Chronic stimulation of the Kölliker-Fuse nucleus region for relief of intractable pain in humans

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Chronic electrical stimulation in the periventricular or periaqueductal gray matter regions and the thalamic somatosensory relay nuclei (ventralis posteromedialis and ventralis posterolateralis) provides long-term pain relief in about 50% of patients with intractable pain refractory to other conservative and/or surgical measures. To enhance the success of electrical stimulation in relief of pain, alternative brain and brain-stem targets have been sought. A series of laboratory studies indicated that the Kölliker-Fuse nucleus and the parabrachial region may provide appropriate alternatives to the "classic" targets. This report describes six patients with intractable chronic pain of nociceptive or central origin, in whom an electrode was stereotactically implanted in the region of the Kölliker-Fuse nucleus. Kölliker-Fuse nucleus stimulation alone or in combination with stimulation in the periaqueductal/periventricular gray matter region or the somatosensory thalamic nuclei provided excellent pain relief in three of the six patients.

KEY WORDS • brain stimulation • Kölliker-Fuse nucleus • pain

C HRONIC electrical stimulation of selected subcortical brain targets has been shown to provide relief of intractable pain refractory to other treatment methods. Stimulation provides initial relief to most patients but the rate of successful pain relief drops significantly with observation periods of 5 to 10 years following electrode implantation. Although alternative stimulation sites have been used occasionally, the two primary targets have been the periaqueductal or periventricular gray matter and the somatosensory relay nuclei of the thalamus, ventralis posterolateralis, and ventralis posteromedialis. Animal studies suggest that pain relief due to stimulation in some parts of the periaqueductal or periventricular region may be due to the release of endogenous opioids. The neurotransmitters responsible for pain relief from stimulation in the ventralis posteromedialis and ventralis posterolateralis nuclei have not been identified. Generally, stimulation in the periaqueductal/periventricular region has been recommended for nociceptive (peripheral) pain, whereas stimulation in the somatosensory thalamic nuclei has been recommended for pain related to deafferentation and for central pain. It has also been suggested that simultaneous stimulation involving both sites may provide slightly better success rates than either target alone.

In a series of laboratory studies, Hodge, et al., demonstrated that stimulation of the Kölliker-Fuse nucleus produces an inhibition of activity evoked by noxious stimuli in polymodal neurons in laminae 4 and 5 of the spinal cord. This nucleus was first described by R. A. von Kölliker in 1889 and later by G. Fuse in 1913. Its name, nucleus of Kölliker-Fuse, was first used by Castaldi in 1923. Although the existence of this nucleus in adult humans has been questioned, an aggregation of noradrenergic cells has been confirmed in human neonates and clearly demonstrated in other mammals. According to most authors, the Kölliker-Fuse nucleus is located just ventral to the brachium conjunctivum and provides the major source of catecholaminergic innervation of the spinal cord dorsal horn. Hodge, et al., in fact, demonstrated that depletion of catecholamines by reserpine abolished the inhibitory effect of Kölliker-Fuse nucleus stimulation on dorsal horn nociceptive neuroactivity. A descending noradrenergic pathway from the dorsolateral tegmentum to the spinal cord has been confirmed by other authors.

This report describes an effort to employ stimulation in the region of the Kölliker-Fuse nucleus for the relief of intractable pain in six patients, all of whom were unsuccessful in obtaining pain relief from conservative procedures and from stimulation in the periaqueductal or periventricular gray matter or the somatosensory thalamus. Three patients experienced excellent relief from initial stimulation while a fourth had recurrence of pain in a
few months. Anatomical confirmation of the final electrode position was obtained in all patients via computerized tomography (CT) or ventriculography.

**Clinical Material and Methods**

**Case Material**

This series includes six patients operated on between 1982 and 1989 (Table 1). There were three men and three women, their ages ranging from 36 to 78 years. Five patients suffered from deafferentation pain due to spinal cord injury, a cerebrovascular accident, or post-herpetic neuralgia. One patient (Case 3) suffered from a mixed type of pain due to a multiple myeloma affecting his spine. His back pain was considered mainly nociceptive while his bilateral leg pain due to paraplegia was thought to be deafferentation pain. In five patients, the primary target was the periventricular or periventricular gray matter or somatosensory thalamus; in one patient (Case 2), the Kölliker-Fuse nucleus was chosen as the primary target.

**Implantation Techniques**

Our criteria for patient selection and our general technique of brain electrode implantation for treatment of intractable pain have previously been described in detail. For the six patients described here, ventriculography was used to derive target coordinates in one patient, CT alone was used in a second, and a combination of CT and magnetic resonance imaging was employed in the remaining four patients. Intraoperative physiological target localization was accomplished using macro- and microelectrodes for electrical stimulation and recording.

The anatomical target was 12 to 22 mm below the anterior commissure-posterior commissure (AC-PC) plane, 2 to 6 mm behind the posterior commissure, and 7 to 10 mm lateral to the midline (Fig. 1). Hodge, et al., placed recording electrodes in the mesencephalic trigeminal nucleus of the cat and recorded single unit activity in response to jaw opening, then corrected for the location of the Kölliker-Fuse nucleus as derived from an atlas. A similar approach proved unsuccessful when employed with our first three patients. Microstimulation with square-wave pulses at 50 to 60 Hz, 0.1 msec duration, and intensities up to 5 to 6 V in humans produced no detectable sensory phenomena and no changes in pulse rate, respiration, or blood pressure. At higher stimulator intensities, paresthesias could be elicited in the opposite side of the face, presumably due to activation of the nearby trigeminal lemniscus. At slightly higher stimulus intensities (7 to 8 V), paresthesia were evoked in the contralateral arm, presumably due to current spread to the medial lemniscus. Ipsilateral facial paresthesia were never elicited.

**Illustrative Cases**

**Case 1**

This 36-year-old woman had been involved in a motor-vehicle accident in 1964 in which she sustained a cervical spine injury that resulted in severe pain in the neck and left arm. She underwent several surgical procedures on the cervical spine and then extensive treatment of persistent pain by a variety of nonsurgical techniques. In April, 1982, electrodes were implanted in the right periventricular gray matter and right ventralis posterolateralis nucleus. Excellent pain relief was obtained and the electrodes were internalized. Over the next 3 months, the patient experienced declining effectiveness of stimulation and recurrent pain. In August, 1982, the electrodes were removed and new electrodes were inserted in the right periventricular gray matter and right Kölliker-Fuse nucleus region (Fig. 2). Again excellent pain relief was obtained and the electrodes were internalized. Periventricular gray matter stimulation alone provided moderate pain relief; Kölliker-Fuse nucleus stimulation provided good relief. The patient began to use stimulation for progressively longer periods of time and at higher amplitudes. After several months, she was stimulating virtually continuously at the maximum stimulus strength of 10 V. She became compulsive about the stimulation, refused requests to decrease stimulation, and avoided her husband who attempted to assist her in decreasing stimulation. Pain relief continued. Finally, the patient occupied her entire waking hours with stimulation and virtually ceased interpersonal relationships. Increased tone of contralateral limb muscles was noted during stimulation at maximum amplitude and this appeared to be very gratifying to the patient. In October, 1984, the Kölliker-Fuse nucleus electrode was inactivated and the patient's com-

**TABLE 1**

*Summary of Kölliker-Fuse nucleus (KF) electrode implantation in six patients with intractable pain*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pain Etiology</th>
<th>Sex</th>
<th>Age</th>
<th>Electrode Placement</th>
<th>Follow-Up Period</th>
<th>Pain Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>spinal cord injury</td>
<td>F, 36</td>
<td>yrs</td>
<td>rt PVG, rt KF</td>
<td>2 yrs</td>
<td>excellent</td>
</tr>
<tr>
<td>2</td>
<td>post-herpetic neuralgia, C2-T5, lt</td>
<td>F, 68</td>
<td>yrs</td>
<td>rt KF</td>
<td>3 mos†</td>
<td>excellent</td>
</tr>
<tr>
<td>3</td>
<td>multiple myeloma</td>
<td>M, 68</td>
<td>yrs</td>
<td>lt PVG, lt KF</td>
<td>8 mos§</td>
<td>good</td>
</tr>
<tr>
<td>4</td>
<td>post-herpetic neuralgia, T5-7, lt</td>
<td>F, 78</td>
<td>yrs</td>
<td>rt KF†</td>
<td>6 mos</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>post-herpetic neuralgia, VI nerve, lt</td>
<td>M, 75</td>
<td>yrs</td>
<td>rt VPM, rt KF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>thalamic pain, rt</td>
<td>M, 69</td>
<td>yrs</td>
<td>rt PAG, rt KF</td>
<td>3 mos</td>
<td>none</td>
</tr>
</tbody>
</table>

* Abbreviations: VI nerve = sixth cranial nerve; PVG = periventricular gray matter region; VPM = ventralis posteromedialis nucleus; KF = Kölliker-Fuse nucleus.
† Initial PAG and VPL electrodes were removed because ineffective.
§ Pain relief until death due to underlying disease.
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FIG. 1. Axial (left) and sagittal (right) anatomical sections of the human pontomesencephalic region according to the stereotactic atlas of Schaltenbrand and Wahren (Plates 58 and 37, respectively). The locus ceruleus (arrow), the reference target, is clearly visible. Selected abbreviations: B. cj = brachium conjunctivum; Coe = locus ceruleus; D. b. cj = decussatio brachii conjunctivi; F. l. m = fasciculus longitudinialis medialis; F. r = formatio reticularis tegmenti; Lu. V = lunula trigemini.

Pulsatile stimulation ceased. There was a persistent reduction in pain intensity at follow-up examination in April, 1989, and she employed only non-narcotic analgesics.

Case 3

This 68-year-old man experienced the onset of multiple myeloma in 1976. He underwent laminectomy, Harrington rod fixation, and radiotherapy for a lesion in the T-9 vertebra but was left paraparetic. In 1987, he experienced severe back and bilateral leg pain due to extensive myeloma of the thoracic spine. Treatment with radiotherapy, Adriamycin (doxorubicin hydrochloride), vincristine, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), dexamethasone, and prednisone failed to relieve his pain. Oral and intrathecal opiates and local anesthetic nerve blocks also failed to provide relief. He

FIG. 2. Case 1. Plain skull x-ray films. Left: Anteroposterior view after ventriculography showing two electrodes, one projecting to the periventricular region (smaller arrow), the other projecting toward the pons (larger arrow). Right: Lateral view showing the electrode positioned in the Kölliker-Fuse region.
was bedridden with a markedly depressed level of consciousness due to large doses of intravenous opiates.

In August, 1988, stimulation electrodes were placed in the left periventricular gray matter and left Kölliker-Fuse nucleus region. Excellent pain relief was noted and the electrodes were internalized. Combined stimulation of both electrodes provided better pain relief than either electrode alone, but the major pain relief was due to Kölliker-Fuse nucleus stimulation. His opiate intake was reduced to methadone (5 mg) at bedtime; he became alert and could sit up comfortably. Relief continued until the time of his death 8 months later.

Results

In five of six patients, electrodes were internalized because excellent relief from pain was experienced during a trial stimulation period which lasted up to 14 days using stimulus parameters of 50 to 60 Hz, pulse width 0.1 msec, and amplitudes of 3 to 6 V. In one patient, the Kölliker-Fuse nucleus electrode was ineffective and was not internalized. Three of the patients who obtained pain relief adequate to justify internalization experienced continuing relief for 3 months, 8 months, and 2 years. A variety of alterations in stimulation parameters in the remaining two patients failed to produce relief of pain due to post-herpetic neuralgia and thalamic pain syndrome. Follow-up intervals are shown in Table 1.

Discussion

Stimulation of the "Classic" Targets

Chronic electrical stimulation of the periaqueductal or periventricular gray matter and somatosensory thalamus can provide pain relief to patients who are refractory to other forms of pain therapy. Although stimulation initially provides pain relief to most patients, chronic stimulation affords lasting pain relief to a much smaller number. Hosobuchi reported long-term pain relief in 77% of patients with nociceptive pain and in 58% of those with central pain. Levy, et al., reported long-term pain relief in 48% of patients with nociceptive pain and in 39% with central pain. Evaluation of our results over a 10-year follow-up period shows a decline in effective pain relief to 70% for nociceptive pain and to 50% for central pain. The term "tolerance" has been applied to the situation in which continued electrical stimulation produces progressively less effective pain relief, analogous to the tolerance that develops to opioid analgesics. Although some authors believe that pain relief elicited in humans by periaqueductal or periventricular gray matter stimulation depends on the release of endogenous opioids, there is good evidence that in most patients a nonopioid mechanism is responsible for pain relief from this stimulation. The mechanism of pain relief by ventralis posterolateralis or ventralis posteromedialis nucleus stimulation is unknown.

Stimulation of the Pontomesencephalic Region

In 1985, Katayama, et al., reported pain relief in two patients obtained by electrical stimulation of the pontomesencephalic parabrachial region. In a series of studies in cats, Katayama and colleagues described the inhibitory effect of pontomesencephalic parabrachial region stimulation on spinal nociceptive transmission and demonstrated that the inhibitory effect was dependent on a cholinergic mechanism. For stereotactic surgery in two patients, Katayama, et al., used target coordinates 6.5 to 8.5 mm lateral to the midline, 1 to 5 mm posterior to the posterior commissure, 13 to 15 mm below the AC-PC plane, and 2 to 4 mm anterior to the lateral contour of the base of the fourth ventricle. Their target was the rostral portion of the marginal nucleus of the brachium conjunctivum of Olszewski and Baxter. Although it was not described, a standard positive-contrast ventriculography technique was presumably used. Details of physiological or anatomical confirmation were not given. An absence of physiological response to stimulation frequencies of 10 to 30 Hz, with unspecified amplitude or pulse width, was reported. Pain relief in the two patients was followed for only 2 months until their death from cancer. Although Feinstein, et al., used electrical stimulation of the locus ceruleus-subceruleus in an attempt to treat intractable epilepsy, we are unaware of any other attempts to treat intractable pain in humans by electrical stimulation of this region.

In an effort to provide pain relief for patients who do not obtain it by periaqueductal or periventricular gray matter or somatosensory thalamic nuclei stimulation, we have explored the Kölliker-Fuse nucleus region as a possible alternative target. In 1982, Stevens, et al., demonstrated that the major catecholaminergic innervation of the spinal cord dorsal horn in cats is derived from the Kölliker-Fuse nucleus rather than the locus ceruleus or subceruleus as was previously thought. Hodge, et al., then demonstrated suppression ofnoxious evoked neuronal activity in the sensory lamina of the dorsal horn of the spinal cord when the Kölliker-Fuse nucleus was electrically stimulated. Depletion of catecholamines by pretreatment with reserpine caused a significant decrease in this spinal inhibitory effect of Kölliker-Fuse nucleus stimulation. They therefore proposed that norepinephrine was the important neurotransmitter regulating Kölliker-Fuse spinal inhibition.

The pontomesencephalic parabrachial region is anatomically complex and the exact correspondence between small nuclear groups identified anatomically or physiologically in animals and in man has not been conclusively demonstrated. The Kölliker-Fuse nucleus is not specifically identified in generally used human stereotactic atlases, thus localization of the target is not straightforward. The anatomical human atlas of Olszewski and Baxter, which offers no coordinates for surgery, describes the Kölliker-Fuse nucleus as part of the pedunculopontine nucleus (tegmentosus pedunculopontinus pars compacta) which is located rostrally

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![Image of anatomical atlas](image-url)

**Fig. 3.** According to the anatomical atlas of the human brain stem of Olszewski and Baxter,25 the Kölliker-Fuse nucleus is identical with the pars compacta pontis nucleus (Tg. cm) indicated by arrows. This nucleus lies more rostrally at the level of the decussatio pedunculi cerebelli superioris (Dec. Pe. ce. S., right). Selected abbreviations: Coe = locus ceruleus; F. lo. m = fasciculus longitudinales mediales; Gr. cm = griseum centrale mesencephali; Pb. 1 = nucleus parabrachialis lateralis; Tg. ds = nucleus tegmenti pedunculopontinus, subnucleus dissipatus.

and dorsolaterally in relation to the brachium conjunctivum. This is the originally described location of Kölliker’s Kern nucleus and Fuse’s description of the “Bindearm-Kölliker” nucleus. This discrepancy in the determination of the location of the Kölliker-Fuse nucleus has already been recognized by Petrovický.26 Most of the authors of the commonly used animal altaties locate the Kölliker-Fuse nucleus more caudally at the ventral edge of the brachium conjunctivum.

The Kölliker-Fuse nucleus described by Berman1 in cats is located just ventral to the brachium conjunctivum and near its lateral edge. It lies ventrolateral to the locus ceruleus and subceruleus. In determining stereotactic surgical coordinates, Katayama, et al.,18 used the atlas of Olszewski and Baxter,25 implanting the electrode in the parabrachial nucleus (nucleus marginalis brachii conjunctivi of Berman) and the nucleus tegmenti pedunculopontinus based on translation of the coordinates. Recognizing the problems inherent in this translation, we approached the problem as did Hodge, et al.,13 by attempting to identify neurons of the mesencephalic nucleus of the trigeminal nerve with jaw opening by the patients. When this proved unsuccessful and there were no useful electrophysiological signs, the locus ceruleus was targeted and the coordinates corrected for the Kölliker-Fuse nucleus. If the total anatomical breadth encompassed by the four leads along the length of the chronic stimulation electrode is considered, the final target included the Kölliker-Fuse nucleus (nucleus tegmentosus pedunculopontinus) more rostrally and the lateral parabrachial nucleus more caudally (Fig. 3). The discrepancy in terminology is one reason for the wide range of the z coordinate (12 to 22 mm) of the stereotactic device. In addition, the locus ceruleus and the “gray of the brachium conjunctivum” have a long extension in the rostrocaudal direction in the human brain stem (Fig. 1).

A ceruleospinal pathway, originating in the ventral portion of the locus ceruleus and subceruleus and descending in the ventral and ventrolateral funiculus to innervate bilaterally the ventral horn, the intermediate gray matter, and ventral parts of the dorsal horn at all levels of the spinal cord, is anatomically well established.4,16,39,41 But besides this pathway, there also exists a tegmentospinal noradrenergic pathway,4 which originates in the cell groups A1, A5, and A7 (including the Kölliker-Fuse nucleus) and descends mainly ipsilaterally in the dorsolateral funiculus to the intermediolateral cell column of the thoracic spinal cord and to the dorsal horn of all spinal levels. Close connections of the dorsolateral tegmentum and particularly of the Kölliker-Fuse nucleus to the periaqueductal gray matter2 and the raphe nuclei have been demonstrated (Fig. 4). Which roles these interconnections of the different pain modulating systems play is a subject of ongoing research.

Conclusions

This report suggests that the Kölliker-Fuse nucleus may provide an alternative target for pain relief produced by chronic electrical stimulation. In three of six
patients, significant pain relief was experienced with stimulation of either the Kölliker-Fuse nucleus alone or in combination with stimulation of the periventricular or periaqueductal gray matter for 3 months to 2 years. Because of the limited number of patients, no conclusions have been drawn as to the choice of this stimulation for nociceptive versus central and deafferentation pain.

References

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