JPP Journal of Pharmacy and Pharmacology

JPP 2003, 55: 1365–1370

Received December 11, 2002
Accepted June 5, 2003
DOI 10.1211/0022357021828
ISSN 0022-3573

Attenuating effect of mexiletine hydrochloride on herpetic pain in mice infected with herpes simplex virus

Kazuhito Asano, Tatsuo Sameshima, Hiroshi Shirasawa and Tadashi Hisamitsu

Abstract

The influence of mexiletine hydrochloride on herpes-related pain responses was examined using mice infected with herpes virus. BALB/c mice were inoculated with herpes simplex virus (HSV; 1×10^6 plaque-forming units) on the right hind paw, and the contralateral hind paw was without inoculation. The changes in nociceptive threshold were examined using electric von fray meter. BALB/c mice inoculated with HSV showed a decrease in nociceptive threshold. Intraperitoneal administration of mexiletine prevented the decrease in nociceptive threshold dose-dependently in HSV-inoculated mice, which was firstly observed at a dose of 15.0 mg kg^{-1}, and peaked at doses more than 17.5 mg kg^{-1}. This antinociceptive effect of mexiletine attained peaks at 60–90 min after administration and declined gradually to non-treated levels by 150 min. Intraperitoneal administration of mexiletine at a dose of 17.5 mg kg^{-1} (but not 10.0 mg kg^{-1}) caused significant increase in β-endorphin levels in the mid brain and hypothalamus of HSV-inoculated mice. However, mexiletine scarcely affected noradrenaline (norepinephrine) levels in the pons and medulla oblongata, even when HSV-inoculated mice were treated with 17.5 mg kg^{-1} mexiletine. These results strongly suggested that mexiletine exerts antinociceptive effects on herpes-related pain through enhancement of β-endorphin levels in the central nervous system in HSV-inoculated mice. It is also suggested that mexiletine will be a good candidate for an antinociceptive drug in the treatment of acute herpetic pain in man.

Department of Physiology, School of Medicine, Showa University, Tokyo, Japan

Kazuhito Asano, Tatsuo Sameshima, Tadashi Hisamitsu

Department of Virology, Graduate School of Medicine, Chiba University, Chiba, Japan

Hiroshi Shirasawa

Correspondence: K. Asano, Department of Physiology, School of Medicine, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan. E-mail: asanok@med.showa-u.ac.jp

Acknowledgement: We thank Nihon Boeheringer Ingelheim Co. Ltd (Tokyo, Japan) for kind donation of mexiletine hydrochloride. We also thank Professor K. Oguchi and Dr M. Inagaki for measurement of noradrenaline contents.

Introduction

Varicella-zoster virus is well known to be the smallest of the double-strand DNA herpesviruses, and the only one capable of producing two different diseases – a systemic infection, such as varicella (chicken pox) and a localized infection known as herpes zoster or shingles (Liesegang 1999). The localized infection, which typically occurs in elderly individuals, represents a recrudescence from a latent phase in which the virus is dormant in dorsal ganglia (Rowbotham & Petersen 2001). Herpes zoster results from reactivation and spread of virus from a sensory ganglion to the corresponding dermatome (Rowbotham & Petersen 2001). Although the presentation of herpes zoster is variable, a prodrome of dermatomal pain typically precedes the appearance of the rash (Dworkin & Portenoy 1996; Dworkin et al 2001). In almost all cases, this prodome, so-called acute pain, disappears with healing of acute eruptions (Dworkin & Portenoy 1996; Dworkin et al 2001). On the other hand, unfortunate patients experience pain for a long time even after the healing of herpes zoster. This type of pain is termed postherpetic neuralgia, and is characterized by a continuous burning and aching pain, a periodic piercing pain and allodynia elicited by tactile stimulation (Dworkin & Portenoy 1996; Rowbotham & Petersen 2001). The postherpetic neuralgia is often so severe that it significantly compromises the patient's quality of life (Galer et al 1999). A lot of studies have demonstrated that herpes zoster patients with severe acute pain have an increased risk of developing postherpetic neuralgia, indicating that relief of acute pain is most important to prevent the development of postherpetic neuralgia (Dworkin & Portenoy 1996; Dworkin 1999; Galer et al 1999; Dworkin et al 2001; Rowbotham & Petersen 2001). Although the

treatments currently recommended and most frequently prescribed for acute pain are antiviral agents, a substantial number of patients still have chronic pain despite adequate therapy (Dworkin & Portenoy 1996; Dworkin 1999). Tricyclic antidepressants, which are used for the treatment of neuropathic pain (McQuay et al 1996), and opiates are also reported to abbreviate the duration of acute pain and reduce the incidence of postherpetic neuralgia (Watson & Babul 1998), when the treatment is started very soon after onset of the rash. However, in clinical practice these agents result in poor pain relief and intolerable side effects in some cases (Galer et al 1999). Therefore, there exists a need for more effective and better-tolerated therapies.

Intradermal inoculation of mice with herpes simplex virus type I (HSV) causes extensive infection of primary sensory neurons and produces unilateral herpes-zoster-like skin lesions in the same dermatome (Takasaki et al 2000a, b, 2002). In addition, they show aversive responses to innocuous tactile and noxious mechanical stimulation (Takasaki et al 2000a, b).

Mexiletine hydrochloride, a lidocaine (lignocaine)-like anti-arrhythmic drug, is reported to be effective in the treatment of neuropathic pain, such as painful diabetic neuropathy, in man and mice (Chabal et al 1992; Kamei et al 1992). Although mexiletine also inhibits postherpetic pain-related responses in mice infected with HSV (Takasaki et al 2002), the influence of the agent on acute herpetic pain is not understood. In this study, therefore, we examine the influence of mexiletine on acute herpetic pain-related responses using a mouse/HSV model.

Materials and Methods

Materials

Mexiletine hydrochloride was kindly donated by Nihon Boeheringer Ingelheim Co. Ltd (Tokyo, Japan) as a preservative-free pure powder. Aciclovir, a human-injection grade, was purchased from Nihon Wellcome (Kobe, Japan). Pentobarbital was supplied by Abbott Laboratories (North Chicago, IL). A chemical depilatory cream, Hair Remover Milkcream, was purchased from Kanebo Co. Ltd (Tokyo, Japan).

Animals

Specific pathogen-free BALB/c female mice, 6 weeks of age, were purchased from Charles River Japan Inc. (Atsugi, Japan). After arriving at our university, mice were housed in filter (0.2 μm)-barriered cages and given free access to autoclaved food and water to prevent unwanted microbiological infections. All animal experimental procedures were approved by the Showa University Animal Ethics Committee, and carried out in accordance with the guidelines of the Physiological Society of Japan.

Virus infection

Mice were anaesthetized with pentobarbital (50 mg kg^{-1}, i.p.), and then depilated with a chemical depilatory cream. After three days, HSV (1×10^6 plaque-forming units in 10.0 μL) was inoculated on the shin of the right hind paw after scarification with 27-gauge needles (Takasaki et al 2000a). The contralateral hind paw was not inoculated. Heat (60 °C, 1 h) inactivated HSV was also inoculated in a similar manner to serve as controls (Takasaki et al 2000a).

Treatment of mice with agent

Various doses of mexiletine in a volume of 0.2 mL phosphate-buffered saline (PBS) were administered once intraperitoneally into experimental mice. Control mice received, intraperitoneally, 0.2 mL PBS alone. Aciclovir was administered intraperitoneally at a dose of 25 mg kg^{-1} twice a day (0700 and 1900 h). Aciclovir administration was started 2 h before, and 2, 5 and 6 days after, HSV inoculation (Takasaki et al 2000a).

Assessment of pain-related responses

Pain-related responses were assessed by measuring changes in nociceptive threshold in mouse hind paw with an Electronic von Frey Anesthesiometer (Model 2290; IITC Inc., Woodland Hills, CA). Mice were placed individually in stainless-steel cages with a wire mesh bottom. After acclimation for approximately 15 min, the probe was applied perpendicularly against the plantar skin and measured maximum force applied to flinch the hind paw. The probe was applied five times to each hind paw at intervals of several seconds and the average force per mouse was obtained. Pain-related responses were expressed as percent of nociceptive threshold calculated as follows: % nociceptive threshold = (average force in HSV-inoculated paw/average force in non-inoculated paw) × 100. The results were shown as the mean % of nociceptive threshold ± s.e. of five mice.

Measurement of β-endorphin in brain

The mid brain and hypothalamus were removed from a mouse killed by decapitation, and homogenized in 4 volumes of PBS by glass tissue homogenizers for 1 min at 4 °C. After centrifugation at 15 000 *g* for 30 min at 4 °C, the supernatants were obtained and used for water-soluble brain extracts. β-Endorphin levels in brain extract were measured by commercially available enzyme linked immunosorbent assay kits (Peninsula Laboratories, Inc., San Carlos, CA) according to the manufacturer's recommendation. The minimum detectable level of β-endorphin is 0.04 ng mL^{-1}. The protein concentrations of the supernatants were also measured with a Bio-rad Protein Assay kit (Bio-Rad Laboratories, Hercules, CA). β-Endorphin levels were expressed as mean ± s.e. (pg (mg protein)$^{-1}$) of five mice.

Measurement of noradrenaline (norepinephrine) in brain

The noradrenaline level in the brain was measured by HPLC (TOSOH Co. Ltd, Tokyo, Japan) with electro

current detector (EICOM Co. Ltd, Kyoto, Japan) according to the method described previously (Shinozuka et al 2001). The pons and medulla oblongata were removed from the brain of a mouse killed by decapitation, and were suspended in 4 volumes of PBS and homogenized by glass tissue homogenizers for 1 min at 4 °C. After centrifugation at 15 000 *g* for 30 min at 4 °C, the supernatants were obtained and used for measurement of noradrenaline and protein. Noradrenaline levels were expressed as mean ± s.e. (pg (mg protein)$^{-1}$) of five mice.

Statistical analysis

The statistical significance of the data between control and experimental groups was analysed by analysis of variance followed by Fisher's PLSD test.

Results

Appearance of pain-related responses after HSV inoculation in mice

The first set of experiments was undertaken to examine whether HSV inoculation into mice could cause pain-related responses. Mice were intradermally inoculated with HSV into the unilateral hind paw, and pain-related responses were assessed by measuring changes in nociceptive threshold in hind paw. HSV inoculation caused a decrease in nociceptive threshold in the inoculated hind paw. As shown in Figure 1, these nociceptive thresholds were almost constant until day 5 post-inoculation and then dramatically decreased on day 6. The next experiments were designed to examine whether the decrease in nociceptive threshold was due to activation of inoculated HSV or to the inflammatory responses to herpetic protein. Mice were inoculated with heat-inactivated HSV into the hind paw, and the nociceptive threshold was examined. No pain-related responses were observed in mice inoculated with inactivated HSV (Figure 2). Furthermore, the data in Figure 2 clearly showed that aciclovir treatment of mice before and after HSV inoculation could prevent completely the decrease in nociceptive threshold induced by HSV.

Suppressive activity of mexiletine on pain-related responses induced by HSV inoculation

The second set of experiments was undertaken to examine the influence of mexiletine on pain-related responses induced by HSV inoculation. Mice were injected intraperitoneally with 17.5 mg kg^{-1} mexiletine on day 6 post-HSV inoculation, and changes in nociceptive threshold were monitored at 30-min intervals. As shown in Figure 3, mexiletine could exert suppressive effects on pain-related responses, which peaked at 60–90 min after administration and then gradually declined to non-treated levels by 150 min. We next examined the dose–response profile of mexiletine. Mice were injected intraperitoneally with either 10.0, 15.0, 17.5 or 20.0 mg kg^{-1} mexiletine on day 6 post-HSV inoculation, and nociceptive threshold

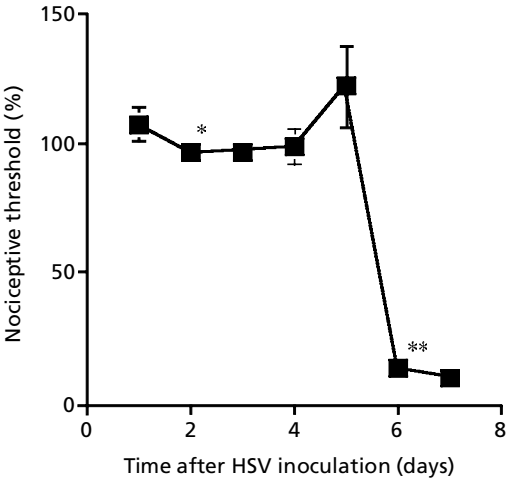

Figure 1 Influence of HSV infection on nociceptive threshold in mice. BALB/c mice were inoculated with herpes simplex virus (HSV; 1×10^6 plaque-forming units) on the right hind paw on day 0, and the contralateral hind paw was without inoculation. Data show the percentage of nociceptive threshold calculated as follows: (average force in HSV-inoculated paw/average force in non-inoculated paw) × 100 and are means ± s.e. of five mice. *$P > 0.05$ compared with day 1; **$P = 0.0001$ compared with day 1.

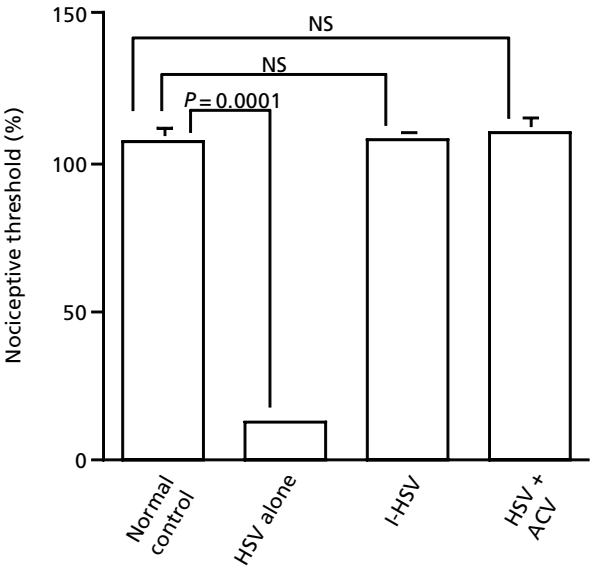

Figure 2 Effect of inoculation with heat-inactivated HSV and repeated treatment with aciclovir (ACV) on nociceptive threshold in mice. BALB/c mice were inoculated with either viable or heat-inactivated herpes simplex virus (HSV; 1×10^6 plaque-forming units) on the right hind paw on day 0 and were treated intraperitoneally with aciclovir (25 mg kg^{-1}) twice a day from 2 h before, 2, 5, and 6 days after HSV inoculation. The changes in nociceptive threshold were examined on day 6. I-HSV, inactivated HSV; NS, not significant ($P > 0.05$). Data are means ± s.e. of five mice.

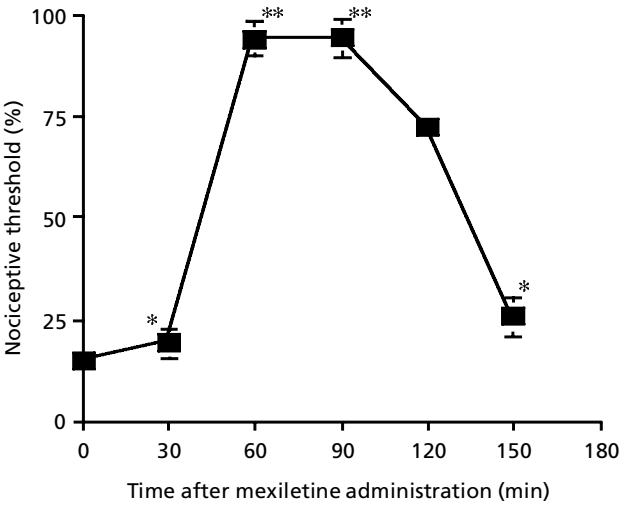

Figure 3 Influence of mexiletine on nociceptive threshold in mice inoculated with HSV. BALB/c mice were inoculated with herpes simplex virus (HSV; 1×10^6 plaque-forming units) on right hind paw on day 0. Mexiletine hydrochloride at a dose of 17.5 mg kg^{-1} was administered once intraperitoneally on day 6, and the nociceptive threshold was measured as indicated. $*P > 0.05$, $**P = 0.0001$ compared with 0 min (before mexiletine administration). Data are means ± s.e. of five mice.

was measured 60 min after mexiletine administration. Mexiletine at a dose of 10.0 mg kg^{-1} did not change the pain-related responses: the nociceptive threshold in treated-mice was nearly identical to that observed in non-treated, HSV-inoculated mice (Figure 4). However, mice treated with 15.0 mg kg^{-1} mexiletine showed a significant suppression of decrease in nociceptive threshold induced by HSV inoculation. This effect reached a peak when experimental mice were treated with more than 17.5 mg kg^{-1} mexiletine.

Influence of mexiletine on β-endorphin and noradrenaline contents in brain from HSV-inoculated, mexiletine-treated mice

The final set of experiments was designed to examine the possible mechanisms by which mexiletine could suppress development of pain-related responses in HSV-inoculated mice by examining β-endorphin and noradrenaline contents in brain. Mice inoculated with HSV were treated with either 10.0 or 17.5 mg kg^{-1} mexiletine, and the β-endorphin content in the brain was measured 60 min after treatment. Mexiletine treatment at a dose of 17.5 mg kg^{-1} did not influence the β-endorphin content in the brain of normal control mice (Figure 5). Treatment of HSV-inoculated mice with 10.0 mg kg^{-1} mexiletine scarcely affected brain β-endorphin levels: β-endorphin levels in brain from 10.0 mg kg^{-1} mexiletine-treated, HSV inoculated mice and controls (Figure 5). However, β-endorphin levels in the midbrain and hypothalamus significantly increased when mice were treated with 17.5 mg kg^{-1} mexiletine (Figure 5). In the final experiments, we examined noradrenaline levels in the pons and medulla oblongata. As shown in Figure 6, mexiletine treatment of HSV-inoculated mice did not affect noradrenaline levels in brain, even when 17.5 mg kg^{-1} of mexiletine was used for treatment.

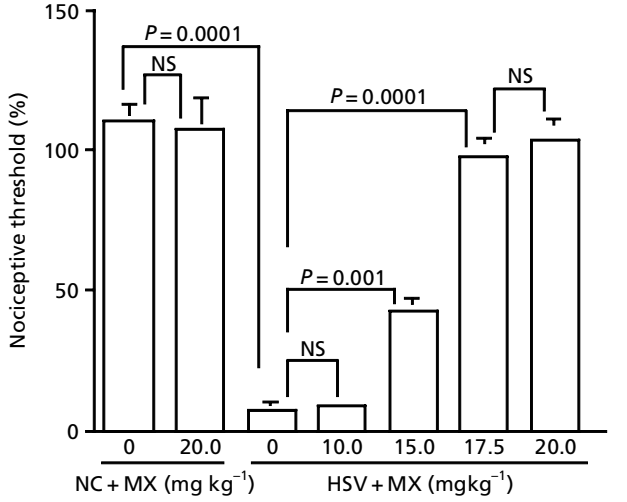

Figure 4 Dose–response profile of mexiletine on nociceptive threshold in mice inoculated with HSV. BALB/c mice were inoculated with herpes simplex virus (HSV; 1×10^6 plaque-forming units) on right hind paw on day 0. Various doses of mexiletine hydrochloride (MX) were administered once intraperitoneally on day 6, and the nociceptive threshold was measured 60 min after MX administration. NC, normal control; NS, not significant ($P > 0.05$). Data are means ± s.e. of five mice.

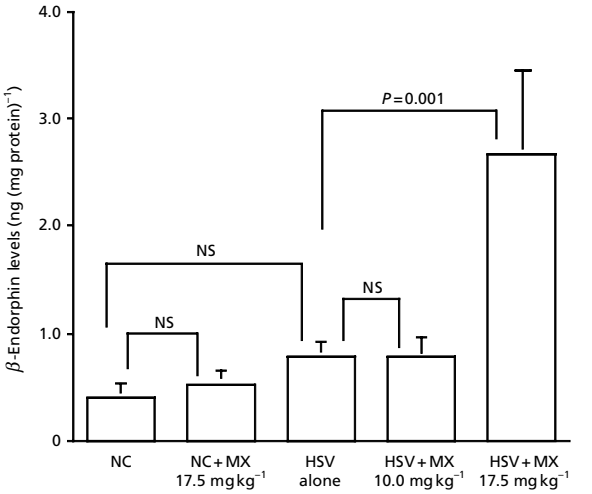

Figure 5 Influence of mexiletine on β-endorphin levels in mid brain and hypothalamus prepared from mice infected with HSV. BALB/c mice were inoculated with herpes simplex virus (HSV; 1×10^6 plaque-forming units) on right hind paw on day 0. Mexiletine hydrochloride (MX) at doses of either 10.0 or 17.5 mg kg^{-1} was administered once intraperitoneally on day 6. After 60 min, β-endorphin contents were examined by ELISA. NC, normal control; NS, not significant ($P > 0.05$). Data are means ± s.e. of five mice.

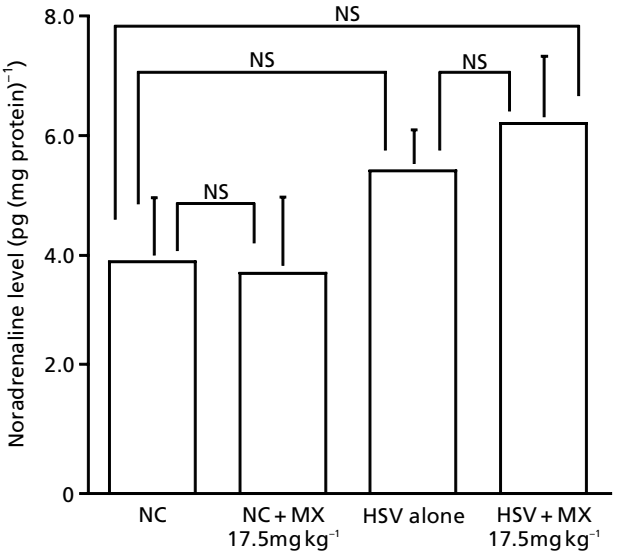

Figure 6 Influence of mexiletine on noradrenaline (norepinephrine) levels in pons and medulla oblongata prepared from mice infected with HSV. BALB/c mice were inoculated with herpes simplex virus (HSV; 1×10^6 plaque-forming units) on right hind paw on day 0. Mexiletine hydrochloride (MX) at a dose of 17.5 mg kg^{-1} was administered once intraperitoneally on day 6. After 60 min, noradrenaline contents were examined by HPLC. NC, normal control; NS, not significant ($P > 0.05$). Data are means ± s.e. of five mice.

Discussion

Herpes zoster is caused by reactivation of latent varicella-zoster virus in the sensory ganglia and is characterized by neurocutaneous symptoms including dermatic rash and severe pain (Dworkin & Portenoy 1996; Dworkin et al 2001). Although there is circumstantial evidence that greater acute pain severity in herpes zoster patients is associated with a significantly greater risk of developing postherpetic neuralgia (Dworkin 1999; Rowbotham & Petersen 2001), the medications used for the treatment of herpes zoster patients are reported to be unable to completely prevent the establishment of postherpetic neuralgia (Galer et al 1999), indicating that the development of antinociceptive drugs for acute herpetic pain to prevent postherpetic neuralgia is urgently needed.

Mexiletine is shown to be effective and extremely well tolerated in the treatment of neuropathic pain syndromes, such as diabetic neuropathy, in experimental animal models and human cases (Chabal et al 1992; Kamei et al 1992). Therefore, we examined the influence of mexiletine on acute herpetic pain, which is classified as a neuropathic pain syndrome, by using HSV-inoculated mice.

In this study, we firstly examined whether HSV inoculation into the hind paw could induce pain-related responses in mice. The results clearly show that HSV inoculation caused decrease in the nociceptive threshold of the inoculated hind paw with the contralateral hind paw being unaffected. Furthermore, inoculation with heat-inactivated HSV produced no pain-related responses, a finding that excludes the possibility that the responses were due to inflammation to herpetic protein in the inoculated hind paw. It is reported that HSV DNA was detectable in the dorsal root ganglia on the inoculated side from day 2 post-inoculation and peaked on day 5 (Takasaki et al 2000a, b), suggesting that HSV reached the dorsal root ganglia in a few days and proliferated around day 5. Therefore, the pain-related responses, which became apparent day 6 post-inoculation and were abolished by aciclovir treatment, may be due to propagation of HSV rather than herpetic infection in sensory neurons and the dorsal root ganglia. This interpretation is supported by the observation that aciclovir is highly effective against HSV in animal models and can inhibit the replication and proliferation of HSV, but not kill the active HSV (Elion 1982).

We then examined the influence of mexiletine on pain-related responses induced by HSV inoculation in mice. The results clearly showed that mexiletine exerts an inhibitory effect on pain-related responses, which was firstly noted at a dose of 15.0 mg kg^{-1} and reached a maximum at 17.5 mg kg^{-1}. It was also observed that this inhibitory action was prolonged for 120 min after mexiletine administration.

Infection of nerve cells obtained from dorsal root ganglia with HSV is reported to alter conformation of the sodium channels and to reduce the number of available sodium channels in plasma membrane, which are responsible for generation of abnormal spontaneous discharge (Fukuda et al 1983). It is also reported that HSV infection in peripheral nerves causes demyelination of nociceptive fibres and the formation of neuromas (Rowbotham & Petersen 2001). These morphological changes are associated with the production of nerve impulses in the absence of any noxious stimulus (Fukuda et al 1983). Electrophysiological observations revealed that sodium-channel blockers are able to suppress spontaneous injury and neuroma discharge in Aδ and C fibres and favourably modify the clinical condition of neuropathic pain, such as diabetic neuropathy, postherpetic neuropathy and phantom limb pain (Chabal et al 1989; Tanelian & Brose 1991; Devor et al 1992). The mechanisms of the antinociceptive effect of mexiletine on neuropathic pain were extensively analysed in diabetic mice and revealed that mexiletine exerts antinociception by blocking sodium channels in both axon and dorsal root ganglion cells (Courtney 1981; Chabal et al 1992; Kamei et al 1992, 1993). Taken together, these results may suggest that the mechanisms of action of mexiletine may involve modulation of nociceptive input at the level of the central nervous system or suppression of afferent discharges at the site of the peripheral nerve by blocking sodium channels in the plasma membrane.

Experimental evidences showed the ability of mexiletine to activate endogenous opioid-mediated antinociceptive systems, resulting in relieving neuropathic pain (Chabal et al 1992; Kamei et al 1995; Asano et al 2001). Therefore, to further examine the possible mechanisms of mexiletine on HSV-induced pain responses, we examined the influence of mexiletine on endogenous opioid levels in brain. Administration of mexiletine into HSV-infected mice enhanced β-endorphin levels in the mid brain and hypothalamus, indicating that mexiletine affects the central nervous

system by increasing in β-endorphin levels and that the activation of descending β-endorphinergic system may be involved in the antinociceptive effects of mexiletine on pain-related responses by HSV infection. In addition to the β-endorphinergic antinociceptive system, it is well accepted that the presence of the descending adrenergic antinociceptive system raised from the pons, in which catecholamines such as noradrenaline in the brain function, is the most important mediator. We, therefore, finally examined noradrenaline levels in pons and medulla oblongata prepared from HSV-inoculated, mexiletine-treated mice. Our data clearly showed that mexiletine did not cause an increase in noradrenaline levels in pons and medulla oblongata, suggesting that activation of the descending adrenergic antinociceptive system is minor in induction of antinociception by mexiletine in HSV-inoculated mice.

Conclusion

These results may suggest that mexiletine will be a good candidate for an antinociceptive agent in the treatment of acute herpetic pain. It is also suggested that administration of mexiletine in the acute phase of herpes zoster may reduce the risk of developing postherpetic neuralgia in man.

References

Asano, K., Hisamitsu, T., Sameshima, T. (2001) Enhancement of β-endorphin contents in mid brain of streptozotocin-induced diabetic rats by mexiletine hydrochloride. *Pain Clinic.* **22**: 807–811

Chabal, C., Russell, L. C., Burchiel, K. J. (1989) The effect of intravenous lidocaine, tocainide, and mexiletine on spontaneously active fibers originating in rat sciatic neuromas. *Pain* **38**: 333–338

Chabal, C., Jacobson, L., Mariano, A. (1992) The use of oral mexiletine for the treatment of pain after peripheral nerve injury. *Anesthesiology* **76**: 513–517

Courtney, K. R. (1981) Comparative actions of mexiletine on sodium channels in nerve, skeletal and cardiac muscle. *Eur. J. Pharmacol.* **74**: 9–18

Devor, M., Wall, P. D., Catalan, N. (1992) Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* **48**: 261–268

Dworkin, R. H. (1999) Prevention of postherpetic neuralgia. *Lancet* **353** (May 15): 1636–1637

Dworkin, R. H., Portenoy, R. K. (1996) Pain and its persistence in herpes zoster. *Pain* **67**: 241–251

Dworkin, R. H., Nagasako, E. M., Johnson, R.W., Griffin, D. R. (2001) Acute pain in herpes zoster: the famciclovir database project. *Pain* **94**: 113–119

Elion, G. B. (1982) Mechanisms of action and selectivity of acyclovir. *Am. J. Med* **73**: 7–13

Fukuda, J., Kurata, T., Yamaguchi, K. (1983) Specific reduction in Na currents after infection with herpes simplex virus in cultured mammalian nerve cells. *Brain Res.* **268**: 367–371

Galer, B. S., Rowbotham, M. C., Perander, J., Friedman, E. (1999) Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain* **80**: 533–538

Kamei, J., Hitosugi, H., Kawashima, N., Aoki, T., Ohhashi, Y., Kasuya, Y. (1992) Antinociceptive effect of mexiletine in diabetic mice. *Res. Commun. Chem. Pathol. Pharmacol.* **77**: 245–248

Kamei, J., Hitosugi, H., Kasuya, Y. (1993) Effects of mexiletine on formalin-induced nociceptive responses in mice. *Res. Commun. Chem. Pathol. Pharmacol.* **80**: 153–162

Kamei, J., Saitoh, A., Kasuya, Y. (1995) Involvement of δ1-opioid receptors in the antinociceptive effects of mexiletine in mice. *Neurosci Lett.* **196**: 169–172

Liesegang, T. J. (1999) Varicella zoster viral disease. *Mayo Clin. Proc.* **74**: 983–998

McQuay, H. J., Tramer, M., Nye, B. A., Carroll, D., Wiffen, P. J., Moore, R. A. (1996) A systemic review of antidepressants in neuropathic pain. *Pain* **68**: 217–227

Rowbotham, M. C., Petersen, K. L. (2001) Zoster-associated pain and neural dysfunction. *Pain* **93**: 1–5

Shinozuka, K., Ishii-Nozawa, R., Takeuchi, K., Minakawa, N., Matsuda, A., Nakata, H., Kunitomo, M. (2001) Effect of 9-(6,7-dideoxy-beta-D-allo-hept-5-ynofuranosyl) adenine on noradrenalin release from vascular sympathetic nerves. *Clin. Exp. Pharmacol. Physiol.* **28**: 312–314

Takasaki, I., Andoh, T., Shiraki, K., Kuraishi, Y. (2000a) Allodynia and hyperalgesia induced by herpes simplex virus type-1 infection in mice. *Pain* **86**: 95–101

Takasaki, I., Nitta, M., Takahata, H., Nemoto, H., Nojima, H., Shiraki, K., Kuraishi, Y. (2000b) Pharmacological and immunohistochemical characterization of a mouse model of acute herpetic pain. *Jpn. J. Pharmacol.* **83**: 319–326

Takasaki, I., Sasaki, A., Andoh, T., Nojima, H., Shiraki, K., Kuraishi, Y. (2002) Effects of analgesic on delayed postherpetic pain in mice. *Anesthesiology* **96**: 1168–1174

Tanelian, D. L., Brose, W. G. (1991) Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blocker: lidocaine, carbamazepine, and mexiletine. *Anesthesiology* **74**: 949–951

Watson, C. P., Babul, N. (1998) Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology* **50**: 1837–1841