Neuronal hyperactivity in experimental trigeminal deafferentation

Lloyd S. Anderson, M.D., Richard G. Black, M.D., Jacob Abraham, M.D., and Arthur A. Ward, Jr., M.D.

Department of Neurological Surgery, School of Medicine, University of Washington, Seattle, Washington

Postoperative facial paresthesias frequently occur in patients following retrogasserian rhizotomy. To investigate the etiology of these paresthesias, microelectrode recordings of neuronal activity were made from the brain stem of the cat at variable times after trigeminal root section. Spontaneous neuronal hyperactivity was recorded from the deafferented spinal trigeminal nucleus in animals studied 8 to 10 days following rhizotomy. After this time the hyperactivity was found to progressively increase and was greatest in animals 1 month after rhizotomy, which was the longest time interval between rhizotomy and microelectrode recordings studied. The neuronal hyperactivity was similar to single cell recordings from cerebral epileptic foci both in monkey and man. This supports earlier experimental information that neuronal deafferentation is a factor in the development of epileptic activity. The authors postulate that brain-stem neuronal hyperactivity similar to epileptic activity is the physiological correlate of paresthesias that occur after sectioning the root of the trigeminal nerve. Further, if retrogasserian rhizotomy causes neuronal seizure activity in the spinal trigeminal nucleus, it may also be possible for trigeminal deafferentation produced by certain pathological processes involving the trigeminal nerve or ganglion to be the basis for other sensory disorders involving the face, i.e., trigeminal neuralgia.

Key Words: facial paresthesias, trigeminal neuralgia, retrogasserian rhizotomy, deafferentation neuronal hyperactivity, epilepsy

The occurrence of facial paresthesias following retrogasserian rhizotomy has long been a mystifying and perplexing phenomenon. Frazier first recognized the problem when he analyzed five hundred rhizotomies he performed for trigeminal neuralgia. He said: "The story of the after-effects of the operation would not be faithfully told were mention not made of the patient, now and then, who having been robbed of paroxysmal attacks finds himself or herself possessed of certain paresthesias which sometimes become an obsession and are magnified to the last degree." The incidence of the disorder is greater than this quotation indicates. After operation, 56% of Peet and Schneider's patients and 42% of Stookey and Ransohoff's patients had paresthesias. Rasmussen reported a lower but significant incidence of 26.1%. Therefore, the development of paresthesias following retrogasserian rhizotomy is well recognized, and the incidence, while variable, is quite high. Why paresthesias occur is not known.
Neuronal hyperactivity after trigeminal deafferentation

Their whimsical nature, i.e., itching, tingling, crawling, drawing, or burning, suggests a functional disorder. The high incidence of their occurrence, however, makes psychological factors as the sole etiology unlikely. Neither the sympathetic nerve supply to the face nor intact trigeminal sensory fibers appear responsible for the pain because stellate ganglionectomy and repeat retrogasserian rhizotomy fail to relieve the paresthesias. In fact, the paresthesias frequently are worse after total rhizotomy has been done. The method of deafferentation is not a factor because alcohol injection of the gasserian ganglion rather than rhizotomy results in a similar incidence of paresthesias.

The paresthesias could also originate centrally within the brain stem or higher in the brain. Frazier, frustrated by attempts to relieve the paresthesias by peripheral procedures, favored this concept. Because of our interest in the aftereffects of neuronal deafferentation in the central nervous system, and as retrogasserian rhizotomy produces deafferentation of the secondary neurons in the spinal trigeminal nucleus, we also believed a central site for the paresthesias was possible.

This study is an effort to investigate the pathophysiological effects of deafferentation of the spinal trigeminal nucleus. If an alteration in neuronal function in the spinal trigeminal nucleus is found after rhizotomy, this may provide insight into the mechanism of facial paresthesias. Enhanced understanding into the mechanisms of other pain syndromes involving the face which may be related to deafferentation could also result from such an investigation.

Methods

Eleven adult cats of both sexes with no evidence of facial or head trauma and with normal-appearing teeth were used in these experiments. Body weights varied from 2.1 to 5 kg. The animals were anesthetized with sodium pentobarbital, and the left temporal region was shaved and prepared with iodoine and alcohol and draped. A vertical temporal skin incision was made with the electric knife, and the temporals muscle was separated to expose the temporal bone. A 1 cm circular cranectomy was made with an air drill. Extradurally the temporal lobe was elevated and the root of the trigeminal nerve exposed. With the use of a Zeiss dissecting microscope and microsurgical instruments, the trigeminal root was sectioned completely. To protect the anesthetized cornea, a partial tarsorrhaphy was done. The animals were kept in separate cages and examined regularly for changes in behavior and appearance.

Each animal was prepared for recording from 1 to 35 days following rhizotomy. Under ether anesthesia, tracheostomy was done and the femoral artery and vein cannulated. All pressure points and wound margins were anesthetized with a long acting local anesthetic, and the cat was placed in a stereotaxic instrument. The posterior fossa was bilaterally exposed using a midline incision. Ether was discontinued 2 to 3 hours before microelectrode recording was begun. Gallamine triethiodide was used to immobilize the animal in the stereotaxic device, and breathing was artificially controlled with an automatic ventilator. During microelectrode recording, saline agar and bilateral pneumothoraces were used to further prevent motion of the brain stem from the pulse and respiratory movement.

Glass micropipettes filled with 3 molar (M) KCl (3 to 6 megohm) or 2 M NaCl (3 to 6 meghom) were used to record neuronal activity from the brain stem. After advancing the electrode it was left in place at least 10 minutes before collecting data. Whenever possible, recordings were made from both sides of the brain stem sequentially with the same electrode. The low frequency component (0.1 to 75 Hz) of the microelectrode was displayed on the polygraph record synchronous with the blood pressure and expired pCO₂ tracing for identification of any respiratory or pulse artifact. The high frequency components (0.1 to 10 KHz) were monitored with the oscilloscope and a loud speaker. They were magnetically taped and photographed in the usual way.

At the end of the experiment the animal was given an anesthetic dose of pentobarbital and then perfused through the abdominal vessels with buffered formalin. The operative site, brain stem, and trigeminal nerves were examined both grossly and histologically.
Results

Clinical Results

There were no significant complications following retrogasserian rhizotomy. A small ulceration that occurred around the mouth in one animal on the denervated side healed spontaneously. Partial tarsorrhaphy prevented ulcerations of the cornea. In the long-surviving animals the vibrissa on the rhizotomy site tended to break off and become uneven. Some animals frequently rubbed the denervated side of their face against the cage. In contrast, others appeared to avoid contact with the deafferented side. Sleeping cats would not respond to stimulation of the denervated side of the face, whereas immediate withdrawal and awakening occurred when they were stimulated on the intact side of the face.

Physiological Results

Neuronal activity on the side of the brain stem that was not deafferented was similar to recordings previously made in this laboratory from animals with intact trigeminal nerves. Recordings from the pars interpolaris and pars caudalis on the side of the rhizotomy were grossly abnormal with spontaneous hyperactivity resembling that seen in epilepsy.20

Intact Side. On the intact side, the spinal trigeminal nucleus was quiet with no recordable neuronal activity unless the ipsilateral side of the face or the contralateral thalamus was stimulated (Fig. 1A). The average response to stimulation had a short latency (5.5 msec) and prolonged afterdischarges were not seen. The responses were found in only small areas of the spinal trigeminal tract and nucleus and not generally throughout the brain stem. No spontaneous low frequency activity was recorded by the electroencephalogram (EEG) on this side.

In one cat studied 31 days after rhizotomy a small area less than 100 μ in depth on the nondeafferented side exhibited spontaneous neuronal activity which was not influenced by thalamic or peripheral stimuli. These neuronal discharges were 0.3 msec or less in duration and were not accompanied by low frequency and background activity, which were always seen with hyperactive units on the deafferented side of the brain stem.

Deafferented Side. Spontaneous neuronal activity was not found on the deafferented side in animals studied from 1 to 2 days after rhizotomy. Therefore, this was similar to the intact side except a response to peripheral stimulation was not evokable.

Between 2 and 10 days after rhizotomy, areas of low-voltage spontaneous slow-wave activity were found throughout the pars caudalis and interpolaris of the deafferented side. This activity was intermittent and irregular without an apparent pattern. By 8 days, the slow activity was accompanied by spontaneous unit discharges (Fig. 1B).

From 10 to 20 days after rhizotomy, generalized hyperactivity of single cells was found throughout the spinal trigeminal complex. The activity was regular and continuous. It was accompanied by higher amplitude slow wave activity which, for purposes of illustration, was eliminated by increasing the low frequency response of the amplifier to 100 Hz.

At 19 days after rhizotomy, neurons were observed to be firing in brief bursts separated by equally short periods of inactivity (Fig. 1C). These had a rapid, repetitive firing pattern which produced a characteristic staccato sound on the loud speaker. This hyperactivity had no relationship to the pulse and respiratory rates recorded on the polygraph.

At 31 days after rhizotomy, the hyperactivity became even more pronounced. The high frequency activity was continuous and found throughout the pars interpolaris and caudalis (Fig. 1D).

Variations in these patterns of hyperactivity occurred spontaneously or, in some cases, could be induced by light tactile stimulation of the C-2 dermatome. Repeat injections of gallamine triethiodide (Flaxedil) to maintain immobilization had no observable effect on the hyperactivity as described by Halpern and Black12 in a different preparation. The continuous and regular hyperactivity of single cells found in the longer surviving animals in our series occasionally would change and develop into rapid repetitive bursts with regular pauses between the bursts (Fig. 1E). Again the timing of these bursts was not related to pulse or respirations. After a period of time the altered pattern of hyperactivity would return to its previous more regular pattern.
Neuronal hyperactivity after trigeminal deafferentation

Hyperactivity in the caudal portion of the pars caudalis could be altered by light tactile stimulation of the most rostral cervical dermatomes. This stimulation provoked temporary bursts of even greater activity (Fig. 1 F).

In the animals with implanted thalamic electrodes, appropriate short latency responses were found on the deafferented side as they had been found on the intact side. The cells within the deafferented trigeminal complex that responded to thalamic stimulation did not, however, exhibit spontaneous hyperactivity. This might suggest that these cells were interneurons not directly deafferented by rhizotomy.

Anatomical Results

Examination of the trigeminal root showed complete sectioning in all animals. No gross abnormalities were detectable within the central nervous system. Histological examination of Nauta-Gygax sections showed massive changes typical of degeneration. This degeneration was well circumscribed and confined to the trigeminal nu-

![Figure 1](image_url)

**Fig. 1.** Microelectrode recordings from the spinal-trigeminal nucleus of the cat following retrogaserian rhizotomy. **A.** Intact side showing lack of neuronal activity except when the face is stimulated. On the deafferented side, progressive development of hyperactivity is shown at sequential times after rhizotomy at 8 days (**B**), at 19 days (**C**), and at 31 days (**D** and **E**). The influence of stimulation of the upper cervical dermatome on the hyperactivity is shown in **F**.
nucleus on the deafferented side of the brain stem, as well as some projections into the adjacent lateral reticular nucleus (Fig. 2). These were similar to previous degeneration studies performed in the trigeminal system. The degeneration was so massive that it prevented detailed analysis of the system involved in the relatively thick sections studied.

Discussion

Ward, et al., in studying the pathophysiology of the cerebral epileptic focus found the epileptic neuron to be characterized by spontaneous high frequency bursts of hyperactivity and reduction of synaptic drive. Absence of dendritic spines of synaptic contacts on neurons seen on histological examination of the epileptic focus was felt to be responsible for the "loss of synaptic drive." Effectively the epileptic neuron was therefore partially deafferented. To support this theory and study the effect that deafferentation had upon neuronal physiology, Loeser and Ward made microelectrode recordings of the neuronal activity in the cat spinal cord where localized deafferentation could be produced by dorsal rhizotomy. Spontaneous neuronal hyperactivity was found which was very similar to the epileptic activity recorded from the cerebral cortex of the monkey and man. Because of the relatively small size of the spinal cord and close association of various neuronal groups in the gray matter, it was difficult to be certain which neurons had become hyperactive.

The spinal trigeminal system, on the other hand, lends itself well to the study of neuronal deafferentation since it is supplied by a large nerve containing only afferent fibers; and its brain stem representation is a relatively large, well-circumscribed nucleus of secondary neurons. The localization of the recording microelectrode using surface features and established coordinates is thus facilitated and the identification of the secondary neuron, deafferented by rhizotomy, is made with greater certainty than in the spinal cord.

A delay in the development of hyperactivity was noted following retrogasserian rhizotomy. No hyperactivity occurred during the
Neuronal hyperactivity after trigeminal deafferentation

first 24 to 48 hours after retrogasserian rhizotomy. The hyperactivity slowly developed thereafter, increasing quantitatively for 4 weeks, the maximum time of our study. A similar delay before the onset of hyperactivity has been noted after previous denervation or deafferentation experiments. This delay before abnormal physiological activity becomes apparent may be related to structural alterations in the cell brought about by deafferentation. Although several days are required before deafferentation produces histological changes in the central nervous system with Nauta-Gygax or other stains, earlier ultrastructural alterations are known to occur. Fine structural changes in the spinal-trigeminal nucleus involving the axodendritic synapse have been examined by Westrum and Black after retrogasserian rhizotomy in the cat. Over a period of days the presynaptic processes degenerate and are phagocytized. The deafferented postsynaptic processes of the neuron remain relatively intact. The development of hyperactivity may be related to the gradual increase in “axon-bare” postsynaptic processes on the deafferented neuron.

It is reasonable to assume that this massive degree of neuronal hyperactivity in the spinal trigeminal complex should result in a sensory disturbance. In cats after trigeminal rhizotomy, excessive rubbing of the denervated side of the face at one time while avoiding contact with it at other times indicates a sensory disturbance. However, conclusions regarding such behavioral activities in animals are admittedly difficult and perhaps impossible to make. If, after retrogasserian rhizotomy in man, deafferentation neuronal hyperactivity is the physiological correlate of paresthesias, a delay should exist after the procedure before the onset of paresthesias. This time interval would be required for neuronal hyperactivity to develop. Clinically such a delay (which can be variable lasting days, weeks, or months) is always found. Thus, there is clinical support for events that may be occurring pathophysiological in the development of neuronal hyperactivity.

On the other hand, the constant barrage of neuronal activity projected to higher levels of consciousness may “turn off” sensory information from the area resulting in no sensory disturbance. Therefore, paresthesias may not exist in some cats just as they do not occur in some humans following retrogasserian rhizotomy. As in cerebral epilepsy, where neuronal hyperactivity may exist without producing a clinical seizure, a threshold may have to be reached before the seizure, in this case involving the brain stem, is displayed clinically. It could be possible, then, to have continuous neuronal hyperactivity in the spinal trigeminal nucleus without conscious awareness or discomfort.

Some physiological results from this experiment indicate that information from the area of hyperactivity can be transmitted to “consciousness.” Antidromic responses recorded in the spinal trigeminal complex from the thalamus demonstrate an intact trigeminal-thalamic pathway. Information from the area of hyperactivity was capable of reaching higher levels to the thalamus over this tract. The antidromic responses did fail to elicit a prolonged afterdischarge within the spinal trigeminal complex and were not recorded from spontaneously hyperactive cells. The hyperactive cells, therefore, are probably internuncial neurons that connect to the thalamus only by synaptic relay. The “busy signal” phenomenon, i.e., continuous axonal volleys preventing an antidromic impulse from traveling retrograde, is not likely since a corresponding degree of hyperactivity was not detected in the thalamus. Moreover, in a cat studied 31 days after rhizotomy, one small area of hyperactivity with spikes characteristic of axons was found in the spinal trigeminal complex on the intact side. This activity was probably transmitted from the deafferented side as there was a lack of both adjacent hyperactive units and slow wave activity, which constantly accompanied this activity on the deafferented side. It would appear, therefore, that the hyperactivity could be projected away from the deafferented side to other parts of the brain stem and levels higher in the brain.

If abnormal neuronal hyperactivity can occur after complete trigeminal rhizotomy, it is possible that interruption of a smaller number of trigeminal root fibers may also result in deafferentation neuronal hyperactivity. In this event, a smaller, more localized focus of hyperactivity within the spinal trigeminal nucleus would be anticipated.
ing as an “epileptic focus,” the cells could fire spontaneously in high frequency bursts or possibly be provoked by a stimulus from closely adjacent neurons. The influence of neurons adjacent to the area of hyperactivity was documented in this experiment by stimulation of the adjacent second cervical dermatome. As a result, even faster activity or modulation of the frequency of firing of hyperactive cells occurred. A similar excitatory influence of neurons adjacent to or near a cerebral epileptic focus occurs in photogenic epilepsy. With only a portion of the trigeminal root deafferented, another part of the face, mouth, tongue, or eyelid acting as the adjacent excitatory stimulus could provoke or trigger the hyperactive focus to fire.

Such smaller foci of neuronal hyperactivity could produce other facial pain syndromes besides paresthesias, such as trigeminal neuralgia. Sudden, intermittent bursts of hyperactive neurons triggered by a touch stimulus from adjacent neurons could result in the characteristic pain of trigeminal neuralgia. Because of its intermittency, explosive character, therapeutic response to anticonvulsants, etc., trigeminal neuralgia mimics an epileptic seizure. King, et al., created a tic-like syndrome in cats by applying aluminum gel to the surface of the brain stem over the spinal trigeminal complex. We have reproduced a similar syndrome in the monkey and the cat using, in addition to the above epileptogenic agent, tungstic acid gel and tetanus toxin. 4 As additional evidence that trigeminal neuralgia may represent a brain-stem seizure disorder, epileptic neuronal discharges were recorded with microelectrodes from the spinal trigeminal complex in some of these animals. It is clear, therefore, that an experimental epileptic focus involving the spinal trigeminal nucleus can result in a pain syndrome similar to trigeminal neuralgia.

Partial interruption of the trigeminal root fibers resulting in deafferentation hyperactivity is a possible explanation for the natural occurrence of an epileptic focus in the spinal trigeminal nucleus. A variety of conditions, such as cerebellopontine angle tumors, primary trigeminal tumors, aberrant and atherosclerotic arteries, hyperostosis of the petrous bone, and demyelinated plaques at or near the trigeminal root entry zone, can involve or compress the root of the trigeminal nerve and thereby produce deafferentation. With deafferentation of the spinal trigeminal complex, a hyperactive neuronal focus can occur, resulting in the facial pain syndrome. Therefore, it is not surprising that trigeminal neuralgia occurs secondarily in all of these conditions. 6,11,14,15

In “idiopathic” trigeminal neuralgia, where an obvious lesion is not found, a more subtle form of neuronal deafferentation may exist. Myelin degeneration and axonal denudation in the gasserian ganglion and adjacent trigeminal root fibers have been found with the electron microscope in “idiopathic” trigeminal neuralgia by Beaver, et al., and confirmed by Kerr and Miller. 17 These findings indicate minimal ganglion cell destruction. Regardless of how minute, brain-stem neuronal deafferentation could result. Again, a focus of neuronal hyperactivity or epileptic activity could be created, being expressed clinically as the pain of trigeminal neuralgia.

We have been impressed, as others have, with the frequency in which “tic” patients date the onset of their pain to a dental problem. These complaints have been considered coincidental or perhaps secondary to the basic condition of trigeminal neuralgia. Such assumptions may be false. Strassburg 26 found inflammatory changes in the rabbit gasserian ganglion after tooth extraction. The acute inflammatory reaction was noted to subside, and the ganglion appeared “normal” under the light microscope after a short interval. Conceivably, the inflammatory reaction results in selected ganglion cell death, producing changes in the root not seen by light microscopy. Other processes involving the distal nerve endings, such as the shedding of deciduous teeth or the progressive shrinkage of the pulp cavity of teeth that occurs with age, 3 may also result in loss of neurons in the gasserian ganglion and subsequent deafferentation of secondary neurons in the spinal trigeminal complex. In conclusion, we are postulating a universal mechanism for a wide variety of seemingly diverse facial pain syndromes: the production of focal neuronal hyperactivity by deafferentation. Such a focus in the spinal trigeminal complex can, on the one hand, fire intermittently and be provoked by stimulation of adjacent neurons resulting in a clin-
Neuronal hyperactivity after trigeminal deafferentation

...cal entity known as trigeminal neuralgia. On the other hand, after subtotal or complete retrogasserian rhizotomy, the neuronal hyperactivity may be widespread and continuous and result in paresthesias or more unremitting pain syndromes classified as atypical neuralgia.

Summary

Retrogasserian rhizotomy was performed in 11 cats. At varying times following rhizotomy, microelectrode recordings were made from the trigeminal spinal complex. These recordings revealed the progressive development of neuronal hyperactivity similar to epileptic activity.

Because of the frequent occurrence of facial paresthesias in humans following retrogasserian rhizotomy, deafferentation neuronal hyperactivity may be the physiological substrate for this abnormal sensation.

In addition, a relationship of deafferentation neuronal hyperactivity to other facial pain syndromes, such as trigeminal neuralgia, has been proposed.

References

13. Harris W: An analysis of 1,433 cases of paroxysmal trigeminal neuralgia (trigeminal tic) and the end-results of gasserian alcohol injection. Brain 63:209-224, 1940
27. Torvik A: Afferent connections to the sensory trigeminal nuclei, the nucleus of the solitary tract, and adjacent structures: an experimental study in the rat. J Comp Neurol 106:51-141, 1956


Received for publication July 27, 1970.
This study was supported in part by Grant No. NB 04053 from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, U. S. Public Health Service.
Presented in part at the annual meeting of the American Association of Neurological Surgeons, April 19, 1967, San Francisco, California.
Dr. Abraham is Visiting Research Associate, Department of Neurological Sciences, Christian Medical College & Hospital, Vellore, South India.
Address reprint requests to: Lloyd S. Anderson, M.D., Department of Surgery, Division of Neurosurgery, University of North Carolina School of Medicine, Chapel Hill, North Carolina 27514.