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RESEARCH ARTICLE

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Characterization of heat-hyperalgesia in an experimental trigeminal neuropathy in rats

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Abstract Secondary trigeminal neuralgia (STN) follows an injury to the trigeminal nerve or one of its branches. Although rare, this condition results in great suffering and it is notoriously difficult to treat. The experimental analysis of painful neuropathy due to damage to the innervation of the limbs (e.g., the sciatic nerve) has progressed rapidly in recent years, but very few reports have appeared concerning experimental neuropathy in the trigemenial region. We report here an experimental rat model of trigeminal neuropathic pain produced by a chronic constriction injury to the infraorbital nerve (CCI-ION), and on a method that detects heat-evoked pain-related behavior. Rats with the CCI-ION have clear signs of heat-hyperalgesia when stimulated on the snout (the vibrissal pad). The hyperalgesia is seen both ipsi- and contralateral to the side of nerve injury, but is significantly more severe ipsilaterally, and lasts about 12 days.

Key words Chronic constriction injury · Infraorbital nerve · Painful trigeminal neuropathy · Heat-hyperalgesia · Rat

Introduction

Trauma, dental treatments, and orofacial surgery sometimes produce chronic neuropathic pain syndromes, which are variously diagnosed as secondary trigeminal neuralgia (STN), peripheral neuropathy, or reflex sympathetic dystrophy (Hanowell and Kennedy 1979; Khoury et al. 1980; Massler 1981; Jaeger et al. 1986). Although they have some features in common, STN is distinct from idiopathic trigeminal neuralgia (ITN; tic douloureux). The pain of ITN is described as paroxysmal and similar to an electric shock. The pain attacks are usually triggered by light mechanical contact from a more or less restricted site. The site that triggers the attack may be distant from the region in which the pain is felt. The attacks are usually of brief duration and it is sometimes possible to demonstrate a brief post-ictal period during which pain cannot be evoked immediately after an attack. The patient is free of pain between attacks, although attacks that are severe or that follow one another quickly may result in a lingering soreness. Neurological examination is generally negative, but an area of facial hypoaesthesia may be present. The lesion of ITN is considered to lie in the trigeminal ganglion or trigeminal root (Jannetta 1967; Rappaport and Devor 1994).

The presentation of STN is different and it more closely resembles the symptoms seen following injury to nerves of spinal origin. The pain is described as burning and superficial, often with a dysaesthetic component, and/or as a constant deep aching pain, which may be worse at night. Sharp lancinating "tabetic" pains sometimes are present. STN-evoked pains follow innocuous or noxious stimulation of the painful region, and distant trigger points are absent, as are the post-ictal periods (Merskey and Bogduk 1994).

The importance of ITN and of painful peripheral neuropathy in the extremities is widely recognized, but case reports of STN, trigeminal causalgia, trigeminal reflex sympathetic dystrophy, etc., are rare. Nevertheless, it has been reported that the prevalence of STN is 5–10% following facial fractures, 1–5% after removal of impacted teeth, and "common" after reconstructive orthognathic surgery (Merskey and Bogduk 1994).

Studies of STN in experimental animals have only recently begun to appear (Vos and Maciewicz 1991; Kryzhanovskii et al. 1991; Kawamoto and Imamura 1993; Imamura and Kawamoto 1993; Vos et al. 1994; Imamura and Bennett 1995). Rats with STN-producing injuries show few or no signs of motor impairment, in contrast to the models using injury to mixed nerves of spinal origin. However, as with injuries to nerves of spinal origin, rats with STN show signs of abnormal spontaneous pain-related behavior, and hypersensitivity to tactile stimuli (Vos and Maciewicz 1991; Kryzhanovskii et

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al. 1993; Vos et al. 1994). Nevertheless, heat-hyperalgesia, which is a prominent symptom in the models of injury to nerves of spinal origin, has received little study (Kryzhanovskii et al. 1992). When studying experimental pain syndromes that involve the extremities, tests of heat-hyperalgesia can be done on the glabrous skin of the paws. In the trigeminal region of the rat, the only skin that is not thickly covered by hair is the rhinarium (the area at the tip of the snout, surrounding the nares), and this is difficult to stimulate with radiant heat because the light will shine in the rat's eyes. As we described here, rats with a chronic constriction injury to the infraorbital nerve have heat-hyperalgesia that can be measured by radiant heat stimulation of the hairy skin on the lateral snout (the vibrissal pad).

Materials and methods

Animals

Eighteen male Sprague-Dawley rats (Charles River; 200–350 g) were used. Two or three rats were housed per cage; standard rat chow and water were available ad libitum. Animals were treated and cared for according to the regulations of the Kyushu Dental College Animal Care and Use Committee and the ethical standards and guidelines for investigations of experimental pain in animals prescribed by the International Association for the Study of Pain (Zimmermann 1983).

Surgery

Eleven rats received a chronic constriction injury (CCI) to one intraorbital nerve (ION) and a sham operation on the other side (CCI group). All surgery was performed under general anesthesia with 50 mg/kg (i.p.) of pentobarbital sodium. All incisions were made intraorally, which allowed the hair on the snout and the vibrissae to remain intact. An incision approximately 1 cm long was made along the gingivobuccal margin (Fig. 1). The incision was begun just proximal to the first molar. About 0.5 cm of the ION was freed of adhering tissue, and two ligatures (4.0 chromic gut) were tied loosely around it. The loose ligature method was patterned after the method that has been used successfully with the sciatic nerve (Bennett and Xie 1988). The incision was sutured at three points using 4.0 silk. The sham operation was identical except that the nerve was not ligated. An additional 11 rats received only a unilateral sham operation (SHM group). All operations were performed aseptically; no antibiotics were administered.

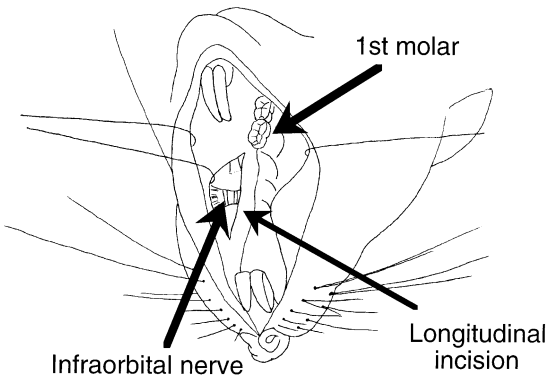

Fig. 1 Surgery. In the CCI group, the infraorbital nerve (ION) was exposed and freed from adhering tissue, and two loosely constrictive ligatures were tied around it (chronic constriction injury, CCI). A sham operation was performed contralaterally. Rats in the SHM group received a sham operation. The contralateral ION was kept intact

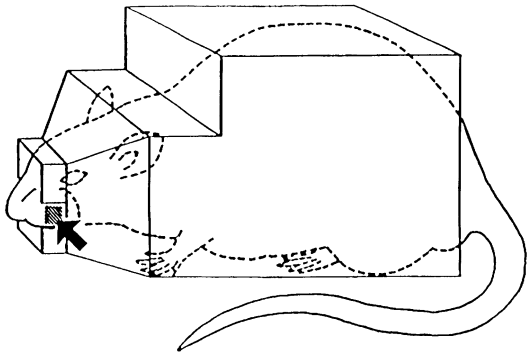

Fig. 2 Restrainer and heat stimulus source. The rats were loosely restrained within specially made paper boxes, which had a small opening at their front end. The opening was shaped such that the rat could put its snout through it, but small "blinders" along the upper edge of the hole occluded the animal's vision. There was a sufficient room in the box for the animal to quickly and completely withdraw its snout from the hole. After thorough habituation to the box, rats stood calmly and spent most of their time with the snout protruding through the hole. A beam of noxious radiant heat was aimed at the side of the snout (vibrissal pad: *arrow*). The light source was made from the lamp housing of a fiber optic microscope illuminator (Nikon). Guidelines marked on the floor of the test environment assured a nearly constant distance between the skin and the heat source

Heat-hyperalgesia test

The rats were loosely restrained within specially prepared boxes that had an opening at one end that allowed the rat's snout to poke through (Fig. 2). The upper lateral margins of the opening were fitted with flaps ("blinders") that occluded the rat's vision when its snout was protruding. The box and opening were large enough for the rat to easily withdraw, flick or rotate its snout. Pilot studies showed that reliable measurements were critically dependent on animals that were thoroughly habituated to handling, to the loose restraint of the box, and that habitually stood calmly with their snouts protruding. A few days of handling and exposure to the box restraint followed by 2–3 days for application of heat stimulation were usually sufficient to observe their behavior throughout the experimental period, but an occasional animal never evinced the desired behavior and these were eliminated from the study.

The radiant heat stimulus was a focused 7×7 mm beam of light from a modified microscope (Nikon) illuminator whose aperture was 10 cm from the stimulation site. Head withdrawal latencies (WLs) were measured automatically. Withdrawal or flicking of the snout was detected by a photocell that terminated the stimulus and a timer. Skin temperature rose above 45° C within 8.5 s (Fig. 3). WLs were determined three times on each side with 2-min intervals between tests. An 18-s cut-off was used to prevent tissue damage. All rats were tested preoperatively and on postoperative days (POD) 4, 8, 12, 16, 20, 24, and 28.

Body weight change

Body weight (BW) of eight CCI rats and eight SHM rats was measured every 3 days after operation.

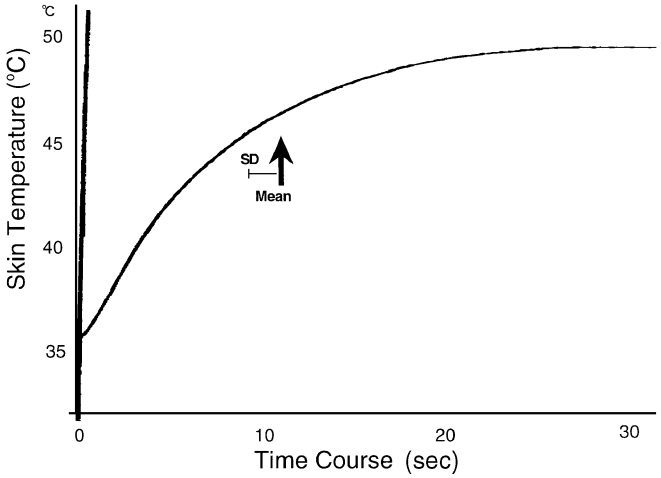

Fig. 3 Skin temperature after radiant heat application. The temperature reached 43° C in 3.3 s and the rose above 45° C in 8.5 s. The mean (±SEM) preoperative withdrawal latency is shown on the graph

Statistics

A mean average value was calculated for each rat from the three WLs on each side. One-factorial ANOVA was used to analyze the difference between groups and sides of the face. Repeated measures ANOVAs (RMANOVA) were used to analyze the latency according to the time course. Post-hoc pairwise comparisons were performed with Fisher's PLSD. The unpaired *t*-test was used to compare differences of body weight between the SHM group and the CCI group. A *P*-value of 0.05 or less was defined as statistically significant.

Results

General observations

We observed four types of responses to the noxious heat: (1) Vigorous withdrawal or flicks without a preceding sniff. Rats responding with this or the second pattern sometimes rubbed their snouts between their forepaws after flicking or withdrawing. (2) Some rats first sniffed then withdrew or flicked their snouts vigorously. (3) A few rats sniffed vigorously but did not flick or withdraw within the 18 s allowed. (4) A few rats did not sniff vigorously and failed to flick or withdraw. The third and fourth types of responses were occasionally seen in animals that usually flicked or withdrew vigorously. WLs were measured again after at least a 2-min interval in the rats that showed these two types of responses.

Four rats were excluded before operation for two reasons: no response to the heat stimulation and retraction of the snout that made heat application impossible. Two rats in each group repeatedly showed WLs of more than 18 s on POD 4 and 16. Once a rat repeatedly showed no response on one side of the snout at a given time, it always showed a delayed or no response on the other side. These rats are exhibiting a fear-related behavior, rather than reduced sensitivity. Such rats kept their snouts retracted in the box after this point. WL was no longer measured in these rats and all data concerning these animals were excluded. Nine rats from each of the two groups were eventually used in this study. Three of nine in the SHM group and four of nine in the CCI group needed additional stimuli at certain measuring points to produce a response.

Groups, time course, side of the face and WLs

Significant variations of WLs were observed within "groups" and "time course" by one-factor ANOVA analysis (F=17.77, P=0.0001 and F=3.30, P=0.0012 respectively).

In the SHM group, preoperative WLs were very similar on the two sides of the face: 10.6±0.3 s and 11.3±0.3 s (mean±SEM, n=9). There was no significant difference between the variances of the two sides (F=0.016, P=0.8996) and the data on both sides of the SHM group were used as controls (n=18). Following unilateral sham surgery, the SHM group WLs displayed no statistically significant change over the 28 days of observation (RMANOVA, Fig. 4).

As shown in Fig. 5, rats with the CCI (n=9) had significantly shorter WLs on both sides throughout the 28 days of testing compared with preoperative data (contralateral: F=2.23, P=0.0291; ipsilateral: F=4.76, P=0.0001). For example, on the nerve-injured side the group's average preoperative WL was 11.8±0.4 s (mean±SEM) compared with a mean of 7.9±0.6 s on POD 8 (P=0.0001) and 8.5±0.8 s on POD 12 (P=0.0009). The contralateral side showed significantly decreased

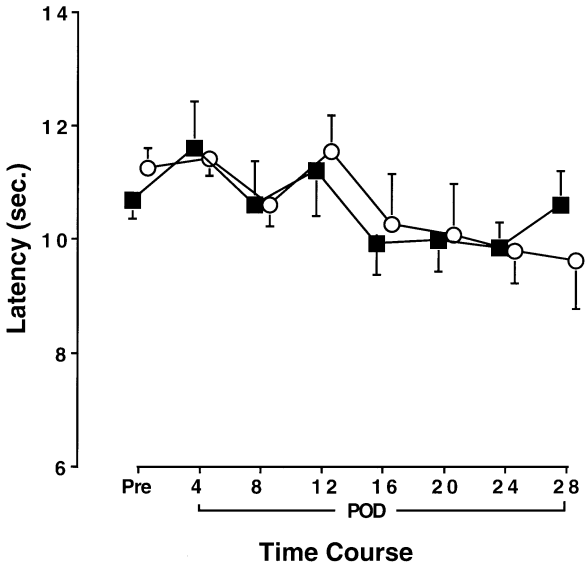

Fig. 4 Withdrawal latencies (WLs) in the group with unilateral sham surgery. *Filled squares* SHM contralateral (SHMC), *open circles* SHM ipsilateral (SHMI) (mean±SEM). None of the WLs from the postsurgical period is significantly different from the presurgical baseline, and there are no statistically significant side-to-side differences at any time. *POD* postoperative day

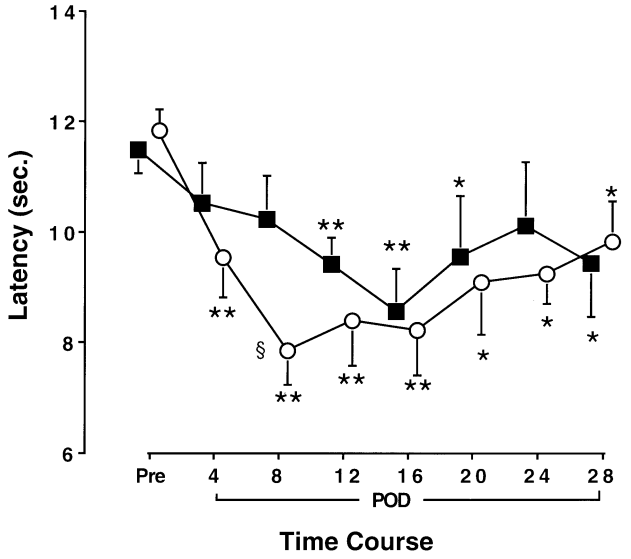

Fig. 5 Time course of WLs in the CCI group. *Filled squares* CCI contralateral (CCIC), *open circles* CCI ipsilateral (CCII) (mean±SEM). * $P<0.05$ versus preoperative value; ** $P<0.01$ versus preoperative value; § $P<0.05$ versus CCIC. WLs in the CCI group decreased bilaterally. Reduced latencies were observed from postoperative day (POD) 4 onwards on the ipsilateral side and from POD 12 onwards on the contralateral side. WLs decreased more significantly on the ipsilateral side than on the contralateral side. However, a significant difference was observed between the two sides only on POD 8

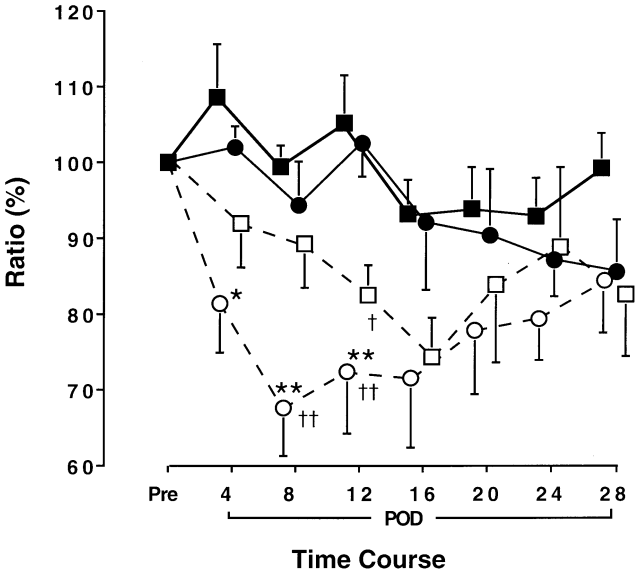

Fig. 6 Heat-hyperalgesia in the SHM and CCI groups. *Filled squares* SHMC, *filled circles* SHMI, *open squares* CCIC, *open circles* CCII (mean±SEM). * $P<0.05$ versus SHMC; ** $P<0.01$ versus SHMC; † $P<0.05$ versus SHMI; †† $P<0.01$ versus SHMI. A significant difference between CCII and the SHM groups was observed in an early period (POD 4 to 12). WL in CCIC decreased significantly compared with the SHM groups only on POD 12

postoperative WLs as well: for example, the preoperative WLs were 11.5±0.4 s and 9.4±0.5 s on POD 12 (P=0.0098) and 8.6±0.8 s on POD 16 (P=0.0004). The degree of WL decrease in the CCI group was generally greater on the nerve-injured side (F=3.009, P=0.0037), but the side-to-side difference in severity was statistically significant only on POD 8 (P=0.0179).

Figure 6 shows postoperative variations compared among groups and sides of the face. Significant difference was observed among SHM ipsilateral and contralateral (SHMI, SHMC) and CCI ipsilateral and contralateral (CCII, CCIC) on POD 4, 8, and 12 (F=3.37, P=0.0349; F=3.91, P=0.0173; and F=5.00, P=0.0096 respectively). The CCII group was more significantly sensitive to the noxious heat (heat-hyperalgesia) than was the SHM group on POD 4 (P-value was 0.0432 vs SHMI), POD 8 (P=0.0067 vs SHMC and 0.0065 vs SHMI) and POD 12 (P=0.0083 vs SHMC and 0.0035 vs SHMI). The CCIC group showed a statistically significant decrease in WL on POD 12 (P=0.0376 vs SHMI).

These data show that heat-hyperalgesia was marked on the nerve-injured side of the CCI group between POD 4 and POD 12. Mild heat-hyperalgesia was observed in the CCIC group.

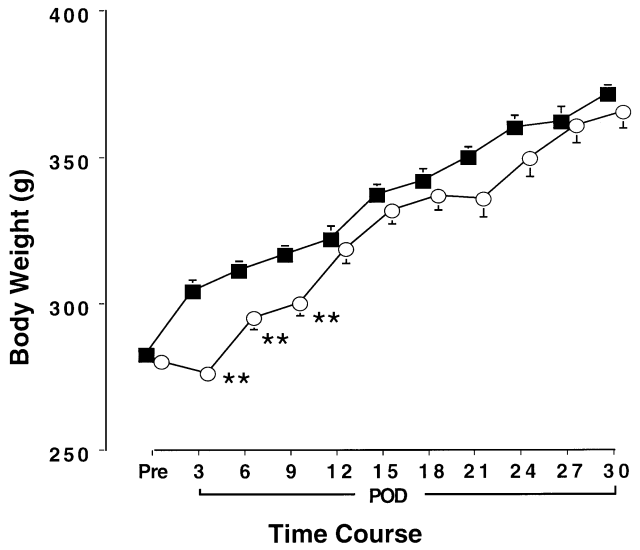

Fig. 7 Body weight change after operation. *Filled squares* SHM group, *open circles* CCI group. ** $P<0.01$ versus SHM (mean±SEM). Body weight kept increasing after the sham operation; however, it decreased transiently after the CCI operation. A significant difference between the CCI group and the SHM group was observed from POD 3 to 9

BW change

Rats with the CCI underwent a transient weight loss after operation, although the SHM group did not. There was a significant difference in BW change between the two groups with time (F=159.3, P=0.0001). The average BW of the SHM group on POD 3 was 304.9±4.0 g (mean±SEM) versus 277.0±2.9 g in the CCI group (P=0.0001), on POD 6 was 311.9±3.7 g versus 295.9±3.6 g (P=0.0078) and on POD 9 was 317.6±3.4 g

versus 300.9±3.9 g (P=0.0060). BW of the CCI rats recovered, however, after POD 12 and further significant differences versus the SHM rats were not observed (Fig. 7).

Discussion

CCI and heat-hyperalgesia

The WL measure was a clear expression of a pronounced heat-hyperalgesia in rats with the CCI. The hyperalgesia was present bilaterally, but was more severe on the side of the nerve injury. The hyperalgesia was apparent within 4 days of surgery and lasted for 8 days, with peak symptom severity occurring during the period approximately 8–12 days postoperatively. Rats receiving a unilateral sham operation showed no significant change in WL during the 28 days of observation. The absence of change in the group with unilateral sham surgery indicates that the bilateral hyperalgesia of the CCI group is an effect of nerve injury, rather than an effect of intraoral surgical trauma. Moreover, the absence of any change in the unilateral sham surgery group indicates that the CCI group's contralateral hyperalgesia was a specific effect of unilateral nerve injury. It is of interest to note that the mechano-allodynia and mechano-hyperalgesia produced by the intraorbital nerve injury model of Vos et al. (1994) do not appear until approximately 12 days post-injury, a clear delay relative to the heat-hyperalgesia reported here.

Food intake in the CCI rats was reduced transiently, but it recovered after POD 12. The period of weight loss corresponded to the heat-hyperalgesic period in the CCI-ION rats. Hyperalgesia after the CCI operation on ION seems to continue for a shorter time than that in the sciatic CCI model (Bennett and Xie 1987). Feeding is one of the most important activities of daily living. No creature can live without eating, although it can function without the use of an extremity. Some patients suffering from postherpetic neuralgia in the extremities guard the affected hands and arms from stimuli and never use them, but those who are suffering from postherpetic neuralgia in trigeminal divisions cannot stop using their mouths. Muscle contracture and atrophy progress by disuse of extremities in complex regional pain syndrome (CRPS). There may be a mechanism that prevents the progress of hyperalgesia after the CCI-ION, and using the jaws and mouth per se may prevent the progress of functional disability.

Hyperalgesia contralateral to sciatic nerve injury has been reported by several groups. In the sciatic nerve CCI model, contralateral heat-hyperalgesia of modest severity (compared with the ipsilateral effect) has been noted in some laboratories (Attal et al. 1989) but not by others (Bennett and Xie 1988). A modest contralateral effect has been noted in the spinal nerve ligation model of Kim and Chung (1992). Pronounced contralateral heat- and mechano-hyperalgesia are present in the partial nerve ligation model of Seltzer et al. (1990), and a pronounced contralateral mechano-hyperalgesia (without heat-hyperalgesia on either side) is reported in the cryoneurolysis method of DeLeo et al. (1994). A pronounced mechano-hyperalgesia and mechano-allodynia on the contralateral side also are reported to occur in trigeminal CCI models (Vos et al. 1994; Kryzhanovskii et al. 1993).

The mechanisms producing contralateral hyperalgesia are unknown. There are several reports of trigeminal primary afferent projections to the contralateral subnucleus caudalis (Arvidsson and Gobel 1981; Jacquin et al. 1990; Westrum and Henry 1991). Contralateral effects other than pain have also been reported. For example, Sugimoto et al. (1985) reported that unilateral section of the inferior alveolar nerve produced transsynaptic degeneration bilaterally in the subnucleus caudalis. Moreover, Tokunaga (1992) has shown that unilateral noxious stimulation evokes a contralateral increase in preprodynorphin and preprotachykinin mRNAs in the subnucleus caudalis. In the clinic, mirror-image pain is an unusual, but not rare, phenomenon in post-traumatic neuropathies of the limbs. However, we are not aware of any clinical reports of mirror-image trigeminal neuropathic pain.

Patients with STN complain of spontaneous pain and mechano-allodynia. We are not aware of any case reports that document the existence of heat-hyperalgesia in trigeminal neuropathy. It may be that this symptom has simply not been looked for. It is commonly, although not universally, present in post-traumatic neuropathies of the extremities, but such patients do not frequently complain of heat-hyperalgesia. On careful questioning, however, they often report that exposure to strong sunlight or hot bath water is abnormally painful and careful psychophysical testing is necessary to confirm the presence of hyperalgesia (Price et al. 1989).

Noxious heat-evoked behavior from the trigeminal region

In the rat, the most thoroughly studied trigeminal nocifensive response is the jaw-opening reflex, an analog of the limb withdrawal reflex, which is typically studied in lightly anesthetized preparations with electrical stimulation of the dental pulp (Mitchel 1964). However, this reflex appears to be most readily evoked by intraoral stimulation. Nocifensive responses evoked from the rat's facial skin previously have been studied with various kinds of contact thermodes (Rosenfeld et al. 1978, 1983; Morris et al. 1982; Clavelou et al. 1989). Noxious heat-evoked responses obtained with contact thermodes include head withdrawal, face rubbing (repetitive wiping motions with the forepaws), and vocalization. Pain-related responses elicited by mechanical stimulation of the facial region include sniffing, face rubbing, head withdrawal, and sometimes freezing (Vos and Maciewicz 1991).

For the study of heat-evoked responses, stimulation with contact thermodes has the problem that it first activates low-threshold mechanoreceptors innervating facial hairs and the vibrissae (mystacial, superorbital, and buc-

cal groups), thereby possibly signaling the animal about pain. In the neuropathic case, where mechano-allodynia (touch-evoked pain) may be present, more contact with the thermode may produce pain, preventing simple analysis of heat-evoked pain. The method used in the present study employed radiant heat, according to the method of Hargreaves et al. (1988) for the rat paw. The rats responded to this stimulus in a way that is consistent with their experiencing pain. The withdrawal and "flick" responses are obviously nocifensive in that they avoid the stimulus. The paw withdrawal ("flick" response is a spinally mediated reflex, but it is not certain whether "flicking" the snout is similarly reflexive. Snout withdrawal is most likely to be an integrated escape response, akin to leg lifting and jumping in the hot plate test.

When rats feel anxiety or fear, responses to noxious stimuli might be modified by stress. Stress facilitates secretion of adrenocortical hormones (Mueller 1981; Sourxes 1983) and induces "fear-induced opiate analgesia" (Fanselow 1986). Rats may freeze in such a circumstance (Fanselow 1986; Helmstetter 1993; Rudy 1993). These modifications were conceivable in every procedure during measurement so that rats had to be observed carefully throughout the test. We emphasize that the method that we describe here works well only with thoroughly habituated rats that have learned to stand quietly in the restraining boxes with their snouts protruding. Some animals never acquire the desired behavior and these must be eliminated before the experimental intervention. As with any behavioral method, extraneous stimuli (with special emphasis on sounds and odors) in the testing environment must be minimized and standardized. In the present study, skin temperature rose above 45º C in 8.5 s and the cut-off time (18 s) was a reasonable interval in which to judge rats as freezing or indicating severe hypoesthesia. A paired comparison is useful to avoid the influence of stress on different individuals. The evidence that there was no significant difference between bilateral WL in the SHM group throughout this observation period shows the appropriateness of our protocol.

A chronic constriction injury to the rat's infraorbital nerve produces clear signs of neuropathic heat-hyperalgesia. Previous studies on CCI models have demonstrated that mechano-allodynia depends on the neuroplasticity of larger fibers. The present study revealed that CCI-ION elicits heat-hyperalgesia, which more than likely depends on the neuroplasticity of smaller fibers. Studies at the light- and electron-microscopic levels are currently being carried out in our laboratory to determine the damage to these fibers. With the use of this heat-hyperalgesic model, future work may clarify the mechanisms that produce STN and may prove to be useful as preclinical tests of new drug therapies for STN.

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