Chronic motor cortex stimulation in patients with thalamic pain

TAKASHI TSUBOKAWA, M.D., D.SC., YOICHI KATAYAMA, M.D., PH.D., TAKAMITSU YAMAMOTO, M.D., PH.D., TERUYASU HIRAYAMA, M.D., PH.D., AND SEIGOU KOYAMA, M.D.

Department of Neurological Surgery, Nihon University School of Medicine, Tokyo, Japan

Analysis of the authors' experience over the last 10 years has indicated that excellent pain control has rarely been obtained by thalamic relay nucleus stimulation in patients with thalamic pain. In the present study, 11 patients with thalamic pain were treated by chronic stimulation of the precentral gyrus. In eight patients (73%), the stimulation system was internalized since excellent pain control was achieved during a 1-week test period of precentral gyrus stimulation. In contrast, no clear effect was noted or the original pain was even exacerbated by postcentral gyrus stimulation. The effect of precentral stimulation was unchanged in five patients (45%) for follow-up periods of more than 2 years. In the remaining three patients, the effect decreased gradually over several months. This outcome was significantly better than that obtained in an earlier series tested by the authors with thalamic relay nucleus stimulation (p < 0.05). The pain inhibition usually occurred at intensities below the threshold for production of muscle contraction (pulse duration 0.1 to 0.5 msec, intensity 3 to 8 V). When good pain inhibition was achieved, the patients reported a slight tingling or mild vibration sensation during stimulation projected in the same area of distribution as their pain.

The authors discuss the possibility that, in deafferentation pain, sensory neurons below the level of deafferentation cannot exert their normal inhibitory influences toward deafferented nociceptive neurons because of the development of aberrant connections. Thus, while stimulation of the first- to third-order sensory neurons at the level of the thalamic relay nucleus or below cannot bring about good pain inhibition in patients with thalamic pain, activation of hypothetical fourth-order sensory neurons through precentral stimulation may be able to inhibit deafferented nociceptive neurons within the cortex. None of the patients developed either observable or electroencephalographic seizure activity.

Key Words • brain stimulation • motor cortex • central pain • thalamic pain

The term “deafferentation pain” has been used to refer to pain in which the flow of afferent nervous impulses has been partially or completely interrupted.46 As such a definition implies, patients with deafferentation pain usually display sensory loss. The symptom common to all patients is a disturbance of temperature and pain sensibilities.13,22,33 Lesions that interrupt any level of the neospinothalamic system therefore appear crucial to the development of deafferentation pain; in contrast, vibration and touch sensibilities are not always disturbed in patients with deafferentation pain.13,22,33 suggesting that interruption of the dorsal column-medial lemniscal system is not necessary for the production of deafferentation pain.

There is increasing physiological evidence to suggest that nociceptive neurons, including those within the neospinothalamic system, are subject to inhibitory influences from the system mediating non-noxious somatosensory information, such as light tactile sense, at multiple levels of the central nervous system (CNS).8,12,28,29,49 In agreement with this possibility, peripheral non-noxious stimulation and dorsal column or thalamic sensory relay nucleus stimulation can attenuate nociceptive responses of the CNS in experimental animals 0,21,48 and reduce pain in some patients.11,15,16,27,32,43–45,48,50,51,57 In many patients with deafferentation pain, however, peripheral non-noxious stimulation frequently provokes abnormal pain sensation.6,22,33,46 Thus, the pain inhibitory function of the system mediating non-noxious somatosensory information does not appear to be functioning properly in patients with deafferentation due to abnormal interactions between the somatosensory system mediating non-noxious information and nociceptive neurons, presumably through aberrant neural connections.

The pain control provided by stimulation therapy appears to vary depending on the site of stimulation. Concerning pain secondary to deafferentation in the peripheral nervous system (PNS), peripheral nerve stimulation rarely achieves satisfactory pain control as ex-
TABLE I
Clinical data of patients with thalamic pain treated by motor cortex stimulation

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex. Age (yrs)</th>
<th>Original Disease</th>
<th>Barbiturate Test</th>
<th>Morphine Test</th>
<th>Results* (2 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 72</td>
<td>putaminal hemorrhage</td>
<td>sensitive</td>
<td>resistant</td>
<td>excellent</td>
</tr>
<tr>
<td>2</td>
<td>F, 66</td>
<td>putaminal hemorrhage</td>
<td>sensitive</td>
<td>resistant</td>
<td>excellent</td>
</tr>
<tr>
<td>3</td>
<td>F, 55</td>
<td>putaminal hemorrhage</td>
<td>sensitive?</td>
<td>sensitive?</td>
<td>fair†</td>
</tr>
<tr>
<td>4</td>
<td>M, 54</td>
<td>thalamic infarct</td>
<td>sensitive</td>
<td>resistant</td>
<td>excellent</td>
</tr>
<tr>
<td>5</td>
<td>M, 52</td>
<td>thalamic infarct</td>
<td>sensitive?</td>
<td>resistant</td>
<td>excellent</td>
</tr>
<tr>
<td>6</td>
<td>F, 59</td>
<td>thalamic infarct</td>
<td>sensitive</td>
<td>resistant</td>
<td>good → poor</td>
</tr>
<tr>
<td>7</td>
<td>F, 58</td>
<td>thalamic infarct</td>
<td>resistant</td>
<td>resistant</td>
<td>good → poor</td>
</tr>
<tr>
<td>8</td>
<td>M, 62</td>
<td>thalamic hemorrhage</td>
<td>sensitive</td>
<td>resistant</td>
<td>excellent</td>
</tr>
<tr>
<td>9</td>
<td>F, 53</td>
<td>thalamic hemorrhage</td>
<td>sensitive</td>
<td>resistant</td>
<td>excellent → poor</td>
</tr>
<tr>
<td>10</td>
<td>F, 58</td>
<td>thalamic infarct</td>
<td>resistant</td>
<td>resistant</td>
<td>poor→poor</td>
</tr>
<tr>
<td>11</td>
<td>F, 59</td>
<td>thalamic infarct</td>
<td>resistant</td>
<td>resistant</td>
<td>poor†</td>
</tr>
</tbody>
</table>

* Pain reduction expressed on a visual analog scale: excellent ≥ 80%; good 60% to 79%; fair 40% to 59%; poor < 40%.
† Stimulation system not internalized.

pected. In contrast, thalamic relay nucleus stimulation has repeatedly been confirmed to provide satisfactory pain control in many cases. It is tempting therefore to hypothesize that the pain inhibitory function of the somatosensory system mediates non-noxious information is still functioning above the level of deafferentation. This suggests in turn that abnormal interactions of non-noxious somatosensory information with nociceptive neurons tend to occur predominantly, if not exclusively, at the level of deafferented nociceptive neurons.

Deafferentation pain secondary to CNS lesions, such as thalamic pain, has proved the most difficult pain syndrome to control even with stimulation therapy.11,33,39,46–48 It is thus, dorsal column stimulation rarely produces pain inhibition, and stimulation of the thalamic relay nucleus and related structures is often unsatisfactory in controlling such pain.49 These results appear to be consistent with the hypothesis of an abnormal interaction between non-noxious somatosensory information and deafferent nociceptive neurons. If such an interaction is confined to the level of deafferentation, as suggested in deafferentation pain secondary to PNS lesions, better pain control may be provided by stimulation at a level more rostral to the thalamic relay nucleus.

Based on these considerations, we have examined the effect of stimulation of the cerebral cortex in patients with thalamic pain. We soon realized that stimulation applied to the precentral gyrus, rather than the postcentral gyrus, sometimes produced strong pain inhibition in such patients. We have previously reported our initial experience of chronic precentral stimulation in patients with various types of pain.50 We summarize here the long-term follow-up results with this therapy in a consecutive series of patients with thalamic pain.

Clinical Material and Methods

Patient Population

A total of 11 patients with thalamic pain were selected to test cortical stimulation during the period between 1989 and 1990 (Table I). Among these patients, eight had either a small thalamic infarct or thalamic hemorrhage and the remaining three had a small lesion in the posterior limb of the internal capsule caused by a putaminal hemorrhage. Patients with central pain secondary to other lesions, such as pontine hemorrhage, were not included in the present study. The interval between the onset of the original disease and the occurrence of pain was 1 to 4 years. The patients had been treated with various kinds of medication (anticonvulsant and/or antidepressant drugs), and no patient reported a beneficial effect of either peripheral or dorsal column stimulation.

All patients displayed hemiparesis of varying degrees. The patients complained of spontaneous pain of great intensity which they described as burning, tearing, or deep boring pain mostly in the upper extremities and trunk area. Two patients complained of pain in the lower as well as the upper extremities. Analgesia to pinprick tests of varying degrees was observed in all 11 patients. Light tactile stimuli applied to the painful area resulted in a dyesthetic response. Fine discrimination of light tactile stimuli was poor.

Patients who demonstrated severely depressive or neurotic responses on psychological assessment were not subjected to the present therapy. We recognized soon after beginning trials of this therapy that nonpainful paresthesia cannot be relieved at all by cortical stimulation. In addition, pain that is not attenuated during barbiturate tests is poorly attenuated by either thalamic or cortical stimulation.50 In order to maximize the benefit to the patients, we decided to exclude patients who complained mainly of nonpainful paresthesia or barbiturate-resistant pain after our initial experience with a few cases.

The patients and their families gave informed consent for the procedures described below. This study was approved by the Committee for Clinical Trials and Research on Humans at our university, and by the Japanese Ministry of Health and Welfare as part of an advanced medical care program.

Surgical Procedures

The location of the precentral gyrus was estimated...
from bone landmarks using the conventional method. Under local anesthesia, a paramedian skin incision was made 1 to 4 cm lateral to the midline, depending on the location of the painful area. A small craniotomy, 3 to 4 cm in diameter, was then carried out at the midline in the estimated area of the motor cortex. An electrode array* with four plate electrodes 0.5 cm in diameter, each separated by 1 cm, was inserted into the epidural space (Fig. 1). In the two patients who complained of pain over the lower as well as the upper extremities, two electrode arrays were used.

The locations of the precentral and postcentral gyri were confirmed from phase reversal of the N20 wave of the somatosensory evoked potential recorded from the electrode, according to the method established by Wood, et al.24 Various changes in N20 were observed in the present series of patients, supporting the notion that lesions in the neospinothalamic system but not in the dorsal column-medial lemniscal system14 are crucial for the development of deafferentation pain.12,22,23 When the electrode was moved from the postcentral gyrus to the precentral gyrus, the N20 wave became positive.

The location of the precentral gyrus was also confirmed from muscle contraction in response to stimulation with the electrode. Bipolar stimulation employing two appropriate electrodes was performed (with an interpolar distance 10 to 30 mm), usually placing the electrode array parallel to the mediolateral orientation of the precentral gyrus. We have previously found that this stimulation procedure is the most practical in clinical settings for recording corticospinal responses from the spinal epidural space in humans and allows us to identify the precentral stimulation from postcentral stimulation.20 The location from which good muscle twitch can be obtained was mapped as carefully as possible. Contractions of the lower-extremity muscles were induced by precentral stimulation at the medial edge of the hemisphere with relatively higher intensity (Fig. 1A). The effect of postcentral stimulation on the pain was also examined.

Once we had established the best location and orientation of the electrode array for producing muscle contraction of the painful area with the lowest thresh-
old, the electrode array was tightly sutured on the surface of
the dura. This surface was carefully coagulated so as to prevent
any clot formation and future growth of connective tissue.

The stimulation system was internalized after a period of 1
week for test stimulation. During that period, the pair of
electrodes that provided best pain inhibition was selected, and
the effects of stimulation with various parameters and polarities
were examined. Most of the patients were selected stimulation
with an interpolar distance of 30 mm in order to cover a relatively
broad painful area. No apparent difference was noted by most
patients when the polarity of the stimulation current was
reversed.

Electroencephalographic (EEG) recordings were repeatedly
made at predetermined intervals. Diphenylhydantoin and
phenobarbital were administered in all patients. We had previous-ly
performed intermittent precentral stimulation in five cats (10
minutes of stimulation at an intensity above the threshold of
muscle contraction, three times a day) with chronically
implanted epidural electrodes for 1 year, and confirmed the
absence of any spontaneous convulsions. EEG seizure activity,
or morphological damage.

**Stimulation Procedures**

Stimuli were delivered by monophasic square wave pulses
(duration 0.1 to 0.5 μsec, mostly 0.2 μsec). Stimulation was usually applied continuously for 5 to 10
minutes on each occasion, and no stimulations were
given at night. Chronic stimulation was performed after
internalization of the electrode using a wireless stimulation
system.† While the parameters for chronic stimulation
were chosen so that the best pain inhibition was
achieved, frequency and intensity were restricted to a
level slightly lower than the threshold for muscle con-
traction, except as otherwise noted (see below). The
effects of stimulation of the precentral gyrus were evaluated
at predetermined intervals after initiation of the
therapy.

**Pain Assessment**

Changes in the pain level of each patient were evaluated
by a physician at a pain clinic independent of
our service. Each patient was asked to describe the pain
levels on a visual analog scale. The effects of stimulation
were classified into four categories: excellent, reduction
of the pain level by 80% to 100%; good, reduction of
the pain level by 60% to 79%; fair, reduction of
the pain level by 40% to 59%; and poor, reduction of
the pain level by less than 40%. The pain level was evaluated
daily during the period of test stimulation and
once a month subsequently.

The pain level in each patient was also determined
from responses to stepwise intravenous administration
of thiopental and morphine (barbiturate and morphine
tests). The changes in pain level in response to
thiopental or morphine were again evaluated by each
patient on a visual analog scale.

† Wireless stimulation system, Model 3425, manufactured
by Medtronic, Inc., Minneapolis, Minnesota.

**Results**

In eight (73%) of the 11 patients, satisfactory pain
control was obtained by precentral stimulation during
surgery. The remaining three patients reported no
change in their pain with precentral stimulation. No
pain inhibition was induced in any of the 11 patients
by postcentral stimulation. Two patients reported that
their original pain was even exacerbated by postcentral
stimulation and caused pain similar to the dysesthesia
from which these patients suffered. The area more
rostral to the precentral gyrus was stimulated in three
instances with no apparent effects.

The pain typically subsided within 5 minutes after
the onset of precentral stimulation, and, if effective,
completely faded away within approximately 10
minutes. This effect continued for 2 to 6 hours following
the termination of 10 minutes of stimulation. The pain
inhibition usually occurred at intensities below the
threshold for production of muscle contraction (intensity
3 to 8 V). When good pain inhibition was achieved,
the patients reported a sensation of light tingling or
mild vibration projected in the same area of distribution
as their pain during stimulation at an intensity even
below the threshold for muscle contraction. The pa-
tients selected varying stimulation frequencies (5 to 120
Hz), although again a relatively lower frequency with a
longer pulse duration was preferred.

The stimulation system was internalized in the eight
patients with satisfactory pain control. The maximum
intensity available to the patients was mostly restricted
to levels below the threshold for muscle contraction.
One patient who complained of pain in the lower and
upper extremities reported that complete pain control
was achieved when stimulation caused muscle con-
traction. This may have been due to a longer distance
between the electrodes and the foot area of the precen-
tral cortex. The pain in these eight patients was mostly
sensitive to barbiturates and resistant to morphine. The
remaining three patients who did not respond favorably
to the therapy tended to show different characteristics
pharmacologically: their pain was only questionably
sensitive or even resistant to barbiturates and was some-
times questionably sensitive to morphine (Table 1). In
addition, the major complaint in two of these patients
appeared to be nonpainful paresthesia rather than se-
vere pain. It was found that nonpainful paresthesia was
not improved by precentral stimulation in other pa-
tients.

The excellent effect of precentral stimulation was
unchanged in five patients during the follow-up period
of 2 years (Table 1). In the remaining three patients,
the effect decreased gradually over several months.
Thus, five of the eight patients displayed a lasting effect
of the therapy, which corresponded to nearly one-half
(45%) of the patient group examined in the present
study. These patients were stimulated five to seven
times a day. Interestingly, subjective improvement of
motor deficits was also reported in most of these cases;
however, this improvement was not evident objectively.

Three patients required two or three revisions of the
electrode each, due to either growth of connective tissue.
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above the dura or dislocation of the electrode. Revisions of the electrode as a result of such changes were especially required in patients with brain atrophy. It was extremely difficult sometimes to determine the best location and orientation of the electrodes, presumably because the voluminous cerebrospinal fluid (CSF) space prevented satisfactory current spread. The effect of stimulation on pain and the capability of producing muscle contraction with a higher stimulation intensity disappeared simultaneously in these cases but reappeared after the revisions, indicating that appropriate stimulation of the precentral gyrus was definitively necessary for securing satisfactory pain control in these patients. None of the patients subjected to this therapy developed either observable or EEG seizure activity.

**Discussion**

**Effect of Precentral Gyrus Stimulation for Pain Control**

Analysis of our experience with deep-brain stimulation had indicated that excellent pain control has rarely been achieved by thalamic relay nucleus stimulation in patients with deafferentation pain secondary to CNS lesions, such as thalamic pain.\(^{48-50}\) Even when the initial effect of such stimulation appears satisfactory, tolerance tends to develop within 7 months. In that series, excellent pain control was never achieved and good pain control was obtained in only 38% of patients with thalamic pain at 2 years following the initiation of such therapy (Table 2). This is in clear contrast to the effect of thalamic relay nucleus stimulation in patients with deafferentation secondary to PNS lesions, as mentioned above: in that series, 85% of patients displayed excellent or good pain relief with thalamic relay nucleus stimulation.\(^{48-50}\) The present observations demonstrate that excellent pain control was accomplished in 45% by motor cortex stimulation during the follow-up period of 2 years. This result is significantly better than that obtained in our earlier series treated by thalamic relay nucleus stimulation (p < 0.05, chi-squared test).

**Complications of Precentral Gyrus Stimulation**

We have not yet encountered any serious complications with chronic precentral stimulation. While possible development of seizure activity with intermittent chronic stimulation of the motor cortex had been the problem of greatest concern, no such complication actually resulted. As mentioned above, we had confirmed in cats that intermittent precentral stimulation with chronically implanted epidural electrodes does not cause EEG seizure activity or morphological damage. This technique does not appear to be hazardous as long as a stimulation intensity below the threshold for muscle contraction is employed.

The main problem associated with this technique may be the tissue reaction in the dura, which increases the impedance of the stimulation site. This can be confirmed by loss of the capability to produce muscle contraction at a higher stimulation intensity. We believe that careful coagulation of even trivial bleeding during surgery can serve to considerably reduce the incidence of this problem. In patients with severe brain atrophy, a higher stimulation intensity is needed, presumably due to CSF intervening between the cortex and the electrodes. One patient with pain secondary to pontine hemorrhage, who was not included in the present study, reported that this technique produced pain at the stimulation site. Since this patient suffered from pain in the trigeminal area, stimulation of the dura was probably the cause of his pain. Indeed, the pain disappeared after isolation of the dura around the electrodes and resurfacing.

**Physiological Characteristics of Stimulation Procedure**

Microstimulation and single neuron recording in experimental animals have greatly advanced our knowledge of the cortical arrangements of motor and sensory functions.\(^{5,17,29,30,38}\) In humans, however, stimulation and recording can be performed only through the surface of the cortex.\(^{9,20,24,35,36,35}\) Large portions of the sensory and motor cortices on the walls of the central sulcus of humans are not accessible to direct stimulation. This indicates that activation of the cortex directly beneath the surface electrode is not necessarily responsible for the observed effects.

Woolsey, et al.,\(^{23}\) have reported that the threshold for postcentral stimulation resulting in muscle contraction was generally not significantly higher than that for precentral stimulation. They indicated that the quality of movement obtained on postcentral stimulation does not differ in any significant way from that obtained on precentral stimulation. In contrast, Penfield and Boldrey,\(^{35}\) Lewin and Phillips,\(^{23}\) Libet,\(^{24}\) and Schmid, et al.,\(^{45}\) as well as many others have reported that precentral stimulation can cause muscle contraction at a much lower intensity than postcentral stimulation. The effects of pre- and postcentral stimulation appear therefore to be dependent on the stimulation procedure employed.
We have found previously that bipolar stimulation with an interpolar distance of 30 mm is the most practical in clinical settings for recording corticospinal responses from the spinal epidural space in humans. This technique has allowed us to distinguish precentral stimulation from postcentral stimulation. We employed basically the same stimulation procedure in the present study. It appears that, so far as the stimulation procedure used in our present and previous studies is concerned, precentral stimulation more easily activates the corticospinal tract neurons originating from the motor cortex.

The bipolar stimulation with a longer interpolar distance employed in the present and previous studies has characteristics similar to those of deep monopolar stimulation, so that corticospinal tract neurons originating from the deep layer and running perpendicularly toward the white matter are readily activated. Experimental studies have demonstrated, however, that bipolar stimulation basically tends to activate intracortical interneurons running horizontally within the superficial layers. Thus, the stimulation procedure employed in the present study may have activated multiple elements within the cortex depending on the stimulation parameters.

Woolsey, et al., reported that in severe Parkinson's disease, marked inhibition of the tremor and rigidity was induced by precentral stimulation but rarely by postcentral stimulation. Adams and coworkers stimulated the posterior limb of the internal capsule, which resulted in a sensation of light tingling and vibration and a further increase in intensity produced muscle contraction. Their patient reported that he could use his arm better than before the electrodes were implanted, although this was not evident to the examiner. Many patients in the present series also reported improvement of their motor deficits, which seems most likely to have resulted from inhibition of their rigidity.

**Paresthesias Induced by Precentral Gyrus Stimulation**

It is worth noting that, when precentral stimulation caused pain inhibition, the patients felt a light tingling or vibration sensation within the painful peripheral area. Penfield and Boldrey reported that there is no localization of quality of sensation with either pre- or postcentral stimulation. They indicated that extension of sensation over the motor cortex is more frequent than that of motor responses over the sensory cortex. Sensation induced by precentral stimulation has also been described by many investigators. Thus, sensation on precentral stimulation appears to be a more universally observed phenomenon, as compared to muscle contraction on postcentral stimulation, suggesting that the sensation on precentral stimulation is not simply due to the spread of current to the sensory cortex.

Amassian, et al., recently demonstrated that transcranial magnetic stimulation elicited paresthesias, usually tingling, from scalp sites similar or anterior to those yielding muscle contraction. Based on careful mapping study, they concluded that these sites are located precentrally. While repetitive stimulation is usually necessary to produce paresthesia from postcentral stimulation, a single stimulation is sufficient to produce paresthesia from precentral stimulation. Amassian, et al., hypothesized that the precentral cortex has access to the "perceptual system" with much briefer discharges to correct fast muscle movement than is required by the postcentral cortex for its special role in long-term analysis.

It is interesting to note that only a minority of normal humans experience paresthesias in response to transcranial magnetic stimulation. This indicates that the sensory threshold of precentral stimulation is usually not lower than the motor threshold. Libet, et al., noted that single-pulse precentral stimulation sometimes caused tingling, which always appeared to accompany muscle contraction. In the present study, however, paresthesias were induced in many patients without muscle contraction. Amassian, et al., suggested that paresthesias experienced by a minority of normal humans are explained by a heightened sensitivity of the perceptual system. If this is the case, paresthesias elicited in the present study may represent such a condition in patients with deafferentation of thalamocortical fibers.

**Cortical Mechanisms of Thalamic Pain**

In a patient with deafferentation pain, Loeser, et al., demonstrated hyperactivity of spinal cord neurons which may have been previously nociceptive. Nashold reported evidence of hyperactivity within the spinothalamic and/or quintothalamic pathways within the level of the midbrain in patients with deafferentation pain. Stereotactic coagulation of the same region was reported to have relieved the pain in these patients. Rin, aldi, et al., recently described hyperactivity of medial and intralaminar thalamic neurons in patients with deafferentation pain. Postcentral stimulation of appropriate areas can exacerbate phantom-limb pain in some patients and removal of these cortical areas can eliminate the pain. These observations are consistent with the hypothesis that hyperactivity of nociceptive neurons underlies deafferentation pain.

Penfield and Jasper reported a case of thalamic pain, in which postcentral stimulation produced attacks of pain similar to those that occurred spontaneously. Removal of the postcentral gyrus brought relief to the patient. Erickson, et al., excised the sensory cortex in patients with thalamic pain, bringing about pain relief. It seems probable that abnormal pain sensation is generated at least partially by hyperactive nociceptive neurons at the cortical level in thalamic pain. Since postcentral stimulation rarely produces pain sensation in patients without pain, as stated by Penfield, it is likely that nociceptive neurons normally have a relatively high threshold for activation and these neurons become more excitable in patients with thalamic pain.

**Possible Mechanisms of Effect of Precentral Gyrus Stimulation**

Since good pain inhibition was evidently achieved only when stimulation was applied in the area from which muscle contractions were induced, the pain in—

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Inhibition obtained by precentral stimulation in the present study appears to be attributable to activation of the motor cortex. Nevertheless, pain inhibition was produced at an intensity below the threshold for muscle contraction. It is therefore unlikely that activation of corticospinal tract neurons is crucial for accomplishing pain inhibition. Similarly, peripheral input originating from muscle contraction does not appear to be necessary for this effect.

Mountcastle and Powell demonstrated that non-noxious peripheral stimulation excites neurons in a restricted area of the sensory cortex and at the same time inhibits neurons in the large surrounding field. They emphasized that this inhibitory receptive field component is important in the process of spatial analysis whereby the precise localization of stimuli is subjectively determined. The activities of nociceptive neurons can be attenuated by this inhibitory mechanism driven by non-noxious stimuli. Fields and Adams proposed that the essential feature of deafferentation pain is the loss of this inhibitory area, due presumably to aberrant connections in the system mediating non-noxious information to nociceptive neurons. Loss of the inhibitory area will result in divergence of excitation and an abnormal quality of sensation, leading to decreased spatial discrimination and dysesthesia.

It is worth noting that, when the precentral stimulation caused pain inhibition, the patients felt a light tingling or vibration sensation within the painful peripheral area. There is a highly organized set of reciprocal connections between the motor cortex and the sensory cortex, which appear to carry primarily non-noxious information such as that related to target muscles. It is therefore likely that precentral gyrus stimulation activates non-nociceptive neurons in the sensory cortex selectively, either through orthodromic activation of neuronal chains to the sensory cortex or antidromic activation of axons projecting from the sensory cortex. In contrast, postcentral stimulation produces nonselective activation of all elements within the sensory cortex including the hyperactive nociceptive neurons. This may be the reason why postcentral stimulation is often painful in thalamic pain patients. If precentral stimulation can selectively activate non-nociceptive neurons in the sensory cortex, this may restore the function of the inhibitory area and suppression of the patients' pain.

General Hypothesis for Stimulation Therapy of Deafferentation Pain

As mentioned above, peripheral nerve stimulation rarely provides satisfactory pain control in patients with deafferentation in the PNS, suggesting that aberrant connections between the system mediating non-noxious information and nociceptive neurons may exist. An inhibitory receptive field component similar to that in the sensory cortex has been demonstrated by Wall et al., in the dorsal horn of the spinal cord. Non-noxious stimuli excite neurons in a restricted area of the dorsal horn and at the same time inhibit neurons in the large surrounding field. The activities of nociceptive neurons can be prevented by this inhibitory mechanism driven by non-noxious stimuli. If the loss of such an inhibitory mechanism, presumably through aberrant synaptic connections, is responsible for deafferentation pain secondary to PNS lesions, peripheral nerve stimulation would obviously cause pain rather than pain inhibition (Fig. 2).

In contrast, thalamic relay nucleus stimulation has repeatedly been confirmed to provide satisfactory pain relief in patients with deafferentation pain.

![Diagram](image-url)

**Fig. 2.** Schematic representations of the hypothesis for changes in pain inhibitory mechanisms in patients with deafferentation pain. Left to Right: Normal physiology: lesions within the peripheral nerves; lesions within the spinal cord; and lesions at the level of the thalamus. Normally, inhibitory mechanisms driven by non-noxious information exist within the spinal cord, thalamus, and cortex. Stimulation of the peripheral nerves and dorsal column (DC) is effective for relieving pain. In deafferentation pain, the inhibitory mechanism (black arrow) is lost at the level of deafferentation and it is probable that non-noxious information even facilitates the activity of nociceptive neurons (white arrow). Effective stimulation sites (horizontal arrows) are therefore located only above the level of deafferentation. According to this hypothesis, thalamic relay nucleus stimulation is not appropriate for thalamic pain (right). DRG = dorsal root ganglion; ML = medial lemniscus; IC = internal capsule.
control in many cases. 41, 15, 16, 27, 32, 48, 50 It seems likely, therefore, that the pain inhibitory function of the system mediating non-noxious stimuli is still functioning above the level of the dorsal horn (Fig. 2). This also suggests that, while nociceptive neuronal chains climbing up to the cortex become hyperactive even after PNS deafferentation, 5, 7, 14, 23, 26, 31, 40, 53, 55 aberrant connections of the system mediating non-noxious information to nociceptive neurons appear to occur predominantly at the level of the deafferentation.

In thalamic pain, cortical nociceptive neurons may be the neurons that are deafferented. The above-mentioned principle implies that stimulation of the thalamic relay nucleus may be unable to inhibit pain in these patients since aberrant connections may exist between the third-order sensory neurons and deafferented nociceptive neurons at the cortex (Fig. 2). Stimulation of the third-order sensory neurons at the thalamic relay nucleus may have the same effect at peripheral stimulation, which causes dysesthesia in these patients. It may be hypothesized, as mentioned earlier, that precentral stimulation selectively activates non-nociceptive fourth-order sensory neurons, either orthodromically or antidromically, which in turn inhibit hyperactive nociceptive neurons within the sensory cortex (Fig. 3).

The hypothesis presented here for the mechanism underlying the observed effects of precentral stimulation on thalamic pain has yet to be confirmed. We believe, however, that this technique of stimulation therapy warrants further clinical study.

Fig. 3. Schematic representations of the hypothesis for the pain-inhibitory mechanisms of precentral stimulation in patients with thalamic pain (right) compared with the normal physiology (left). Normally, an inhibitory mechanism (black arrow) driven by non-noxious information exists at the cortical level. In patients with thalamic pain, the inhibitory mechanism is lost at the cortical level and it is probable that non-noxious information in the sensory cortex (SCX) activates nociceptive neurons (white arrows). Thalamic relay nucleus stimulation is therefore inappropriate. Postcentral gyrus stimulation is also not appropriate because the sensory cortex (SCX) is the level of deafferentation. Precentral stimulation activates non-nociceptive neurons within the sensory cortex orthodromically or antidromically, which, in turn, inhibit (black arrow) hyperactive nociceptive neurons in the sensory cortex. This schema represents only antidromic activation of neurons within the sensory cortex. MCX = motor cortex.

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