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Thalamic field potentials during deep brain stimulation of periventricular gray in chronic pain

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Abstract

Stimulation of the central gray matter areas has been used for the treatment of chronic pain for decades. To better understand the mechanism of action of such treatment we studied the effects of stimulation of the periventricular gray (PVG) on the sensory thalamus in two patients with chronic central pain. In each case, two electrodes were implanted in the PVG (Medtronic 3389) and the ventroposterolateral thalamic nucleus (Medtronic 3387), respectively, under guidance of CT/MRI image fusion. The PVG was stimulated in the frequency range of 2–100 Hz in alert patients while pain was assessed using the McGill–Melzack visual analogue scale. In addition, local field potentials (FPs) were recorded from the sensory thalamus during PVG stimulation. Maximum pain relief was obtained with 5–25 Hz stimulation while 50–100 Hz made the pain worse. This suggests that pain suppression was frequency dependent. Interestingly, we detected low frequency FPs at 0.2–0.4 Hz closely associated with the pain. During 5–25 Hz PVG stimulation the amplitude of this potential was significantly reduced and this was associated with marked pain relief. At the higher frequencies (50–100 Hz) however, there was no reduction in the FPs and no pain suppression. We have found an interesting correlation between thalamic activity and chronic pain. This curious low frequency potential may provide an objective index for quantifying chronic pain, and may hold further clues to the mechanism of action of PVG stimulation. © 2002 Published by Elsevier Science B.V. on behalf of International Association for the Study of Pain.

Keywords: Pain; Field potentials; Sensory thalamus; Periventricular gray; Deep brain stimulation

1. Introduction

Attempts to alleviate medically intractable pain through chronic stimulation of deep brain structures have been reported for nearly half a century (Heath, 1954; Pool et al., 1956). Over the years several targets have been tried with varying degrees of success. These include the septal region (Heath, 1954), caudate (Ervin et al., 1966), ventroposterolateral (VPL) nucleus (Mazars, 1975), several other thalamic nuclei including the dorsal medial nucleus, the parafascicular nucleus and the centromedian nucleus (Thoden et al., 1979; Boivie and Meyerson, 1982; Andy, 1987), Kolliker-Fuse nucleus (Young et al., 1992), periacquecductal and periventricular gray matter (PAG and PVG) (Hosobuchi et al., 1977; Richardson and Akil, 1977; Meyerson et al., 1978; Plotkin, 1980; Young et al., 1985). It is now common practice to recommend PAG/PVG stimulation for the treatment of so-called nociceptive, peripheral or non-deafferentation pain based on the hypothesis that pain relief elicited by such stimulation is mediated by an endogenous opioid pathway and that opioids are by and large effective for relief of nociceptive pain. Stimulation of other targets, especially the thalamic sensory relay nuclei VPL or VPM or the internal capsule, has been suggested for the alleviation of central pain related to deafferentation or so-called neuropathic pain (Young and Rinaldi, 1997).

The mechanism of PAG/PVG pain relief is believed to involve the opioid pathways that contact serotoninergic neurones that descend from the raphe nuclei to the dorsal horn of the spinal cord (Hosobuchi et al., 1979; Young and Dawson, 1987; Young et al., 1993). However, there are very few studies that have explored the effect of PAG/PVG stimulation on the activity of the sensory thalamus (Rinaldi et al., 1991). In this report we describe field potential (FP) recordings from the VPL during PVG stimulation in two patients with chronic intractable central pain.

FP recording allows sampling of abnormal synchronous discharge in a population of neurones as opposed to the single-unit recording more commonly used in functional stereotactic neurosurgery (Liu et al., 2000). We believe

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that this permits better understanding of abnormal electrical activity in a functionally cohesive subcortical area in a pathological condition. This is especially true if there is a concurrent record of abnormal electrical activity from related peripheral tissue, e.g. tremor EMG from corresponding muscle groups (Ford-Dunn et al., 2000; Liu et al., 2000a,b) or cortical electrical activity (Marsden et al., 2000). The use of macroelectrode FP recording offers other clinical advantages over microelectrode single-unit monitoring. It is very much less time consuming – a matter of considerable importance in functional neurosurgery as this often involves a conscious patient whose alert co-operation may be vital to the final siting of the stimulating electrode (operations involving microelectrode recordings can take several hours). Also it requires many fewer penetrations of the brain, thereby decreasing the risk of complications like intracerebral haemorrhage (Carrol et al., 1998). In addition, the use of the stimulating macroelectrode for FP recording ensures avoidance of the siting error possible when replacing microelectrodes with the stimulating macroelectrode. We have found that FP recording has improved our ability to target effective sites for chronic deep brain stimulation in various movement disorders (Ford-Dunn et al., 2000; Liu et al., 2000a,b).

2. Methods

2.1. Patients

We report our findings in two patients with intractable neuropathic pain.

2.1.1. Case 1

A 60-year-old female developed right sided trigeminal neuralgia at the age of 42 years. An initial glycerol injection failed to alleviate the pain and she then underwent a microvascular decompression, which resulted in anaesthesia dolorosa of the right side of the face. This was then treated by a pontine tractotomy, which resulted in a right hemiparesis and neuropathic pain affecting the right side of her body, worse in the face and arm. Hyperaesthesia and a continuous burning sensation were her predominant symptoms.

2.1.2. Case 2

A previously fit 61-year-old female had a subarachnoid haemorrhage at the age of 58 years secondary to a right middle cerebral artery aneurysm. This was treated by a craniotomy and clipping of the aneurysm and she subsequently developed a right sided stroke with a right hemiplegia and intractable right sided neuropathic pain manifested predominantly by severe right hemi-body hyperaesthesia such that the slightest touch was agonizing.

2.1.3. Surgery

Informed consent was obtained from each patient. A CRW base ring was applied to the patients' head under local anaesthesia. A stereotactic CT scan was then performed and using the Radionics Image Fusion and Stereoplan programme the co-ordinates for the anterior and posterior commissures were calculated. After washing the patient's scalp with alcoholic chlorhexidine, a parasaggital posterior frontal scalp incision 3.0 cm from the midline was made contra-lateral to the side of pain. The VPL nucleus was implanted with a Medtronics 3387 electrode when stimulation induced parasthesia in the area of pain and the PVG with a Medtonics 3389 electrode when stimulation induced relief of pain or a sensation of warmth in the area of pain. Both electrodes have four exposed contacts, each 1.5-mm long, placed linearly. The Medtronic 3387 has a gap of 1.5 mm between contacts (span of 10.5 mm between the most proximal and the most distal contacts) while the Medtronic 3389 has a gap of 0.5 mm between contacts (span of 7.5 mm between the most proximal and the most distal contacts). We used the 3389 electrode in the PVG in anticipation that the area of stimulation would be smaller compared to that in the VPL. In subsequent cases we have found that this is not the case and hence we now use the 3387 at both sites. The ranges of co-ordinates of the final targets with reference to the mid-commissural point are listed in Table 1.

In both patients the electrodes were externalized for a week's trial stimulation and recording of FPs to ensure that pain relief was sustained.

Pain was assessed before and after surgery and during stimulation by a self-rated visual analogue scale (VAS; McGill–Melzack).

2.2. Field potential recording

FPs were recorded through the thalamic DBS leads in the ward after the patient had recovered from the operation and pain had returned to the pre-operative level. FPs were amplified $\times 1000$ (CED 1902, Cambridge, UK), filtered between 0 and 100 Hz, digitized at 250 Hz and continuously displayed on-line with an adjustable window. Records were obtained before, during and after sessions of stimulation of the PVG leads at different frequencies. Off-line analysis was

Table 1
This table details the ranges of the stereotactic co-ordinates of the PVG and the VPL targets used in the final placement of the DBS electrodes (the co-ordinates are given in millimeters relative to the mid-commissural point and refer to the position of the tip of the Medtronic electrode)

Target	Axis		
	Anteroposterior	Lateral	Vertical
VPL	− 10 to −13	14 to 18	2 to −5
PVG	− 10	3 to 4	0

performed using Matlab software (Mathworks Inc., Natick, MA).

3. Results

3.1. Clinical results

In patient 1 in the 7-day post-operative trial period, during PVG stimulation at particular frequencies, the self-rated VAS scores fell from a pre-operative level of 8.8 ± 0.44 (mean ± SD, $n = 5$) to 5.0 ± 2.34 (mean ± SD, $n = 5$; $P < 0.05$, two-tailed paired *t*-test). In patient 2 pain scores reduced from a pre-operative level of 9.0 ± 0.70 (mean ± SD, $n = 5$) to 5.8 ± 1.09 (mean ± SD, $n = 5$; $P < 0.01$, two-tailed paired *t*-test).

Pain suppression was related to the frequency of stimulation of the PVG. Maximum pain relief was obtained with 5–25 Hz stimulation while 50 and 100 Hz made the pain worse. However, each patient responded to a specific narrow range of PVG stimulation frequencies, which, though in the low frequency range in both cases, was not identical. Thus one patient responded best to stimulation at 10 Hz, while another had maximum pain relief with 5 Hz and 25 Hz PVG stimulation.

Interestingly despite a 35% reduction in self-rated pain scores the second patient elected not to proceed to a full implantation as she wanted total alleviation of pain. The electrodes were therefore implanted subcutaneously to allow implantation of the pulse generator if she changed her mind later.

3.2. Field Potential recordings (Figs. 1 and 2)

We recorded FPs from the sensory thalamus during PVG stimulation. Switching on the stimulation was followed immediately by change in the thalamic potentials. However, the FPs did not revert to baseline immediately on cessation of stimulation, but only after a lag of 5–15 min depending on the duration of stimulation. The FP consisted of a very low frequency potential, of 0.2–0.4 Hz, in the sensory thalamus; it's amplitude seemed to correlate with the intensity of pain perception. It was much stronger off stimulation and with higher frequency stimulation (50, 100 Hz) when there was no pain suppression, than while stimulating the PVG at low frequencies (5, 25 Hz) with accompanying pain relief. (Please see Figs. 1 and 2).

4. Discussion

We have found that stimulation of the PVG induces changes in the electrical activity recorded from the sensory thalamus. This supports the work by other groups exploring ascending modification of somatosensory activity elicited by PVG stimulation (Rinaldi et al., 1991). The fact that this change is almost instantaneous with the onset of stimulation suggests it is likely to be mediated through a fairly direct neuronal circuit rather than as a consequence of descending modification of the endogenous opioid pathway. There was a strong correlation between the alleviation of pain sensation and the amplitude of the thalamic slow frequency FPs. The PVG projects to the intralaminar nuclei. Hence its direct effects on the thalamus have to be added to any effects on the opioid projections to the raphe. It is known that both PVG/PAG and ventrobasal thalamic stimulation activates the raphespinal and the reticulospinal neurons, which in turn influence the activity of the dorsal horn cells via the dorsal funiculus (Vilela Filho and Tasker, 1994). Perhaps the neural substrate for the ascending effects we have seen lies in the communication with the raphespinal and reticulospinal neurons which is shared by the PVG/PAG and the ventrobasal thalamus.

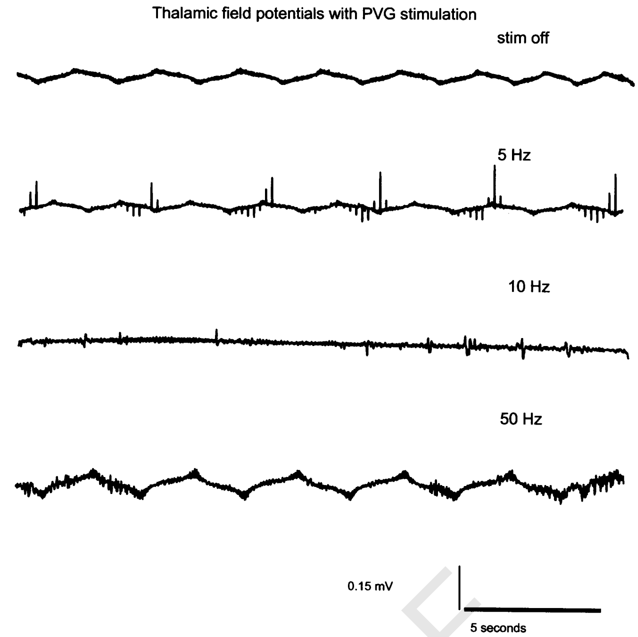

Fig. 1. Shows the sensory thalamic FP recordings during PVG stimulation at different frequencies in a patient with chronic facial pain (case 1). Pain relief is obtained at 10 Hz stimulation and there is a corresponding flattening of the slow frequency trace.

Each of the two patients studied experienced relief from chronic pain when the PVG was stimulated within a narrow frequency band. However, in both cases, only low frequencies were effective in providing pain relief. In fact, higher frequency (≥50 Hz) stimulation worsened the pain. This is at variance with other reports of DBS in chronic central pain (Young and Rinaldi, 1997). It is possible that within the broad definition of central pain there are a host of different pathophysiological mechanisms involved and hence they respond differently to brain stimulation.

To the best of our knowledge this is the first instance that this very slow frequency potential associated with chronic pain has been reported in the sensory thalamus. It appears to be related closely to the sensation of pain rather than in the

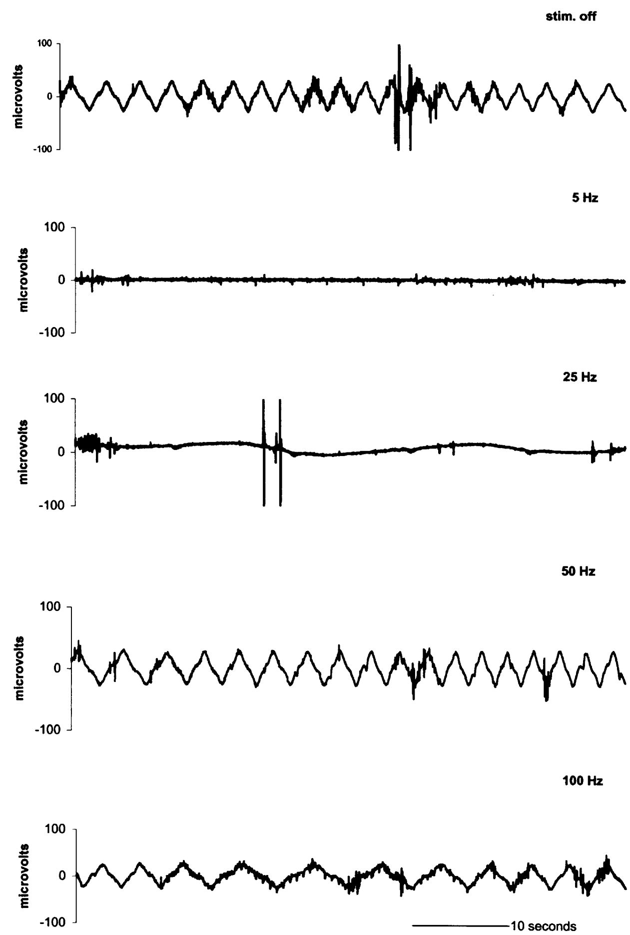

Fig. 2. Shows the sensory thalamic FP recordings during PVG stimulation at different frequencies in another patient with post-stroke hemi-body pain (case 2). Pain relief is obtained at 5 and 25 Hz stimulation and there is a corresponding flattening of the slow frequency thalamic trace.

mechanisms of pain relief. Further exploration of different types of painful syndrome is clearly required to elicit its importance.

Though the effect of PVG stimulation on the thalamic FP was immediate at onset of stimulation, there was a lag period in the decay of this effect after the cessation of stimulation. This was also found by Rinaldi from microelectrode recordings of VPL inhibition by PVG stimulation (Rinaldi et al., 1991). The length of the recovery period corresponded to the duration of stimulation. These delays suggest that there is a combination of neural and opioid pathways at work; the former causes the immediate effect while the latter leads to a build up of opioids that decay over time.

5. Conclusions

Our findings suggest a frequency regulated neural pathway for chronic central pain specific to the origin and nature of the pain.

We have found an interesting correlation between thalamic activity and chronic pain. This curious low frequency potential may provide an objective index for quantifying chronic pain, and may hold further clues to the mechanism of action of PVG stimulation.

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