Effects of Thalamic Sensory Relay Nucleus Stimulation on Trigeminal Subnucleus Caudalis Neurons in the Cat

—Abnormal Bursting Hyperactivity after Trigeminal Rhizotomy—

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Abstract

We studied in the cat the effects of thalamic sensory relay nucleus (TSRN) stimulation on abnormal hyperactivity following trigeminal rhizotomy within the contralateral trigeminal subnucleus caudalis, a trigeminal equivalent of the dorsal horn. The animals were subjected to unilateral retrogasserian rhizotomy 2–6 weeks prior to the experiments. Following the rhizotomy, abnormal bursting and continuous nonbursting hyperactivities were recorded from laminae IV–V of the trigeminal subnucleus caudalis on the rhizotomized side. Some of these neurons responded to peripheral stimuli applied to rostral cervical dermatomes in a manner resembling the nociceptive, wide dynamic range (WDR) neurons of the intact side. However, periaqueductal gray (PAG) stimulation inhibited the hyperactive neurons on the rhizotomized side less frequently than the WDR neurons on the intact side. In contrast to PAG stimulation, TSRN stimulation inhibited the hyperactive neurons on the rhizotomized side as frequently as the WDR neurons on the intact side.

These results are apparently consistent with our clinical observation that neurogenic pain due to deafferentation can be relieved by TSRN stimulation but not by PAG stimulation. This in turn suggests that the pain relief obtained with TSRN stimulation may result at least in part from inhibition of the nociceptive activity or abnormal hyperactivity of dorsal horn neurons.

Key words: trigeminal neuralgia, deafferentation pain, trigeminal subnucleus caudalis, bursting hyperactivity, trigeminal rhizotomy, deep brain stimulation

Introduction

It has been demonstrated that intractable pain can be relieved by electrical stimulation of certain brain sites in humans.^{1,8,9,15,16,19,21,22,24,25)} The thalamic sensory relay nucleus (TSRN)^{1,9,15,16,21–25)} and the periaqueductal gray (PAG)^{8,19)} have frequently been employed as sites of stimulation. Clinical experience with TSRN and PAG stimulation during the last decade has indicated that, in certain groups of patients with pain, these two procedures have different effects. For example, while TSRN stimulation appears to be most effective in ameliorating neurogenic pain due to deafferentation,^{15,21)} PAG stimulation is usually ineffective in relieving this type of pain.²⁾

Animal studies have repeatedly demonstrated that PAG stimulation inhibits nociceptive neural activity within the dorsal horn of the spinal cord.^{3,6,10)} Furthermore, it has been shown that depression of the nociceptive behavior of animals in response to PAG stimulation correlates well with depression of spinally mediated nociceptive reflexes.^{13,14,18)} Thus, facilitation of descending neural pathways that actively inhibit nociceptive neural activity within the dorsal horn may be a major element in the mechanisms of pain relief following PAG stimulation. In contrast, the mechanisms underlying the pain relief following TSRN stimulation are not yet clearly understood. Gerhart *et al.*⁵⁾ showed that, like PAG stimulation, TSRN stimulation can inhibit nociceptive neural activity within the dorsal horn. We obtained similar results in the trigeminal subnucleus caudalis of the cat.²⁰⁾ It is still unclear, however, whether or not in-

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hibition of neural activity within the dorsal horn is a major mechanism in the pain relief associated with TSRN stimulation.

If inhibition of neural activity within the dorsal horn does underly the pain relief achieved with TSRN stimulation, the different effects of PAG and TSRN stimulation on the neural activity within the dorsal horn following dorsal rhizotomy are expected to be demonstrated to account for the clinically different effects these two procedures have on neurogenic pain due to deafferentation. Loeser and Ward,¹¹⁾ Anderson *et al.*,²⁾ and other investigators^{7,12)} have reported that neurons within the dorsal horn of experimental animals become hyperactive and show abnormal bursting hyperactivity after a certain period following dorsal rhizotomy. In this study, we examined the effects of PAG and TSRN stimulation on such bursting activity within the trigeminal subnucleus caudalis, which is a trigeminal equivalent of the spinal cord dorsal horn, following trigeminal retrogasserian rhizotomy in the cat.

Materials and Methods

I. Surgical procedures

Twenty male and female adult cats weighing 2.5–4.0 kg were anesthetized with ketamine (10 mg/kg, i.m., supplemented if necessary) and subjected to unilateral sectioning of the trigeminal root between the Gasserian ganglion and the brain stem. At 4–6 weeks following the rhizotomy, recordings were made from the trigeminal subnucleus caudalis. Preparation for the recordings and stimulation were essentially the same as those described in the preceding report.²⁰⁾

II. Recording procedures

The activity of single neurons within the trigeminal subnucleus caudalis was recorded extracellularly with 3 M NaCl-filled micropipettes containing fast-green dye. Recording procedures were the same as described in the preceding report.²⁰⁾

The neuronal activity investigated in this study was spontaneous firing or, on the intact side, firing in response to stimuli applied to the face. A signal processor was used to create interspike interval histograms (ISIHS), autocorrelation histograms (ACHs), and tracings of the spontaneous spike density variations (SDVs) of the single neuronal activity. After stable recordings of spontaneous firing for analysis of ISIHS and ACHs had been obtained, the effects of touch, light pressure, and noxious pinching applied to the ipsilateral facial and cervical skin were tested. The effects of single-pulse and repetitive

brain stimulation were then examined. Stimulation was directed to the TSRN (nucleus ventralis posteromedialis) or PAG, always contralateral to the trigeminal subnucleus caudalis from which the neuronal activity was recorded. The single-pulse stimulation consisted of a rectangular pulse with a duration of 0.2 msec (frequency, 0.1–0.5 Hz; intensity, 100–400 μ A). Inhibition or facilitation was determined from changes in the spike density, as revealed by the poststimulus spike time histograms (PSTHs). Repetitive stimulation consisted of identical pulses (frequency, 100–400 Hz; intensity, 100–400 μ A) applied repeatedly for 15–20 sec. Inhibition or facilitation was deduced from changes in spike density, as evidenced by the SDVs. Since all neurons on the rhizotomized side, and some on the intact side, exhibited spontaneous firing, these procedures were sufficient for evaluating the effects of brain stimulation. However, spontaneous firing on the intact side was, for the most part, slow or absent. In these neurons, the effects of brain stimulation were interpreted according to PSTHs and SDVs obtained in the presence of background firing induced by continuous peripheral stimuli.

III. Histological confirmation

Histological confirmation of the placement of micropipettes and electrodes was made in the same way as described in the preceding report.²⁰⁾ Sections of the brain were subjected alternatively to hematoxylin-eosin or Klüver-Barrera staining for histological verification of the placement of the micropipettes and electrodes, and degeneration of trigeminal fibers terminating in the trigeminal subnucleus caudalis.

Results

The activity of a total of 46 neurons was recorded between 2 and 6 weeks after retrogasserian rhizotomy, and all were confirmed histologically to be located within the region of laminae IV–V. Of these, 34 were on the rhizotomized side and 12 were on the intact side. Peripheral stimulation evoked no response in 28 of the 34 neurons from the rhizotomized side. The remaining six neurons responded to touch, light pressure, and pinching applied to the most rostral cervical dermatomes and therefore resembled the wide dynamic range (WDR) neurons seen in intact brain.¹⁷⁾ All 12 neurons sampled from the intact side exhibited a wide receptive field in response to these stimuli and were therefore classified as WDR neurons.

All the neurons on the rhizotomized side fired spontaneously; in 12, this firing was characterized by

Fig. 1 Representative examples of bursting hyperactivity recorded from neurons within the trigeminal subnucleus caudalis of the cat following retrogasserian rhizotomy. A, B: Single sweeps of firing of a neuron located in lamina V at 21 days after rhizotomy. Note the bursts separated by approximately equal pauses. Calibrations, 20 msec for A and 50 msec for B; 1 mV for A and B. C: ISIH obtained from the neuron shown in A, exhibiting a bimodal pattern. Bin width, 1 msec; calibration, 24 spikes. D: ACH obtained from the neuron shown in A, revealing a periodic pattern. Bin width, 1 msec; calibration, 12 spikes.

brief bursting activity separated by short pauses (Fig. 1A and B). These rapid bursts were clearly manifested in a multimodal pattern in the ISIHs (Fig. 1C). When the intervals between the bursting activity were relatively regular, a periodic pattern could be distinguished in the ACHs, as illustrated in Fig. 1D. We also found that neurons initially exhibiting bursting hyperactivity at regular intervals later developed bursts at irregular intervals or, occasionally, continuous nonbursting hyperactivity, and *vice ver-*

sa. The spontaneous firing of the remaining 22 neurons consisted of only continuous nonbursting hyperactivity. Among the 12 neurons recorded from the intact side, only four fired spontaneously. Furthermore, the spontaneous activity of these neurons was slow in general. However, one neuron recorded 4 weeks after the trigeminal rhizotomy displayed continuous nonbursting hyperactivity similar to that seen on the rhizotomized side. The remaining eight neurons were silent except when the receptive field of the skin was stimulated.

Although neither single-pulse nor repetitive TSRN stimulation resulted in cessation of the bursting or nonbursting hyperactivity on the rhizotomized side, such stimulation did exert inhibitory effects. As illustrated in Fig. 2A and B, single-pulse TSRN stimulation reduced spikes within the bursts (compare the initial burst following thalamic stimulation in Fig. 2B with the other bursts in A and B). Such an effect was not clearly discernible in single oscilloscopic tracings, especially when the bursting hyperactivity was irregular. However, the PSTHs revealed periods of inhibition following TSRN stimulation even in these cases, as shown in Fig. 2C. Inhibitory periods lasting for 40–60 msec were detected on the PSTHs of five of the 12 neurons (42%) associated with bursting hyperactivity. Similar suppression was seen in 13 of the 22 neurons (59%) on the rhizotomized side associated with nonbursting hyperactivity. The remaining neurons on the rhizotomized side associated with bursting or nonbursting hyperactivity were not affected. Of the 12 neurons on the intact side, eight (67%) were inhibited by a single-pulse TSRN stimulation for periods of up to 100 msec; the remaining four were unaffected.

Repetitive TSRN stimulation reduced the number of firings that outlasted the period of stimulation in seven of the 12 neurons (58%) with bursting hyperactivity. Figure 2D illustrates this reduction, as revealed by the SDV. The inhibitory effect was unrelated to the presence or absence of a response to peripheral stimuli. A similar suppressive action was also noted in 13 of the 22 neurons (59%) on the rhizotomized side associated with nonbursting hyperactivity. Repetitive TSRN stimulation inhibited eight of the 12 neurons (67%) on the intact side.

Repetitive PAG stimulation less frequently suppressed the bursting hyperactivity. Among the 12 bursting neurons, the firing was reduced in only three (25%) in response to PAG stimulation. Furthermore, in contrast to TSRN stimulation, repetitive PAG stimulation facilitated rather than inhibited firing in four neurons. A representative example of this facilitation, as revealed by the SDV, is shown in

Fig. 2D. Similar effects of PAG stimulation were also observed in neurons on the rhizotomized side exhibiting nonbursting hyperactivity. On the intact side, repetitive PAG stimulation inhibited eight of the 12 neurons (67%) and did not facilitate on any occasion.

Discussion

This study confirms the results of earlier investigations,^{2,7,11,12)} which demonstrated that hyperactivity occurs within the spinal cord dorsal horn or trigeminal subnucleus caudalis following dorsal or trigeminal rhizotomy. Since the neurons within laminae IV-V of intact brain rarely fire spontaneously and are never hyperactive,²⁰⁾ it seems clear that some classes of neurons in laminae IV-V become hyperactive in response to rhizotomy. Some neurons within laminae IV-V of the trigeminal subnucleus caudalis on the rhizotomized side displayed bursting hyperactivity, while others showed continuous nonbursting

hyperactivity. The occurrence of these two types of hyperactivity, however, does not appear to indicate that two different classes of neurons become hyperactive in response to rhizotomy, since both bursting and nonbursting types of hyperactivity were sometimes noted in the same neuron at different observation points, and this agrees with an earlier report.²⁾ Hyperactivity appeared to occur on the intact side as well, although much less frequently.

It is difficult, however, to be certain that the abnormally hyperactive neurons within the deafferented trigeminal subnucleus caudalis were equivalent to the nociceptive, WDR neurons in intact animals, although this does seem likely in view of the following observations. First, all hyperactive neurons investigated in this study were from laminae IV-V, where WDR neurons are usually located.¹⁷⁾ Second, some of the neurons associated with abnormal hyperactivity responded to peripheral stimuli applied

Fig. 2 Representative examples of the effect of TSRN stimulation applied to the nucleus ventralis posteromedialis (VPM), on the bursting hyperactivity recorded from neurons within the trigeminal subnucleus caudalis of the cat following retrogasserian rhizotomy. A: A single control tracing of the firing of a neuron located in lamina V at 22 days after rhizotomy. Calibration, 20 msec; 1 mV. B: A single tracing of the firing of the same neuron triggered by a single-pulse TSRN (VPM) stimulation. The single-pulse stimulation resulted in a reduced number of spikes within the burst (arrow) occurring 26 msec after the stimulus in association with a superimposed slow wave change. The following burst, which occurred 66 msec after the stimulus, was not affected. Calibration, 20 msec; 1 mV. C: PSTH obtained from the same neuron as shown in A and B following a single-pulse TSRN (VPM) stimulation. The PSTH consists of 25 stimuli. The bar located at time zero includes stimulus artifacts. Note that the spike density decreased for 60 msec following the stimulus. Bin width, 2 msec; calibration, 4 spikes. D: Single tracing of the SDV obtained from the same neuron, showing an increase in spike density induced by repetitive PAG stimulation and a decrease in spike density with repetitive TSRN (VPM) stimulation. The repetitive stimulation consisted of 300 Hz pulses applied for 20 sec. Note that the decrease in spike density resulting from this stimulation outlasted the period of stimulation. Bin width, 2 sec; calibration, 100 spikes.

to the most rostral cervical dermatomes in a manner that resembles the response of WDR neurons. Anderson *et al.*²⁾ reported similar observations. Third, some of the neurons on the intact side identified as WDR neurons exhibited a hyperactivity similar to that observed on the rhizotomized side. It has been reported²⁾ that, in the cat, a small number of primary afferent fibers of the trigeminal nerve reach the contralateral trigeminal subnucleus caudalis. Thus, it is possible that the hyperactivity of WDR neurons on the intact side resulted from deafferentation of these fibers. These lines of evidence suggest that WDR neurons within the trigeminal subnucleus caudalis, which naturally send pain information to the brain, may become hyperactive following trigeminal rhizotomy.

Our results indicate that the effect of brain stimulation on these hyperactive neurons in the trigeminal subnucleus caudalis on the rhizotomized side differs from that on WDR neurons on the intact side. The latter were generally inhibited by both PAG and TSRN stimulation, which is similar to the response observed in intact brain.²⁰⁾ In contrast, the neurons on the rhizotomized side with bursting hyperactivity were inhibited significantly less frequently ($p < 0.05$, Chi-square test) by PAG stimulation than were the WDR neurons on the intact side. Moreover, PAG stimulation facilitated rather than inhibited some hyperactive neurons on the rhizotomized side — an effect that was not observed in WDR neurons on the intact side. This finding is consistent with the observations recently reported by Hodge *et al.*,⁷⁾ who showed that stimulation of the raphe magnus, in which spinal projection neurons reportedly mediate the descending effects of PAG stimulation,⁴⁾ facilitated some laminae IV–V neurons within the spinal cord dorsal horn following dorsal rhizotomy. This raises the possibility that the mechanisms underlying the inhibitory effects of PAG–raphe magnus stimulation are altered by the consequence of rhizotomy. Unlike PAG stimulation, TSRN stimulation suppressed bursting hyperactive neurons on the rhizotomized side as frequently as it did WDR neurons on the intact side ($p < 0.20$, Chi-square test). TSRN stimulation also did not facilitate neuronal hyperactivity on the rhizotomized side, as it did WDR neurons on the intact side. Since TSRN stimulation did not abolish bursting hyperactivity on the rhizotomized side, and since the duration of inhibition was shorter on the rhizotomized than on the intact side, the hyperactivity on the rhizotomized side may be more resistant to the inhibitory effects of TSRN stimulation than is the nociceptive activity on the intact side. It appeared, however, that the mechanisms underlying the in-

hibitory action of TSRN stimulation on WDR neurons continued to function even after rhizotomy.

In previous experiments in animals with intact brains, we demonstrated the involvement of non-opiate neural pathways in the inhibition of WDR neurons within the trigeminal subnucleus caudalis induced by TSRN stimulation and contrasted it to that induced by PAG stimulation.²⁰⁾ The results of the study reported here provide additional evidence to support our hypothesis that separate mechanisms underlie TSRN and PAG stimulation. These findings are apparently consistent with the clinical observation that neurogenic pain due to deafferentation, which is usually resistant to therapy involving opiate neural pathways, can often be relieved by TSRN stimulation but not by PAG stimulation.²¹⁾ This agreement between clinical experience and the results of animal experiments concerning trigeminal subnucleus caudalis neurons suggests that the pain relief achieved with TSRN stimulation may be due, at least in part, to inhibition of the nociceptive activity or abnormal hyperactivity of dorsal horn neurons.

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