Encoding of Corneal Input in Two Distinct Regions of the Spinal Trigeminal Nucleus in the Rat: Cutaneous Receptive Field Properties, Responses to Thermal and Chemical Stimulation, Modulation by Diffuse Noxious Inhibitory Controls, and Projections to the Parabrachial Area

I. D. MENG, J. W. HU, A. P. BENETTI, AND D. A. BEREITER

1Department of Neuroscience and 2Department of Surgery, Brown University/Rhode Island Hospital, Providence, Rhode Island 02903; and 3Faculty of Dentistry, University of Toronto, Toronto, Ontario M5G 1G6, Canada

Meng, I. D., J. W. Hu, A. P. Benetti, and D. A. Bereiter. Encoding of corneal input in two distinct regions of the spinal trigeminal nucleus in the rat: cutaneous receptive field properties, responses to thermal and chemical stimulation, modulation by diffuse noxious inhibitory controls, and projections to the parabrachial area. J. Neurophysiol. 77: 43–56, 1997. To determine whether corneal input is processed similarly at rostral and caudal levels of the spinal trigeminal nucleus, the response properties of second-order neurons at the transition between trigeminal subnucleus interpolaris and subnucleus caudalis (Vi/Vc) and at the transition between subnucleus caudalis and the cervical spinal cord (Vc/C1) were compared. Extracellular single units were recorded in 68 Sprague-Dawley rats under chloralose or urethane/chloralose anesthesia. Neurons that responded to electrical stimulation of the cornea at the Vi/Vc transition region (n = 61) and at laminae I/II of the Vc/C1 transition region (n = 33) were classified according to 1) corneal mechanical threshold; 2) cutaneous mechanoreceptive field, if present; 3) electrical input characteristics (A and/or C fiber); 4) response to thermal stimulation; 5) response to the small-fiber excitant, mustard oil (MO), applied to the cornea; 6) diffuse noxious inhibitory controls (DNIC); and 7) projection status to the contralateral parabrachial area (PBA). On the basis of cutaneous receptive field properties, neurons were classified as low-threshold mechanoreceptive (LTM), wide dynamic range (WDR), nociceptive specific (NS), or deep nociceptive (D). All neurons recorded at the Vc/C1 transition region were either WDR (n = 19) or NS (n = 14). In contrast, 54% of the Vi/Vc neurons had no cutaneous receptive field. Of those Vi/Vc neurons that had a cutaneous receptive field, 57% were LTM, 25% were WDR, and 18% were D. All Vc/C1 neurons responded to noxious thermal and MO stimulation. Only 22 of 47 and 13 of 19 Vi/Vc corneal units responded to thermal or MO stimulation, respectively. At the Vc/C1 transition region, 12 of 17 neurons demonstrated DNIC, whereas at the Vi/Vc transition region, DNIC was present in only 4 of 26 neurons. Of 15 Vc/C1 corneal units, 12 could be antidromically activated from the contralateral PBA (average latency 6.29 ms, range 1.8–26 ms). None of 22 Vi/Vc corneal units tested could be antidromically activated from the PBA. These findings suggest that neurons in laminae I/II at the Vc/C1 transition and at the Vi/Vc transition process corneal afferent input differently. Neurons in laminae I/II at the Vc/C1 transition process corneal afferent input consistent with that from other orofacial regions. Corneal-responsive neurons at the Vi/Vc transition region may be important in motor reflexes or in recruitment of descending antinociceptive controls.

INTRODUCTION

The spinal trigeminal nucleus (Vsp) is divided into three subnuclei: subnucleus oralis, interpolaris, and caudalis (Vc) (Olszewski 1950). The role of Vc as a primary relay for orofacial pain has been well established (Dubner and Bennett 1983; Sessle 1987). On the basis of similar anatomic and functional properties with the dorsal horn of the spinal cord, Vc often has been referred to as the medullary dorsal horn (Dubner and Bennett 1983; Gobel et al. 1977). Although the role of rostral Vsp in nociception remains uncertain, several studies have characterized neurons in rostral Vsp that respond to noxious oralofacial stimuli (Campbell et al. 1985; Dallel et al. 1990; Davis and Dostrovsky 1988b; Hayashi et al. 1984; Ohya 1992). The cornea has been used extensively as a model for studying trigeminal nociception; however, the response properties of second-order corneal-responsive neurons at rostral and caudal levels of Vsp have not been compared.

Axonal tract tracing studies of corneal primary afferents in the rat have demonstrated projections to two regions within Vsp: the ventrolateral portion of Vsp at the transition between trigeminal subnucleus interpolaris and Vc (Vi/Vc) and the most caudal portions of Vc at the spinomedullary junction (Vc/C1) (Marfurt and Del Toro 1987). In addition, quantitative analyses of Fos-like immunoreactivity (Fos-LI) in the rat following noxious stimulation of the cornea have shown a characteristic bimodal distribution of Fos-LI along the rostrocaudal axis of Vsp, in general agreement with results from axonal tract tracing studies (Bereiter et al. 1996; Lu et al. 1993; Meng and Bereiter 1996; Strassman and Vos 1993). The significance of the bimodal representation of the cornea in Vsp is unclear. Much of the corneal afferent terminations at the Vi/Vc transition region are near or within the trigeminal descending tract, a region often referred to as the interstitial islands of Cajal (Olszewski 1950) or the paratrigeminal nucleus (Chan-Palay 1978). In a detailed examination of cytology...
throughout this region, Phelan and Falls (1989) conclude that although the interstitial islands at the level of the subnucleus interpolaris represent distinct subnuclei within Vsp, the ventrolateral pole at the Vi/Vc transition region that receives corneal input is a rostral extension of laminae I/II of Vc. Likewise, results from axonal tract tracing studies have demonstrated that neurons from the Vi/Vc transition region and laminae I/II of Vc project to similar regions, including the thalamus (Fukushima and Kerr 1979) and parabranchial area (PBA) (Feil and Herbert 1995). Also, substance P (South and Ritter 1986), calcitonin-gene-related-peptide (CGRP) (Kruger et al. 1988), and enkephalin (Schults 1992) immunoreactivity in the Vi/Vc transition region is continuous with that seen in laminae I/II of Vc. Several studies have used neuropeptide staining to delineate the rostral extent and medial displacement of lamina I/II neurons (Meng and Bereiter 1996; Schults 1992; Strassman and Vos 1993; Yoshida et al. 1991). Double immunostaining for CGRP fibers and Fos-positive neurons after corneal stimulation has revealed considerable overlap at the Vi/Vc transition region (Meng and Bereiter 1996).

Despite the similarities between laminae I/II of Vc and the Vi/Vc transition region, recent evidence suggests that corneal input to the Vi/Vc and Vc/C1 transition regions is processed differently. Fos-LI at the Vi/Vc and Vc/C1 transition regions has been quantified after application of a variety of chemical and thermal stimuli to the cornea (Meng and Bereiter 1996). All thermal stimuli, including noxious and innocuous stimuli, caused a similar increase in Fos-LI at the ipsilateral Vi/Vc transition region. In contrast, only 52°C thermal probe and mustard oil (MO) stimulation produced Fos-LI within the superficial laminae at the Vc/C1 transition region. These results indicate that select features of corneal stimuli such as thermal intensity are encoded differently by neurons at the Vi/Vc and Vc/C1 transition regions. Additional experiments in which Fos-LI was used after corneal stimulation have shown that Vc/C1 neurons are more sensitive to circulating adrenal steroid levels and morphine than are Vi/Vc neurons (Bereiter 1996; Lu et al. 1993). Adrenalectomy enhanced the Fos-LI response after 52°C thermal probe stimulation of the cornea at the Vc/C1 but not at the Vi/Vc transition region compared with responses in adrenal-intact animals. Morphine pretreatment diminished the Fos-LI response at the Vc/C1 but not the Vi/Vc transition region after corneal MO stimulation.

Although no study has directly compared the response properties of corneal-responsive neurons located at the Vi/Vc transition region with those at Vc/C1 levels, the receptive field properties of corneal units at the Vi/Vc transition region in the rat (Pozo and Cervero 1993) and caudal Vc in the cat have been reported (Mosso and Kruger 1973; Nishida and Yokota 1991). In superficial laminae of Vc in the cat, corneal units did not have a cutaneous receptive field and responded to thermal, chemical, and mechanical stimuli (Nishida and Yokota 1991). At the Vi/Vc transition region in the rat, more than half of the corneal units were classified as either nociceptive-specific (NS) or wide-dynamic-range (WDR) neurons on the basis of their cutaneous receptive field properties, and all tested neurons responded to noxious thermal stimulation of the cornea (Pozo and Cervero 1993). The present study compares the response properties of neurons within the Vi/Vc and Vc/C1 transition regions that process corneal afferent input. A preliminary report of these findings has been presented (Meng et al. 1995).

**Methods**

**Subjects**

Sprague-Dawley rats (270–485 g, n = 68) were anesthetized initially with pentobarbital sodium (70 mg/kg ip) before surgery. The femoral artery was catheterized to monitor mean arterial blood pressure and collect blood samples. The jugular vein was cannulated for administration of drugs. Arterial blood gases were monitored periodically and respiratory volume was adjusted to maintain a normal pH. After tracheostomy, animals were artificially respired with oxygen-enriched room air. Body temperature was maintained at 38°C with a heating blanket and thermal probe. After completion of all surgery, rats were paralyzed with gallamine triethiodide (10 mg/kg iv) and anesthesia was maintained with supplemental doses of α-chloralose (100 mg/kg iv). Animals were mounted in a stereotaxic frame and the dorsal brain stem was exposed. The occipital bone was partially removed to expose the brain stem 0.5 mm rostral to obex and the C1 vertebral bone was removed in some animals. The brain stem and cornea were kept moist with saline and experiments were terminated if blood pressure was not maintained at >70 mmHg.

In seven additional experiments, rats were anesthetized with urethane (1 g/kg ip) and chloralose (50 mg/kg ip). Only neurons at the Vi/Vc transition region were recorded in these experiments.

**Recording techniques**

Extracellular activity was recorded from single neurons at the Vi/Vc transition region and laminae I/II at the Vc/C1 transition region with the use of tungsten electrodes (9 MΩ, FHC, Brunswick, ME), amplified, digitized via a recording adapter, and stored on video tape for off-line analysis. Data were acquired on a Macintosh IIvx computer with the use of the Lab-NB board (National Instruments) and analyzed with the use of software programmed by I.D.M. For on-line analysis, the analog signal was passed through a window discriminator and monitored with digital and storage oscilloscopes. Discriminated single units triggered an on-line counter-timer, which provided immediate display of firing rates, and were displayed on a digital oscilloscope to confirm constant spike shape and amplitude. Neurons recorded at the Vi/Vc transition region were approached at an angle of 28° off vertical and 45° off midline. Neurons recorded from laminae I/II of the Vc/C1 transition were approached at an angle of 43° off vertical and 60° off midline. To record from laminae I/II neurons, slight tension was placed on the tail of the rat with tape to limit vibrations on the surface of the brain stem. The electrode penetrated the dorsal horn as far laterally as possible. Superficial neurons were recorded just before exiting the dorsal horn, 350–500 μm after surface penetration. A bipolar stimulating electrode (2-mm separation, FHC) was mounted on the ear bar and placed lightly on the cornea. Both mechanical and electrical stimulation (0.1–1 ms in duration, maximum of 1.0 mA, 0.2 Hz) of the cornea were used as search stimuli. In most cases only one neuron per animal was characterized and no additional units were studied after the application of noxious chemical or thermal stimuli. The recording site was localized at the end of the recording session (10 μA, 10 s) and rats were perfused with saline followed by 10% buffered Formalin. The brain stem was removed and frozen coronal sections (40 μm) were cut on a sliding microtome, mounted, and stained with 0.3% cresyl violet.
Projections to PBA

Projections to the lateral PBA contralateral to the recording site were investigated with the use of a stimulating electrode (shaft diameter 250 μm, tip exposed 250 μm, tip distance 300 μm; Rhodes, SNEX-100) positioned with the use of the coordinates of Chiang et al. (1994). Antidromically activated neurons demonstrated a constant latency, the ability to follow high-frequency stimulation (200–300 Hz), and collision with orthodromic spikes (Lipski 1981). Lesions (5 μA, 5 s) were made at the end of each experiment to mark the stimulating electrode site.

Assessment of corneal input

After a corneal-responsive unit was isolated, the mechanical threshold to corneal stimulation was determined with the use of von Frey filaments. The cornea was divided into quadrants and the ability of a von Frey filament to activate the neuron in each of these quadrants was tested. Brushing motions to the cornea also were used when the neuron appeared insensitive to direct filament pressure. The sensitivity of the contralateral cornea to mechanical stimulation also was tested. Graded electrical stimulation was applied to the cornea to determine the electrical threshold and type of primary afferent fiber input (A and/or C fibers). Responses were elicited by delivering current of 0.1–5 mA for 0.01–2.0 ms (1 Hz, 5–10 pulses). Suprathreshold stimuli were used to determine the minimum latency of the first spike. C fiber input was defined as a discharge evoked consistently at a latency >30 ms. Conduction velocity was calculated on a measured distance of 29 mm from the cornea to Vi/Vc sites and 33 mm from the cornea to Vc/C1 sites. To account for peripheral activation time, central narrowing of the afferents in the V spinal tract, and synaptic delay, 1 ms was subtracted from the minimum latency of the first spike (Hu 1990).

Assessment of cutaneous receptive field

Corneal-responsive neurons were examined carefully for cutaneous input, first with the use of innocuous mechanical stimulation and then with noxious pinch and deep pressure. Because not all receptive fields were continuous with the cornea, the entire facial region, especially the nose and underneath the eyelids, was tested. Neurons with a cutaneous receptive field were classified as either low-threshold mechanoreceptive (LTM) units, WDR units, NS units, or deep nociceptive (D) units (Hu 1990). LTM units responded to hair movement and light touch and showed no increase in discharge with more intense stimuli. WDR units were sensitive to both nonnoxious and noxious stimuli and showed an increase in discharge as the intensity of the stimulation increased. NS units were activated only by noxious stimuli applied to the cutaneous receptive field. D units were activated only by deep pressure and did not respond to noxious pinch of the overlying skin. Electrical stimulation was applied to the cutaneous receptive field to determine the minimum latency and afferent fiber input from skin (0.1–5 mA for 0.01–2.0 ms, 1 Hz, 5–10 pulses). Electrical stimulation was applied underneath the eyelids by gently lifting the lid with the stimulating electrode.

Diffuse noxious inhibitory controls

The presence of diffuse noxious inhibitory controls (DNIC) was tested with the use of electrical stimulation of the cornea (1.5–2 times threshold, 0.5–1 Hz) as the test stimulus and placement of the distal 2–4 cm of the rat’s tail in 55°C water for 1 min as the conditioning stimulus. The cornea was stimulated electrically for 15–30 s before the conditioning stimulus (control), during the conditioning stimulus, and within 1 min after removal of the conditioning stimulus. In some cases, the hindpaw was pinched to elicit DNIC. The modulatory effect of the conditioning stimulus was deemed significant if values were <75% of control.

Thermal stimulation

Thermal stimuli, both cooling and heating (20 and 48–52°C), were applied with the use of a contact thermode (LTS 3, Thermal Devices, Golden Valley, MN) with a stimulating area of ~21 mm² and a rate in rise of temperature of 20°C/s. Responses to noxious radiant heat, applied by a focused projector bulb, were also tested. In some cases, when no cutaneous receptive field was present, the eyelids were closed and radiant heat was focused on the lids before corneal sensitivity to heat was tested. The response to repeated noxious thermal stimulation of the cornea also was studied. Noxious heat (contact thermode, 48–52°C) was applied for 5–7 s, two to three times, with an interval of 1–3 min between trials. The average evoked firing rate per trial was calculated by subtracting the mean activity 7–10 s before stimulus onset. Comparison of average firing rates was analyzed with the use of a two-way analysis of variance (ANOVA) (Winer 1971).

Chemical stimulation

At the end of some experiments, the selective small-fiber excitant MO was applied to the cornea. MO at 20% (1 μl) was applied to the cornea from a micropipette. In cases in which a periorbital cutaneous receptive field existed, a small amount of MO was applied to the cornea from a capillary tube.

RESULTS

Locations of recorded units

Thirty-three neurons at the Vc/C1 transition region and 61 neurons at the Vi/Vc transition region were characterized. The locations of 22 Vc/C1 and 36 Vi/Vc sites were recovered and are shown in Fig. 1. Caudal sites were located 3–4.5 mm caudal to obex at the Vc/C1 transition region, exclusively in laminae I/II (Fig. 2B). Rostral sites were located at the Vi/Vc transition region, from 0.5 rostral to 1.0 mm caudal to obex (Fig. 2A).

All corneal units recorded at the Vc/C1 transition region had a cutaneous receptive field, whereas 33 of 61 neurons located at the Vi/Vc transition region had no apparent cutaneous receptive field. Neurons with a cutaneous receptive field and those without a cutaneous receptive field were distributed similarly at the Vi/Vc transition region. In addition, there was no difference in the location of neurons that received A fiber input only and those that received A and C fiber input (Fig. 1).

Corneal receptive fields

All neurons that were found with the use of an electrical search stimulus also responded to mechanical stimulation of the ipsilateral cornea. No neurons responded to stimulation of the contralateral cornea. One significant difference between the corneal receptive field of Vc/C1 and Vi/Vc neurons was that it included the entire cornea for all Vi/Vc units, whereas the receptive field included the entire cornea in only 24 of 33 Vc/C1 units (P < 0.001, Fisher’s exact probability test). There was no significant difference in the mechanical thresholds of Vc/C1 and Vi/Vc neurons, and von Frey thresholds were similar for all categories of Vi/
Vc corneal units ( \( P > 0.05, \text{ANOVA} \)) . The average von Frey threshold was 0.10 ± 0.11 (SD) g for Vc/C1 neurons ( \( n = 10 \) ) and 0.09 ± 0.04 g for Vi/Vc neurons ( \( n = 19 \) ). Neurons at both the Vi/Vc and Vc/C1 transition regions responded best to a brushing motion, thus making von Frey thresholds difficult to determine in many cases.

The threshold for electrical stimulation (0.1 ms) to activate Vc/C1 neurons (0.49 ± 0.28 mA, \( n = 19 \) ) and Vi/Vc neurons (0.41 ± 0.44 mA, \( n = 44 \) ) was similar ( \( P > 0.5, \text{ANOVA} \)) . However, the average minimum latency of Vc/C1 neurons (10.2 ± 3.9 ms, range 5–20 ms, \( n = 27 \) ) was significantly greater ( \( P < 0.001, \text{ANOVA} \)) than the average minimum latency of Vi/Vc neurons (6.7 ± 2.6 ms, range 2–15 ms, \( n = 42 \) ). Conduction velocity was calculated from the average minimum latency, with 29 mm used as the distance from the cornea to the Vi/Vc and 33 mm to the Vc/C1 transition. The conduction velocity of primary afferents that projected to Vi/Vc neurons (7.4 ± 5.3 m/s) was significantly greater ( \( P < 0.025 \)) than that of those that projected to Vc/C1 neurons (4.6 ± 1.9 m/s). Forty-two percent (14 of 33) of the neurons recorded at the Vc/C1 transition region and 28% (17 of 61) of the neurons recorded at the Vi/Vc transition region received A and C fiber input from the cornea ( \( P > 0.05, \text{Fisher’s exact probability test} \)) . No neurons received only C fiber input without convergent A fiber input (Table 1). A common feature of C fiber input to Vi/Vc neurons was the disappearance of the late-latency firing as the intensity of electrical stimulation was increased (Fig. 5C). Also, as the experiment progressed and the cornea was stimulated repeatedly, C fiber input to Vi/Vc neurons often became inconsistent and many times disappeared entirely. This phenomenon was not observed in neurons recorded at the Vc/C1 transition region (Fig. 3C).

Corneal units recorded at the Vc/C1 transition region were more likely ( \( P < 0.05, \text{Fisher’s exact probability test} \)) to have significant levels of spontaneous activity (9 of 33, >1 Hz) than those recorded at the Vi/Vc transition (6 of 61, >1 Hz, Table 1).

Cutaneous receptive fields

All neurons recorded at the Vc/C1 transition region could be classified as either WDR ( \( n = 19 \) ) or NS ( \( n = 14 \) ) on the basis of the characteristics of cutaneous input. The cutaneous receptive field of Vc/C1 neurons always included the periorbital skin and was contiguous with the cornea (Fig. 4). Electrical stimulation of the cutaneous receptive field of Vc/C1 neurons revealed that 56% (10 of 18) of the neurons that received only A fiber input from the cornea also received only A fiber input from the cutaneous receptive field and 79% (11 of 14) of the neurons that received A and C fiber input from the cornea also received A and C fiber input from the cutaneous receptive field (Table 2, see also Fig. 3). Neurons that received different primary afferent input from the cornea and the cutaneous receptive field (Fig. 3B) are evidence that current from the stimulating electrode did not spread from the cornea to the cutaneous receptive field during stimulation. Seventy-four percent (14 of 19) of the WDR Vc/C1 neurons received A and C fiber input from the skin, whereas only 38% (5 of 13) of the NS units received A and C fiber input from the skin; this difference was significant ( \( P < 0.05, \text{Fisher’s exact probability test} \)) .

Unlike Vc/C1 neurons, 54% (33 of 61) of the Vi/Vc neurons had no cutaneous receptive field (Fig. 5). Of those neurons at the Vi/Vc transition region that had a cutaneous receptive field, six had receptive fields around the nose (Fig. 7), and many others had receptive fields that included vibrissae or hairs not on the eyelids. Most Vi/Vc corneal units with a cutaneous receptive field were classified as LTM (16 of 28 units, see Fig. 6 for example). All LTM units received only A fiber input from both the cornea and the cutaneous receptive field (Table 2). Two WDR Vi/Vc neurons received only A fiber input from the cornea and A and C fiber input from the cutaneous receptive field (Fig. 7). One D Vi/Vc neuron received only A fiber corneal input. Nine Vi/Vc neurons that received A and C fiber input from the cornea also had cutaneous receptive fields (Table 2). Four of these
The neurons that received A and C fiber input responded to thermal stimulation, a difference that was significant \( (P < 0.005, \text{Fisher’s exact probability test}) \). Of the 10 Vi/Vc neurons that received only A fiber input and responded to noxious thermal stimulation, 4 were LTM units and the remaining 6 had no cutaneous receptive field.

Repetitive noxious thermal stimulation was applied to the cornea in 12 experiments (Fig. 8). Neurons recorded at the Vc/C1 transition region received either 48°C stimulation followed 1–3 min later by 50°C stimulation \( (n = 2, \text{Fig. 4C}) \) or 50°C stimulation followed by 52°C stimulation \( (n = 3) \). Neurons recorded at the Vi/Vc transition region received either 50°C stimulation followed by 52°C stimulation \( (n = 1) \) or 52°C stimulation followed by 52°C stimulation \( (n = 6) \). In three cases, 52°C stimulation was applied three times to the cornea (Fig. 5A). The average frequency of Vc/C1 neurons during heating in the first trial \( (5.9 \pm 1.9 \text{ spikes/s}) \) was significantly less \( (P < 0.001) \) than the average frequency during the second trial \( (9.4 \pm 2.5 \text{ spikes/s}) \) (Fig. 8). For neurons at the Vi/Vc transition region, the average frequency during the first trial \( (2.3 \pm 0.4 \text{ spikes/s}) \) was significantly greater \( (P < 0.001) \) than the average frequency during the second \( (0.5 \pm 0.2 \text{ spikes/s}) \) and third \( (0.2 \pm 0.2 \text{ spikes/s}) \) trials. The average frequency of Vc/C1 and Vi/Vc neurons during the first trial did not differ. However, during the second trial the average frequency of Vc/C1 neurons was significantly greater than that of Vi/Vc neurons \( (P < 0.001) \). In addition to showing a decrease in responsiveness after repetitive noxious stimuli, neurons at the Vi/Vc transition region typically demonstrated a high rate of firing during the first 1–2 s of the initial trial that adapted rapidly (Fig. 5A). Three of the Vi/Vc neurons tested received only A fiber input and were LTM units. The remaining four neurons received A and C fiber input. Three of these four neurons had no cutaneous receptive field and one was a D unit.

**Response to MO**

The response to MO application to the cornea was tested in 16 neurons at the Vc/C1 transition region. Because each neuron had a periorbital cutaneous receptive field, MO was applied with a small capillary tube to minimize spreading. All neurons tested at the Vc/C1 transition region responded to application of MO to the cornea (Table 1), including four neurons that received only A fiber input from both the cornea and the cutaneous receptive field (Fig. 4).

<table>
<thead>
<tr>
<th>TABLE 1. Characteristics of Vc/C1 and Vi/Vc neurons grouped according to type of corneal afferent fiber input</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corneal Input (Fiber Type)</strong></td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Vc/C1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Vi/Vc</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Values represent number of responsive neurons per number of tested neurons. Vc/C1, trigeminal subnucleus caudalis/upper cervical cord transition; Vi/Vc, trigeminal subnucleus interpolaris/subnucleus caudalis transition; DNIC, diffuse noxious inhibitory controls.
stimulation. The requirement of C fiber input for an MO response in most Vi/Vc neurons can be illustrated in a neuron that received only A fiber input from the cornea and A and C fiber input from the nose (Fig. 7). This neuron did not respond to MO applied to the cornea, yet did respond to MO applied to the nose. In contrast, another neuron that received A and C fiber input from both the cornea and the nose responded to MO applied to either area (not shown).

**DNIC**

At the Vc/C1 transition region, 12 of 17 neurons demonstrated DNIC (Table 1). Among these 12 cells, 7 received convergent input (A and C fiber) from the cornea and/or the cutaneous receptive field and 5 received exclusively A fiber input from both the cornea and the cutaneous receptive field (Fig. 4). At the Vi/Vc transition region, DNIC was significantly less common ($P < 0.01$, Fisher’s exact probability test), present in only 4 of 26 neurons (2 of 8 that received A and C fiber input).

**Projections to contralateral PBA**

Twelve of 15 corneal units at the Vc/C1 transition region could be antidromically activated from a stimulating electrode positioned in the lateral portion of the contralateral PBA, often near Kolliker-Fuse. The average latency for evoked activity was 6.29 ms, with a range from 1.8 to 26 ms and a median of 4.4 ms ($n = 12$). Thresholds for activation ranged from 0.01 ms, 0.8 mA to 0.1 ms, 1.0 mA. None of 22 Vi/Vc corneal units could be activated from the contralateral PBA. However, in one experiment a Vi/Vc corneal-responsive neuron could be antidromically activated from a site immediately caudal to PBA in which the stimulating electrode was found to be within the contralateral trigeminal principal sensory nucleus. In three experiments a Vc/C1 neuron was antidromically activated from the contralateral PBA before a rostral corneal unit was found; however, in none of these experiments could the corneal-responsive neuron at the Vi/Vc transition region be antidromically activated.

**Effect of anesthetic**

Of the 61 Vi/Vc neurons used in this study, 7 were recorded in rats anesthetized with urethan/chloralose. Three neurons received only A fiber input and had no cutaneous receptive field. Two of these three neurons did not respond to noxious radiant heat directed at the cornea. The remaining four neurons received A and C fiber input from the cornea, all responded to noxious radiant heat, and three had no cutaneous receptive field. To ensure that these neurons did not contain a periorbital cutaneous receptive field that responded to noxious input, the eyelids were held closed and radiant heat was applied. In each case in which no cutaneous receptive field was found with the use of mechanical stimulation, the neuron did not respond to noxious radiant heat applied to the periorbital skin.

**DISCUSSION**

This study demonstrates for the first time that neurons at the Vi/Vc transition region and laminae I/II of the Vc/
FIG. 4. Response properties of an NS Vc/C1 corneal unit. A: receptive field included the entire cornea and the cutaneous field was contiguous with the cornea. B–D: peristimulus histograms demonstrating the receptive field properties. The thermal probe was in contact with both the cornea and the cutaneous receptive field. The application of mustard oil (MO) was restricted to the cornea (see METHODS). E: diffuse noxious inhibitory controls (DNIC) were produced by immersing the tip of the tail in 55°C water for 60 s. Dot raster display shows corneal-stimulation-evoked activity before, during, and after the conditioning stimulus. This neuron also could be antidromically activated from the contralateral parabrachial area (PBA).

C1 transition region process corneal input differently. All neurons recorded at the Vc/C1 transition region were classified either as WDR or NS with periorbital cutaneous receptive fields, whereas over half of the Vi/Vc neurons had no cutaneous receptive field. Of those neurons at the Vi/Vc transition region that had a cutaneous receptive field, 57% were LTM, 25% WDR, 18% D, and none NS. In addition, Vi/Vc corneal units often had cutaneous receptive fields that were not contiguous with the cornea; six Vi/Vc neurons had a cutaneous receptive field around the nose. The responses of Vi/Vc and Vc/C1 corneal units to noxious thermal and chemical stimulation also differed. All neurons tested at the Vc/C1 transition region responded to thermal and MO stimulation of the cornea, whereas at the Vi/Vc transition region only 21 of 46 responded to thermal stimulation and 13 of 19 responded to MO. Unlike Vc/C1 corneal units, neurons at the Vi/Vc transition region became desensitized to repetitive noxious thermal stimulation of the cornea. The absence of direct projections from Vi/Vc corneal units to the contralateral PBA is further evidence that the Vi/Vc transition region that processes corneal input is not simply an extension of laminae I/II of Vc. Twelve of 15 corneal units recorded at the Vc/C1 transition region could be antidromically activated from a stimulating electrode positioned in the contralateral...
TABLE 2. Type of primary afferent input from the cornea or cutaneous receptive field to corneal-responsive neurons at the Vc/C1 and Vi/Vc transition regions

<table>
<thead>
<tr>
<th></th>
<th>Corneal Input A Fiber Only</th>
<th>Corneal Input A + C Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutaneous RF Input</td>
<td>Cutaneous RF Input</td>
</tr>
<tr>
<td>RF</td>
<td>n</td>
<td>A only</td>
</tr>
<tr>
<td>Vc/C1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTM</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WDR</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>NS</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>D</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vi/Vc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTM</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>WDR</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>NS</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td>25</td>
<td>2*</td>
</tr>
</tbody>
</table>

n = Total number of units tested for corneal input. Not all neurons were tested for type of fiber input from the cutaneous receptive field. Vc/C1, trigeminal subnucleus caudalis/upper cervical cord; Vi/Vc, trigeminal subnucleus interpolaris/subnucleus caudalis; RF, receptive field; LTM, low-threshold mechanoreceptive; WDR, wide dynamic range; NS, nociceptive specific; D, deep. * Two to 6 units tested responded to electrical stimulation of the eyelid.

PBA, whereas none of 22 corneal units tested at the Vi/Vc transition region could be antidromically activated from the contralateral PBA. The present findings support the notion that the Vi/Vc transition region is a specialized area of Vsp; however, the functional role of this region in trigeminal sensory processing is still unclear.

Properties of Vc/C1 corneal units

On the basis of similar anatomic and functional properties, the Vc/C1 transition region can be considered a rostral extension of the dorsal horn of the spinal cord (Dubner and Bennett 1983; Gobel et al. 1977). The recording sites at the Vc/C1 transition region were similar to the caudal location of Fos-LI after noxious corneal stimulation (Bereiter et al. 1996; Bereiter et al. 1996; Meng and Bereiter 1996; Strassman and Vos 1993) and the caudal location of corneal primary afferent terminals as determined by axonal tract tracing studies (Marfurt and Del Toro 1987). Lesion of the recording site at the Vc/C1 transition region could not provide the precise location of the neuronal somata within the superficial laminae. However, the fact that 80% of these neurons projected to or through the PBA suggests that they likely were laminae I cells (Lima et al. 1991). The projection of Vc/C1 neurons to the contralateral PBA is consistent with axonal tract tracing studies that show a significant projection from superficial laminae of both spinal cord and medullary dorsal horn neurons to the contralateral PBA (Feil and Herbert 1995).

Previous studies have not reported the properties of corneal units in laminae I/II at the Vc/C1 transition region in the rat (e.g., Nagano et al. 1975; Pozo and Cervero 1993). The present results are consistent with those of previous studies that demonstrate a major role for Vc neurons in the transmission of trigeminal nociceptive input (Dubner and Bennett 1983; Sessle 1987). The cutaneous receptive field properties of Vc/C1 corneal units were similar to those of other characterized neurons in laminae I/II of Vc and spinal cord dorsal horn (Craig and Kniffki 1985; Dado et al. 1994; Hu 1990; McHaffie et al. 1994; Mosso and Kruger 1973; Price et al. 1976; Price et al. 1979). All corneal units at the Vc/C1 transition region could be classified as either NS or WDR on the basis of their cutaneous receptive field properties, and the receptive field did not always contain the entire cornea. Six of 20 neurons tested for sensitivity to thermal stimulation responded to both heating and cooling, representing a population of multimodal receptive laminae I neurons often classified as HPC units (Craig and Kniffki 1985). The excitation of all Vc/C1 units, even those that received only A fiber input, by the selective small-fiber excitant MO is further evidence for MO activation of Aδ-fibers (Harris and Ryall 1988; Heapy et al. 1987; Patacchini et al. 1990).

Nagano et al. (1975) recorded from 165 neurons that responded to corneal input in the rat. However, most of the recording sites were located at rostral levels of Vsp, and the few corneal units recorded at Vc were in deeper laminae. Pozo and Cervero (1993) describe one corneal unit recorded from the superficial laminae of the Vc/C1 transition region. This neuron had a periorbital NS cutaneous receptive field, similar to many of the Vc/C1 neurons described in this study. In contrast, Nishida and Yokota (1991) recorded from corneal units in superficial laminae of Vc in the cat and did not find corneal-responsive neurons with cutaneous receptive fields. The corneal receptive fields consisted of three to six spots that included <10% of the cornea. The mechanical threshold for these neurons was higher than that for corneal units in deeper laminae, and responsiveness to thermal stimulation was not studied. In this same study, WDR neurons with corneal input were found in laminae V. Mosso and Kruger (1973) describe five corneal units in Vc in the cat, all without a cutaneous receptive field. Although these neurons probably were located in deeper laminae, the one neuron tested for sensitivity to thermal stimulation gave a robust response. Similar to the corneal receptive fields in the present study, a fast brushing motion was the most effective mechanical stimulus in activating the corneal units in the study by Mosso and Kruger.

Properties of Vi/Vc corneal units

Corneal-responsive neurons recorded at the Vi/Vc transition region were located at the ventrolateral pole of the nucleus at periepithelial levels. These recording sites agree with the distribution of Fos-LI in rostral Vsp after corneal stimulation (Bereiter et al. 1996; Bereiter et al. 1996; Lu et al. 1993; Meng and Bereiter 1996; Strassman and Vos 1993) and with the termination of corneal primary afferent fibers after neuronal tract tracing (Marfurt and Del Toro 1987). However, on the basis of the location of the lesions, no recording sites could be unambiguously identified within the interstitial islands embedded within the V tract. Controversy remains as to whether this ventral transition region is a rostral extension of laminae I/II of Vc. Many studies have demonstrated simi-
FIG. 5. Response properties of Vi/Vc corneal units that receive A and C fiber input and have no cutaneous receptive field. A: initial response to thermal stimulation (top) was a phasic burst of activity. After the 2nd (middle) and 3rd (bottom) trials, discharge during the stimulus was inconsistent, although the afterdischarge remained. B: demonstration of a phasic discharge pattern after MO application to the cornea in a similar corneal unit. C: dot raster display of evoked activity after electrical stimulation of the cornea for the neuron in B. Note that as the stimulus intensity increased, the amount of C fiber evoked activity decreased, a phenomenon also observed for the neuron in A.

FIG. 6. Response properties of a low-threshold mechanoreceptive (LTM) Vi/Vc corneal unit. A: electrical stimulation of the cornea and the cutaneous receptive field (upper eyelid) indicated input from only A fiber primary afferents. B: cutaneous receptive field included the upper eyelid and was responsive only to low-threshold stimuli. Application of MO to the cornea resulted in a minimal response from the mechanical stimulation of the oil.
FIG. 7. Response properties of a WDR Vi/Vc corneal unit. Left: electrical stimulation of the cornea indicated only A fiber input. Electrical stimulation of the tip of the nose indicated A and C fiber input. The cutaneous receptive field included the tip of the nose and responded to low- and high-threshold stimuli (WDR). Right: application of MO to the cornea resulted in no response, whereas application of MO to the nose resulted in a small but prolonged response.

eral PBA (Feil and Herbert 1995), unexpectedly, in the present study we found no evidence for a projection of Vi/Vc corneal-responsive units to the contralateral PBA with the use of antidromic stimulation techniques, including results from three animals in which Vc/C1 neurons could be antidromically activated. Preliminary data indicate that Vi/Vc corneal units also do not project to the ipsilateral PBA (n = 6). The basis for this finding is not certain. Corneal-responsive Vi/Vc neurons may project to other central targets. Indeed, one neuron was antidromically activated by a site located within the contralateral trigeminal principal sensory nucleus. It also is possible that a significant percentage of corneal units at the Vi/Vc transition region is interneurons. It is not likely that the recorded activity was from primary afferent axons, because many of these units displayed convergent receptive fields from cutaneous loci that often included input from A as well as C fibers.

Unlike neurons at the Vc/C1 transition region, the receptive fields of corneal units at the Vi/Vc transition region always included the entire cornea and more than half of the Vi/Vc corneal units did not have a cutaneous receptive field. Of the Vi/Vc corneal-responsive neurons that had a cutaneous receptive field, 57% were LTM and many of the receptive fields were not contiguous with the cornea. In contrast, all corneal units at the Vc/C1 transition region could be classified as either NS or WDR, with cutaneous receptive fields that included the periorbital skin surrounding the cornea. Almost half of the corneal units at the Vi/Vc transition region did not respond to noxious thermal stimulation of the cornea. In addition, heat-responsive Vi/Vc corneal units desensitized to repetitive noxious thermal stimulation of the cornea. These electrophysiological results are consistent with the quantification of Fos-LI after noxious and nonnoxious corneal stimulation (Meng and Bereiter 1996). In the dorsal horn, production of Fos-LI has been a reliable marker for nociceptive activity (Hunt et al. 1987). After noxious corneal stimulation (52°C thermal probe or MO), Fos-LI was produced at both the Vc/C1 and Vi/Vc transition regions. However, after the application of nonnoxious thermal stimuli to the cornea (35 and 44 ± 4°C radiant heat) Fos-LI was produced only at the Vi/Vc transition region. Interestingly, repeated noxious thermal stimulation of the cornea produced more Fos-LI at the Vc/C1 transition region than after MO stimulation, whereas MO stimulation of the cornea produced more Fos-LI at the Vi/Vc transition region than after thermal stimulation. These results could be explained by the desensitization observed in Vi/Vc corneal units after repeated noxious stimulation.
Response properties of neurons recorded from the Vi/Vc transition region that responded to stimulation of the nasal mucosa have characteristics similar to those of the Vi/Vc corneal units of the present study. Many neurons had cutaneous receptive fields on the nose and often received convergent input from the cornea (Peppel and Anton 1993). In the present study, six neurons received convergent input from the nose, suggesting some overlap between these populations of neurons. With the use of CO2 to stimulate the nasal mucosa, Peppel and Anton (1993) found that most neurons showed a phasic response and became desensitized with repeated stimulation. We found similar characteristics in Vi/Vc corneal units after MO and repetitive thermal stimulation of the cornea; those corneal units that responded to noxious thermal stimulation had a phasic response and desensitized with repeated stimulation.

In a study of corneal units at the Vi/Vc transition region, Pozo and Cervero (1993) characterized 54 neurons with the use of electrical stimulation of the cornea as the search stimulus and found that >40% of the corneal-responsive neurons had no cutaneous receptive field. Although we found that a similar percentage of Vi/Vc corneal units had no apparent cutaneous receptive field, we did not test for introral or meningeal inputs. Neurons in rostral Vsp in the cat have been shown to receive convergent input from the cornea and meninges or tooth pulp (Campbell et al. 1985; Davis and Dostrovsky 1988b). Pozo and Cervero (1993) also reported that all corneal units with cutaneous receptive fields could be classified as either WDR or NS with cutaneous fields located on the periorbital skin. Furthermore, all corneal units responded to noxious thermal stimulation and became sensitized with an expansion of the receptive field after repeated noxious thermal stimulation of the cornea. These results are in contrast to the results of the present study, in which LTM, WDR, and D receptive fields were found that were sometimes discontinuous with the cornea, and many corneal units did not respond to noxious thermal stimulation. Sample bias could account for the differences between these results and those of the present study. It is possible that only corneal units receiving A and C fiber input were selected for characterization. Also, electrode impedance was not specified and some experiments were conducted with the use of carbon fiber electrodes.

Primary afferent input

Although the free nerve endings in the cornea appear similar morphologically, electrophysiological evidence obtained mainly from the cat and rabbit indicates substantial functional specialization (Belmonte and Giraldez 1981; Belmonte et al. 1991; Gallar et al. 1993; Maclver and Tanelian 1993a,b; Pozo et al. 1992; Tanelian 1991; Tanelian and Beuerman 1984). In the cat, the most primary afferent fibers that supply the cornea are polymodal nociceptors that respond to mechanical, thermal, and chemical stimuli; however, there are populations of cells that respond only to high-threshold mechanical or mechanical and heat stimulation. Maclver and Tanelian (1991) have correlated the physiological responses of neurons with the anatomy of the free nerve endings in the rabbit cornea. They found that Aδ-fibers mainly run parallel to the corneal surface and are associated with mechanical sensitivity, whereas chemosensitive and cold-sensitive C fiber endings run perpendicular to the corneal surface. It is not known whether different populations of corneal primary afferents terminate in different regions of Vsp.

Two lines of evidence indicate that different types of corneal primary afferentsproject to Vi/Vc and Vc/C1 neurons. First, although the percentage of cells at the Vi/Vc and Vc/C1 transition regions that received C fiber input from the cornea was similar, the minimum response latencies indicate that the fiber afferents that activated corneal units at the Vi/Vc transition region had a higher conduction velocity than those that activated corneal units in laminae I/II of the Vc/C1 transition region. However, the lower conduction velocity of primary afferents projecting to Vc/C1 neurons could also be accounted for by extensive axonal branching or demyelination occurring in Lissauers tract. Second, the responses of Vi/Vc and Vc/C1 corneal units to thermal and MO stimulation of the cornea suggest a difference in the properties of primary afferents that project to Vi/Vc and Vc/C1 corneal units. Most Vi/Vc corneal units that received only A fiber input did not respond to noxious thermal or chemical stimulation, consistent with input from primary afferent fibers that encode only mechanical stimuli. In contrast, all corneal units in laminae I/II of Vc/C1, including those that received only A fiber input from both the cornea and the cutaneous receptive field, responded to the corneal application of MO and thermal stimulation. Corneal units that are insensitive to thermal and MO stimulation may be unique to the Vi/Vc transition region, although corneal-responsive neurons in deeper laminae of the Vc/C1 transition region in the rat have not been examined.

On the basis of minimum response latencies and corneal afferent projections, neurons recorded from both the Vi/Vc and Vc/C1 transition regions likely received direct input from corneal primary afferents. However, the late-latency firing following electrical stimulation that has been attributed to C fiber input into Vi/Vc corneal units could be caused by an indirect excitatory input through the Vc/C1 region. Several studies have demonstrated both excitatory and inhibitory influences of Vc on more rostral regions of Vsp (Davis and Dostrovsky 1988a; Greenwood and Sessle 1976; Sessle and Greenwood 1974; Scibetta and King 1969; Young and Perryman 1984). The unusual properties of Vi/Vc corneal units that received A and C fiber input are suggestive of a modulatory influence from Vc/C1 corneal-responsive neurons. In most Vi/Vc corneal units that received A and C fiber input, the amount of C fiber input decreased as the intensity of electrical stimulation increased, a property unique to Vi/Vc corneal units. The loss of C fiber input to Vi/Vc neurons also could be caused by the recruitment of an inhibitory pathway from Vc/C1, as evidenced by the desensitization of Vi/Vc corneal units after repeated noxious thermal stimulation. Alternatively, the C fiber input to Vi/Vc corneal units could derive an indirect excitatory input from second-order Vc/C1 corneal-responsive neurons and the desensitization observed after repeated thermal stimulation could be caused by desensitization of corneal primary afferent fibers, which has been reported (Belmonte and Giraldez 1981).
that DNIC is seen mainly in WDR neurons that receive convergent A and C fiber input (Dickenson et al. 1980; Le Bars et al. 1979; Villanueva et al. 1984). However, DNIC also was present in NS and nonconvergent neurons that received input from only A fibers. Other studies have found DNIC in NS as well as WDR neurons in both Vsp and spinal dorsal horn (Dallel et al. 1990; Tomlinson et al. 1983), and the presence of DNIC in nonconvergent neurons also has been reported (Dallel et al. 1990). At the Vi/Vc transition region few corneal units, either convergent or nonconvergent neurons, demonstrated DNIC. This finding was surprising because DNIC has been reported in convergent and nonconvergent NS and WDR neurons recorded from more rostral regions of Vsp (Dallel et al. 1990).

Role of Vc/C1 and Vi/Vc corneal-responsive neurons in nociception

Most studies have concluded that irritation or pain is the dominant sensation evoked by corneal stimulation (Beuerman and Tanelian 1979; Kenshalo 1960). However, the relative contribution of Vi/Vc and Vc/C1 corneal-responsive neurons to sensation, affect, muscle reflexes, and autonomic responses evoked by corneal stimulation remains uncertain. Three lines of evidence suggest that Vc/C1 and not Vi/Vc corneal units are important in the sensory-discriminative aspects of pain (Price and Dubner 1977). First, Vc/C1 corneal units responded differentially or exclusively to noxious stimuli. All Vc/C1 corneal units had either NS or WDR cutaneous receptive fields, whereas many Vi/Vc corneal units had LTM cutaneous receptive fields. In addition, all Vc/C1 and only some Vi/Vc corneal units responded to noxious thermal and chemical stimulation. Second, methods that reduce pain sensation also reduced the activity of Vc/C1, but not Vi/Vc corneal units. As evidence, DNIC affected most Vc/C1 but only few Vi/Vc corneal units. Also, c-fos immunocytochemical results after corneal stimulation revealed that morphine pretreatment caused a significant dose-dependent decrease in the number of Fos-positive neurons only at the Vc/C1 transition region (Bereiter 1996). Preliminary electrophysiological studies also have demonstrated morphine inhibition of Vc/C1, but not of Vi/Vc corneal units (Meng et al. 1996). Third, Vc/C1 and not Vi/Vc corneal units likely project to brain regions important in sensory-discriminative aspects of pain. Neuronal tract tracing has demonstrated that >80% of thalamic-projecting dorsal horn neurons also project to the PBA (Hylden et al. 1989).

Corneal units at the Vi/Vc transition region may be particularly important in motor reflexes. The blink reflex in response to stimulation of the supraorbital nerve has been well studied and the circuitry is now known in guinea pig (Pelligrini et al. 1995). Stimulation of the supraorbital nerve, which innervates the upper eyelid, results in a blink reflex that can be measured as electromyographic activity from the lid-closing orbicularis oculi muscle. The supraorbital nerve, like corneal primary afferents, projects mainly to the Vi/Vc and Vc/C1 transition regions. The two-phase electromyographic response from supraorbital nerve stimulation includes a disynaptic response from the Vi/Vc transition region to the facial motor nucleus and a multisynaptic response from the Vc/C1 transition region through the reticular formation to the facial motor nucleus. Although not as clear as with supraorbital nerve stimulation, corneal-evoked blink reflexes in the rat often involve two components as well (Evinger et al. 1993). Therefore corneal units at the Vi/Vc transition region may be important in a disynaptic blink reflex in response to corneal stimulation. Although corneal-responsive Vc/C1 neurons are likely also to be involved in the blink reflex, they are unlikely to be expressed through a disynaptic relay. Retrograde tracer studies in guinea pig have not shown a direct projection to the facial motor nucleus from lamina I neurons at the Vc/C1 transition region (Pelligrini et al. 1995).

Direct projections from Vc/C1 corneal units to the contralateral PBA indicate that these neurons may be important in autonomic and affective responses to nociceptive input (Bernard and Besson 1990; Herbert et al. 1990; Mravotic et al. 1982). The role of Vi/Vc corneal units in autonomic responses to corneal stimulation is less certain. On the basis of the absence of projections from corneal-responsive Vi/Vc neurons to the contralateral PBA, their influence on autonomic responses could be through relays in nucleus tractus solitarii or the hypothalamus (Burstein et al. 1990; Menetrey and Basbaum 1987). One unique feature of the Vi/Vc transition region in the rat is the relatively large projection to nucleus submedius, compared with that from the Vc/C1 transition, as seen by retrograde axonal tract tracing (Yoshida et al. 1991). This projection suggests a possible role for the Vi/Vc transition region in an ascending antinociceptive pathway that may recruit descending modulatory pathways; electrical stimulation of nucleus submedius produces antinociceptive effects by activating the periaqueductal gray descending inhibitory system (Zhang et al. 1995). Determining the projection targets of corneal-responsive Vi/Vc neurons should provide further insight into the role of the Vi/Vc transition region in nociception.

This work was supported in part by National Institute of Neurological Disorders and Stroke Grant NS-26137.

Address for reprint requests: D. A. Bereiter, Brown University/Rhode Island Hospital, Division of Surgical Research, Neuroendocrine Laboratory, Providence, RI 02903.

Received 14 June 1996; accepted in final form 18 September 1996.

REFERENCES


