on day 15 after inoculation. ‡ Results on day 8 after inoculation.

Effect of Acyclovir

When mice were repeatedly given the anti-herpes virus agent acyclovir (25 mg/kg twice a day) from day 2 after inoculation, allodynia and hyperalgesia were markedly inhibited on day 8 after inoculation.⁷ However, when they were given the same dose of acyclovir from day 5 after inoculation, the pain-related responses were not affected, whereas cutaneous lesions were slightly inhibited.⁷ Therefore, in this series of experiments, we repeatedly administered acyclovir from day 5 after inoculation and examined the effects on morbidity conditions. In the vehicle control, one half of inoculated mice showed motor paralysis and then died by day 15 after inoculation (table 1). Although in the acyclovir group (5 mg/kg) 2 out of 5 mice showed motor paralysis and died by day 15 after inoculation, all mice survived without motor paralysis after doses of 10 and 20 mg/kg (table 1). The doses of 10 and 20 mg/kg did not affect allodynia, hyperalgesia, and body weight on day 8 after inoculation. Although the dose of 10 mg/kg did not affect the skin lesions on day 8 after inoculation, there was a decreased tendency of skin lesions in the 20-mg/kg group (table 1). Because the dose of 10 mg/kg completely prevented motor paralysis and death without effects on skin lesions, we used this dose in the following experiments.

Allodynia, Hyperalgesia, and Viral DNA Level

When mice were given acyclovir (10 mg/kg five times a day) from day 5 to day 11 after inoculation, all skin lesions were completely healed by day 15 after inoculation (figs. 1C, 2A, and 2B). In 11 out of 23 mice, allodynia gradually subsided from day 9 after inoculation and completely resolved by day 20 after inoculation (fig. 2C). However, in the rest (12 out of 23 mice), there was an decreased tendency of allodynia from day 8 after inoculation, but even after the complete cure of the cutaneous lesions (from day 15 to day 40 after inoculation), the degree of allodynia was similar to that of acute pain on days 6–8 after inoculation (fig. 2D). With regard to hyperalgesia, in 11 out of 23 mice, it gradually subsided and resolved by day 20 after inoculation (fig. 2E). In the rest (12 out of 23 mice), hyperalgesia apparently de-

creased from day 9 after inoculation, but there was apparent and constant hyperalgesia between day 15 and day 40 after inoculation (fig. 2F). When mice showed either allodynia or hyperalgesia on day 20 after inoculation, we considered that they had postherpetic pain. The skin lesion scores of groups with or without postherpetic pain were similar on day 8 after inoculation (figs. 2A and B). On the same day, the degrees of allodynia of both groups were also similar (figs. 2C and D), whereas the degree of hyperalgesia of the postherpetic pain

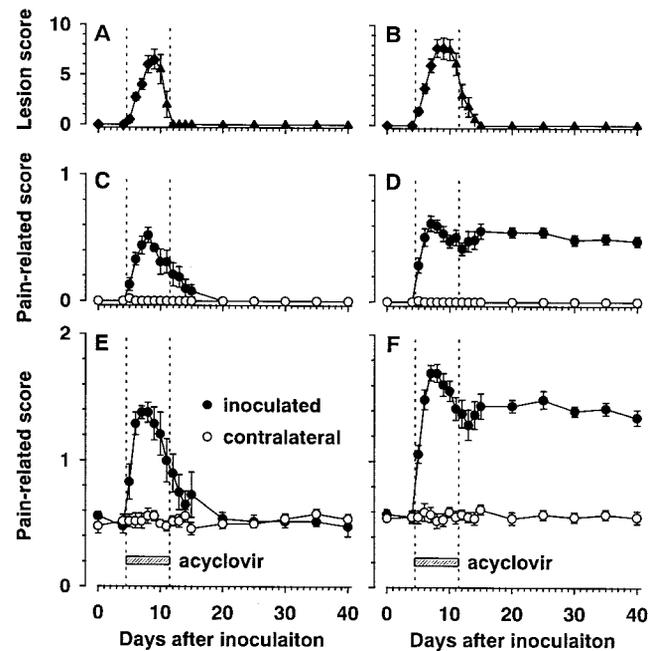


Fig. 2. Effects of acyclovir on skin lesions (A, B), allodynia (C, D), and hyperalgesia (E, F) after herpesvirus inoculation. Mice were given herpes simplex virus type 1 inoculation on the unilateral hind paw on day 0, with the contralateral hind paw untreated, and acyclovir (10 mg/kg, five times a day) from day 5 to day 11 after inoculation. When mice showed either allodynia or hyperalgesia on day 20 after inoculation, they were considered to have postherpetic pain, and 23 mice were classified into two groups, non-postherpetic pain (A, C, E; n = 11) and postherpetic pain (B, D, F; n = 12). (A, B) Lesion scores represented by diamonds and triangles were calculated on the basis of different lesion criteria (see Materials and Methods). The data given are mean and standard error of the mean. Hatched columns and dotted lines indicate the period of acyclovir administration.

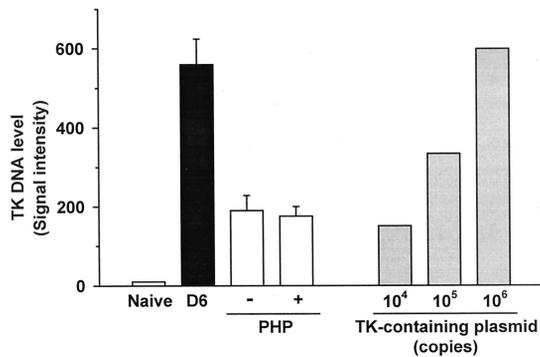


Fig. 3. Effects of acyclovir administration on the concentration of thymidine kinase (TK) gene of herpes simplex virus type 1 in the dorsal root ganglia. Naive = mice given no treatment ($n = 4$). D6 = mice inoculated 6 days before with herpes simplex virus type 1 ($n = 4$). PHP = part of mice shown in fig. 2 were used for the assay of the level of TK gene on day 40 after inoculation; PHP+ ($n = 4$) and PHP- ($n = 3$) = mice with and without postherpetic pain-related responses, respectively. The data given are mean and standard error of the mean. TK-containing plasmid was used as a standard.

group was significantly ($P < 0.05$, Mann-Whitney U test) higher than that of non-postherpetic pain group (figs. 2E and F). In another series of experiments, we observed allodynia and hyperalgesia until day 60 after inoculation, in which there was no tendency for the pain-related responses to subside in the postherpetic pain group during the experimental period (data not shown).

When mice were given an HSV-1 inoculation and no acyclovir medication, the concentration of HSV-1 DNA in the dorsal root ganglia at the level of L4 and L5 was approximately 10^6 copies on day 6 after inoculation (fig. 3). When mice were given acyclovir (10 mg/kg) from day 5 to day 11 after inoculation, the concentration of HSV-1 DNA in the dorsal root ganglia was approximately 10^4 copies on day 45 after inoculation, and the concentrations were not different between groups with or without postherpetic pain (fig. 3).

Effects of Analgesics

In this series of experiments, analgesics were administered to mice that showed pain-related responses after the complete cure of skin lesions. Morphine (3 and 5 mg/kg subcutaneously) significantly ($P < 0.05$, Dunnett test) inhibited allodynia and hyperalgesia, but the inhibition was not complete even after a dose of 5 mg/kg (fig. 4). Inhibitory effects peaked 15–30 min after injection and subsided by 60–90 min. Because morphine (5 mg/kg) apparently increased locomotor activity, higher doses were not examined.

Gabapentin (30 mg/kg perorally) almost completely inhibited both allodynia and hyperalgesia; the effects peaked at 1 h and subsided by 5–6 h (fig. 5). The duration of action was longer after the higher dose of 100 mg/kg (fig. 5). No apparent alterations in gross behaviors and motor functions were observed after the doses tested.

Mexiletine (10–30 mg/kg intraperitoneally) produced a dose-dependent inhibition of allodynia and hyperalgesia (fig. 6). Allodynia was completely inhibited by the dose of 30 mg/kg, whereas the inhibition of hyperalgesia was partial after the same dose. The effect of the 30-mg/kg dose peaked at 15 min and almost subsided by 60 min.

Diclofenac (30 mg/kg intraperitoneally) exerted no apparent influences on allodynia and hyperalgesia ($n = 6$ for diclofenac and vehicle groups, data not shown).

Discussion

Effect of Acyclovir

One important finding in the current experiments is that some mice showed long-lasting and constant pain-related responses even after herpes zoster-like skin lesions healed. Seven-day treatment with acyclovir produced a complete cure of lesions in all mice within 10 days after the start of medication. In approximately half of them, pain-related responses continued to decrease after lesion healing and completely resolved within 15 days after the start of antiviral treatment. However, in the rest, pain-related responses decreased during acyclovir treatment, but after the discontinuation of medication, they slightly increased and then continued for at least 25 days. The results increase the possibility that postherpetic pain was due to incomplete treatment with acyclovir. However, the concentration of HSV-1 DNA in the dorsal root ganglia was markedly decreased by the

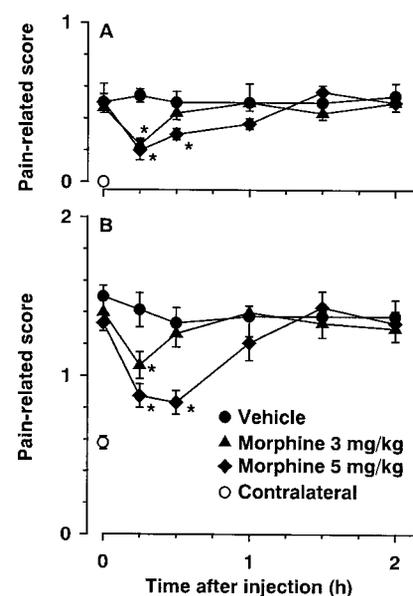


Fig. 4. Effects of morphine on allodynia (A) and hyperalgesia (B) of mice with postherpetic pain-related responses. Morphine at doses of 3 ($n = 5$) and 5 mg/kg ($n = 5$) and vehicle ($n = 4$) were injected subcutaneously on day 25 after inoculation. The contralateral hind paw was given no inoculation ($n = 4$). Data are presented as mean \pm standard error of the mean. * $P < 0.05$ as compared with preadministration values (Dunnett test).

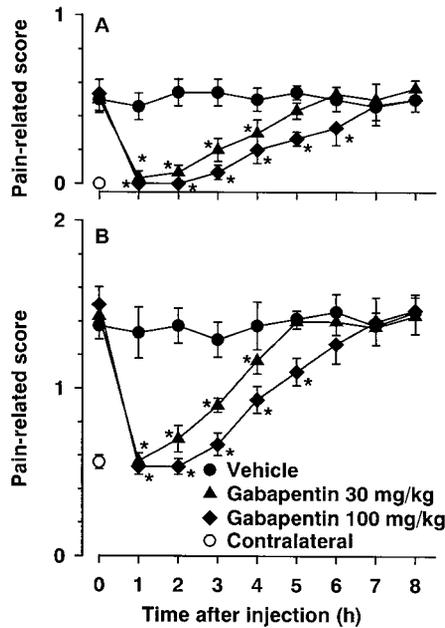


Fig. 5. Effects of gabapentin on allodynia (A) and hyperalgesia (B) of mice with postherpetic pain-related responses. Gabapentin at doses of 30 ($n = 5$) and 100 mg/kg ($n = 5$) and vehicle ($n = 4$) were injected perorally on day 35 after inoculation. The contralateral hind paw was given no inoculation ($n = 4$). Data are presented as mean \pm standard error of the mean. * $P < 0.05$ as compared with preadministration values (Dunnett test).

acyclovir treatment and was not different between these groups on day 45 after inoculation. Therefore, postherpetic pain-related responses may not be due to incomplete antiviral treatment. In humans, the effects of acyclovir treatment of patients with herpes zoster on the incidence of PHN are of inconsistency (for review, see Alper and Lewis¹⁰). Our results do not deny the possibility that proper antiviral treatment decreases the incidence of postherpetic pain.

Effects of Analgesics

Morphine produced antinociceptive effects in mice with delayed postherpetic pain. The results are consistent with the finding that morphine reduces allodynia of patients with PHN.¹¹ However, although morphine at a dose of 5 mg/kg almost completely inhibited acute herpetic pain-related responses,⁹ it only partially suppressed the delayed postherpetic pain-related responses (current experiment). In addition, morphine inhibited acute pain-related responses for 1.5–2.0 h⁹ but delayed postherpetic pain-related responses for 0.5–1.0 h (current experiment). Therefore, delayed postherpetic pain may be more refractory to morphine than acute herpetic pain. It has been reported that morphine is not potent for the management of pain of PHN patients after intravenous and epidural injections.^{12,13} Opioids are less effective against neurogenic pain than nociceptive pain.¹⁴ Reduced or lack of analgesic effects of morphine has been reported in animals with neuropathic pain induced

by peripheral nerve injury or with streptozotocin-induced allodynia.^{15–17} Axotomy of L4–L6 peripheral nerves causes a decrease in μ -opioid receptor-like immunoreactivity in the rat dorsal horn, and the reduction of efficacy of morphine against neuropathic pain is explained by the down-regulation of μ -opioid receptors in the primary afferents.¹⁸ Pathologic studies have revealed degenerative changes in both the peripheral and central nervous systems in PHN.¹⁹ Therefore, whether there are any differences in the expression of μ -opioid receptors in the primary afferents between groups with or without delayed postherpetic pain is an interesting question to be elucidated in future study.

Gabapentin at doses of 30 and 100 mg/kg almost completely inhibited both allodynia and hyperalgesia. With regard to acute herpetic pain-related responses, gabapentin at a dose of 30 mg/kg does not abolish the responses, and an even higher dose of 100 mg/kg produces partial inhibition of hyperalgesia.⁹ Therefore, it may be more effective against delayed postherpetic pain than acute herpetic pain. In humans, although relatively high doses (900–3,600 mg/day) are needed, gabapentin is effective against PHN without aversive side effects.²⁰ Gabapentin may produce antinociception mainly through action on the spinal dorsal horn.²¹ Although the analgesic mechanisms of gabapentin have not been fully elucidated, the involvement of $\alpha_2\delta$ subunit of voltage-dependent calcium channel in the dorsal root ganglion has been suggested.²² Therefore, it may be interesting to

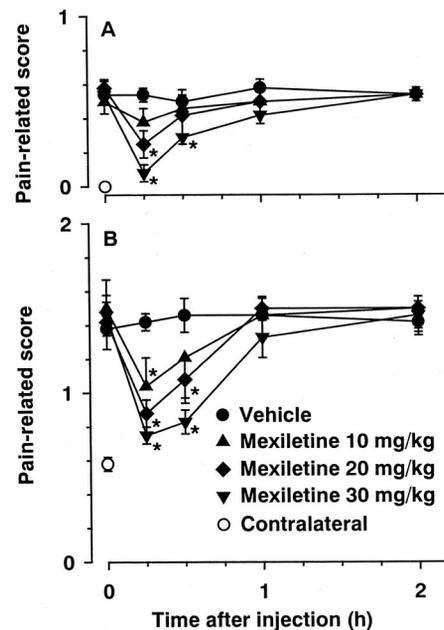


Fig. 6. Effects of mexiletine on allodynia (A) and hyperalgesia (B) of mice with postherpetic pain-related responses. Mexiletine at doses of 10, 20, and 30 mg/kg and vehicle were injected intraperitoneally on day 30 after inoculation. The contralateral hind paw was given no inoculation. Data are presented as mean \pm standard error of the mean of four animals. * $P < 0.05$ as compared with preadministration values (Dunnett test).

examine whether alterations in the expression of the channel subunit in the primary sensory neurons are associated with the development of delayed postherpetic pain.

Mexiletine, an orally active sodium channel blocker, inhibited delayed postherpetic pain-related responses in mice. It suppresses neuropathic pain in humans^{23,24} and the ectopic discharges after peripheral nerve injury.²⁵ It should be examined whether ectopic discharges are apparent in mice with delayed postherpetic pain-related responses.

One key finding in the current experiments is that the nonsteroidal antiinflammatory drug diclofenac (30 mg/kg) did not affect delayed postherpetic pain-related responses in mice. In contrast, the same dose of diclofenac markedly inhibited acute herpetic pain-related responses in mice.⁹ A lower dose (10 mg/kg) also inhibits the acute herpetic pain-related responses.⁹ The results suggest that unlike acute herpetic pain, the ongoing production of prostaglandins is not involved in delayed postherpetic pain-related responses. In humans, topical aspirin has been claimed to be effective against PHN pain, but other nonsteroidal antiinflammatory drugs, such as diclofenac and indomethacin, are not effective.^{26,27} Therefore, prostaglandins may not be critically associated with PHN pain. In an animal neuropathy model with sciatic nerve injury, nonsteroidal antiinflammatory drugs inhibited or delayed the development of allodynia, but they had no effect on established allodynia.^{28,29} With these findings taken into account, the current results strongly suggest that prostaglandins are not associated with the maintenance of delayed postherpetic pain-related responses.

Mechanisms of Development of Postherpetic Pain

Clinically, when patients have pain for 3 or more months after acute herpes zoster, they are generally considered to have PHN. When pain resolves within 2 months, acute herpetic pain is thought to be continuing. In the current experiments, we observed pain-related responses until day 60 after inoculation. However, we think that the pain-related responses may not be the remnants of acute herpetic pain because there was no tendency for the pain-related responses to subside during the experimental period. The idea is also supported by differences in response to the analgesics, such as diclofenac and morphine.

The mechanisms of the development of PHN remain obscure. Although in the current experiments we used inbred mice (BALB/c strain), delayed postherpetic pain-related responses were not observed in all mice examined. The results do not rule out the possibility that genetic factors exert influences on the incidence of PHN in humans, but it is strongly suggested that acquired factors are involved in the development of postherpetic pain. On day 8 after inoculation (the stage of acute

herpetic pain), hyperalgesia was greater in the postherpetic pain group than in the non-postherpetic pain group. Allodynia of the postherpetic pain group was not significantly different from that of non-postherpetic pain group, but the recovery of the postherpetic pain group was apparently slower than that of the non-postherpetic pain group. These results increase the possibility that the degree of acute herpetic pain affected the incidence of postherpetic pain. Similarly, patients in whom chronic pain developed after herpes zoster healing had significantly worse herpes zoster-related pain than patients in whom chronic pain did not develop.³⁰ The incidence of PHN was higher in patients who had severe herpetic pain than patients who did not.³¹ However, details of the effects of inhibition of acute herpetic pain on the incidence of PHN are not clear. Therefore, it seems interesting to examine the effects of the inhibition of acute herpetic pain on the incidence of postherpetic pain in this murine model.

In conclusion, we have shown that approximately half of mice with acute herpetic pain have delayed postherpetic pain. This murine model may be useful for manifesting the mechanisms of PHN and the factors contributing to the transition from acute herpetic pain to PHN. This may also be useful in the development of new analgesics against PHN.

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