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Two-point discrimination thresholds in spinal cord injured patients with dysesthetic pain

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We questioned whether deafferentation following SCI would result in an increase in somatic sensitivity possibly due to cortical reorganization. Dysesthetic pain syndrome (DPS) below the level of a spinal cord injury (SCI) is a common complication. We hypothesized that DPS patients would show increased cortical reorganization because of high levels of sensory stimulation following injury. Sixteen dysesthetic pain SCI patients, 15 SCI patients without pain, and 16 control subjects were examined for two-point discrimination thresholds (2PDT) of the forearm, neck, and spine. The SCI pain group had significantly smaller 2PDTs than either SCI no pain or control groups, particularly over the neck and spine. The SCI pain group had a significant inverse correlation between perceived degree of pain (visual analogue scale) and 2PDT in the spinal skin area. The findings indicate that SCI patients with severe DPS have a higher sensitivity to somatosensory stimuli, particularly in skin areas with projections to primary somatosensory cortex areas adjacent to the deafferentated region. The increase in 2PDT may be due to an increase in the size of the somatosensory cortical areas allotted to the corresponding skin areas.

Keywords: spinal cord injuries; pain; two-point discrimination threshold; plasticity; somatosensory cortex.

Introduction

Dysesthetic pain syndrome (DPS) below the level of a spinal cord injury (SCI) is the most common complaint of individuals with SCI.[1] Serious and persistent pain interferes not only with daily functioning and rehabilitation, but can also result in depression, drug addiction, and general despondency.[2] While precise information is unavailable, some investigators have proposed that dysesthetic pain originates in the brain.[3–5]

Melzack and Loeser[6] described paraplegic patients who had had an entire section of the spinal cord removed (segmental cordectomy) and had bilateral sympathetic blocks in an attempt to alleviate dysesthetic pain. These individuals continued to suffer severe pain in the denervated areas of their bodies, suggesting that the source of the pain was located more centrally in the spinal cord or brain. Recently, Lenz *et al*[4] demonstrated that neurons in the somatosensory thalamus of patients with central pain following SCI, fired in bursts of action potentials more frequently than did similar neurons in patients without pain. In concurrence with Lenz *et al*[4], Cesaro *et al*[7] found patients with central pain had relative hyperactivity in thalamic areas. Further evidence for the central control of DPS comes from the work of Cohen *et al*[8] who induced dysesthetic pain distal to the level of SCI by magnetic stimulation of the brain in patients with thoracic (T9–12) SCI. The results of the research discussed above all indicate that

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the source of DPS below the level of SCI may originate from control mechanisms in the brain.

A likely source for DPS is the cerebral cortex. There is evidence that the cerebral cortex is involved in the sensory discriminative aspects of general pain and contains nociceptive specific neurons.[9] Marshall[10] determined that traumatic penetrating brain injuries with superficial wounds of the parietal cortex resulted in a loss of pain sensation, while surgical resection of the postcentral gyrus areas related to the painful somatic sites relieved pain.[11] Sweet[12] further resolved that stimulation of the exposed somatosensory cerebral cortex and lesions of the cortex in man can produce pain. In addition to the somatosensory cortex, the human anterior cingulate cortex is also involved in pain perception.[13,14] Furthermore, animal experimental studies have shown that nociceptive neurons exist in primary somatosensory areas of the parietal cortex and respond to painful stimulation.[15–17]

Peripheral tissue injury, stimulation, and deafferentation influence the function, structure, and activity of central nervous system neurons. Inflammatory agents, repeated electrical stimulation of unmyelinated nerve fibers, or repeated tissue injury have resulted in enlargements of the receptive fields of neurons receiving afferent input.[18–23] Ovelmen-Levitt *et al*[24] found an increasing change in the spontaneous cellular activity, modalities, and receptive fields of L6–7 dorsal horn in the cat at various times after deafferentation. Spinal cord deafferentation in the cat produced similar hyperactivity in lateral cuneate nucleus[25] and sensory thalamus.[26]

Limited deafferentation from amputation also produces extensive cortical reorganization or remapping of the remaining active inputs.[27–30] Microelectrode recording revealed that the cortical map of the adult monkey progressively changed over several months following surgical amputation of one or two fingers. The representations of adjacent digits and palmar surfaces slowly expanded until they occupied most or all of the cortical regions that had previously represented the amputated finger.[29] This finding of enhanced cortical representations may explain the phenomena of an improvement in 2PDT of the skin surrounding a digital amputation or in the stump following limb amputation.[31]

Plasticity in the central nervous system (both brain and spinal cord) following injury and deafferentation is well documented. Reorganization and regeneration does not occur in a random manner but appears to be regulated and spatially limited. Denervation from an SCI should produce reorganization of the central nervous system, particularly in somatosensory projection areas. If certain types of SCI, such as crush injuries, result in higher levels of stimulation and pain, reorganization of the somatosensory cortex may occur to a greater degree and involve extensive sprouting of nociceptors. Increased reorganization of the somatosensory cortex for processing pain information could help to explain dysesthetic pain below the level of a SCI. We hypothesized that the cortical projection areas of somatic regions adjacent to the deafferentated sites of spinal cord injured people are larger than comparable sites of noninjured individuals. Additionally, these areas remap and regenerate more than areas anatomically distant from the injury, and injuries producing high levels of posttraumatic stimulation and pain produce more reorganization and sprouting.

The two-point discrimination test is a standard method for testing tactile sensation. A number of studies have shown that two-point discrimination is a valid and reliable measure of sensory function.[32–36] Additionally, there is a significant inverse relationship between the two-point threshold on the skin and the cortical representation of the skin, that is, thresholds for two-point discrimination (2PDT) are more sensitive over skin regions having larger projections on the somatosensory cortex.[37] We hypothesized that SCI patients with dysesthetic pain will have better 2PDT, especially in skin areas projecting to somatosensory cortex adjacent to the site of injury, when compared with control subjects or SCI patients without dysesthetic pain. We predicted that SCI patients without pain would have better 2PDT than nonSCI control subjects.

Methods

Subjects

Forty-seven male volunteers participated in this research—selection was not limited to males but the SCI population at the VA Medical Centre, Long Beach is predominately male. There were 16 pain SCI patients (SCI-PAIN), 15 SCI patients without persistent pain (SCI-NoPAIN), and 16 nonSCI individuals (CONTROL). All patients had a traumatic myelopathy at or below T1. No participant had central or peripheral nerve disease or a recent history of ethanol or substance abuse. Each pain patient had a minimum one year history of the persistent presence of DPS distal to the level of the SCI. Members of the CONTROL group were recruited from healthy volunteers and staff members of the medical center. Controls were generally matched for age to the SCI participants.

Five SCI-PAIN patients and 4 SCI-NoPAIN patients had incomplete injuries. Six of 15 (40%) SCI-PAIN patients had dysfunctions of the autonomic nervous system and had experienced surgical spinal stabilization with internal fixation instruments. Conversely, none of the SCI-NoPAIN patients had such problems. The SCI-PAIN group reported an average of 13 years (range 1.5–28 years) of pain. The group's average VAS was 75 mm (range 30–100 mm) on a 100 mm scale. The common words used to describe the pain syndrome were burning, stinging, piercing, throbbing, stabbing, sharp, shocking, and cramping. SCI-PAIN patients reported that suffering was triggered and exacerbated by weather change (75%), infection of the urinary system (31%), and fatigue (50%). Pain was distributed in a diffuse nonradicular pattern persistently localized to the legs and feet, but in some cases it involved any region of the body below the level of SCI. Hyperalgesia often covaried with dysesthetic pain. The most likely site of hyperalgesia was at the injury zone of the SCI. The area was sensitive to scraping which could result in dysesthetic pain below the level of SCI. None of the SCI patients experienced hyperalgesia at the skin test sites. Fifty percent of the SCI-PAIN group took tranquilizers or analgesics to relieve pain and five members of the group had had cordectomies in an attempt to relieve pain, but they still suffered severe pain distal to the level of SCI.

Apparatus

A Lafayette Instruments esthesiometer Model 16011 (Fig 1) was used for 2PDT testing. The esthesiometer had brass tips insulated with a coating of vinyl to minimize the influence of temperature on touch thresholds. The distance between the tips was set using the esthesiometers calibrated vernier. In order to control for variations in the force of applying the esthesiometer to the skin,[38] all subjects were seen by one examiner. The examiner was trained to use a consistent pressure for all trials. The pressure the examiner applied during testing was measured by using a scale and was 66.46 g ± 5.27 g based on an average of 50 applications. During testing, the two legs of the esthesiometer were rapidly placed, with equal pressure, on the skin surface. All subjects were blindfolded during testing.

Procedure

After reading and signing an informed consent form approved by the medical center's human studies subcommittee, each SCI patient answered a questionnaire concerning the history of his SCI and any accompanying pain syndrome. The person was given a general neurologic examination to determine motor and sensory levels and

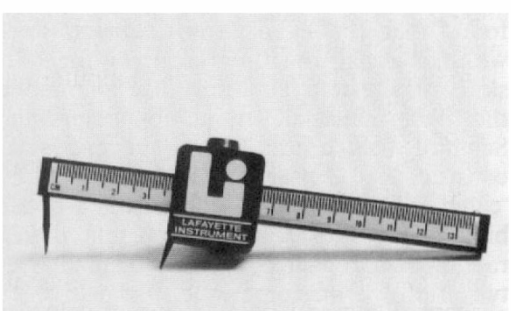

Figure 1 Esthesiometer used for measuring two-point discrimination thresholds in this study.

the degree of completeness of the injury (American Spinal Injury Association criteria).[39]

A visual analogue scale (VAS) was used to assess current level of pain for the SCI-PAIN patients. The VAS consisted of a 100 mm line anchored by 'no pain' and 'pain as bad it could be.' The patient was asked to make a mark on the line that represented his current level of perceived pain intensity. The scale was scored by measuring the distance from the 'no pain' point to the patient's mark.

Four somatic skin sites, with projections to different areas of the primary somatosensory cortex, were examined for 2PDT. The neck and spine areas were chosen because they project to cortical regions in close proximity to the deafferentated region, while the forearms were selected because they project more distally. The specific sites were: the central point of the ventral surface of the left (1) and right (2) forearm; (3) the midpoint between the inion and the process of the seventh cervical vertebra; and (4) the skin area at the midline 2 cm superior to the neurologic level of injury (lowest normal neurological segment). Site 4 was carefully chosen to exclude the potential confounding effects of surgical scars and/or hyperalgesia on 2PDT. For CONTROL subjects, site 4 was the skin over the spine at the process of the ninth thoracic vertebra. All skin areas tested were measured in a transverse orientation to eliminate variability due to different orientations.[33]

With one exception, we used Peters and Schmidt's[40] method for 2PDT. The exception was based on a pilot study in which we found that 2PDTs of all our subjects were within a range of 10–60 cm over the four skin areas tested. Therefore, we eliminated the higher range of stimulation Peters and Schmidt had used. Testing at each site consisted of 60 trials: 50 test trials and 10 'catch trials' used to measure response bias.[41] The 50 test trials were presented, in a random order, once at each distance between the esthesiometer points of 10 to 59 mm. The 10 catch trials (in which the skin area was deliberately touched by only one point of the esthesiometer) were randomly dispersed among the test trials. The particular skin site tested was randomly selected among the four sites and changed every six trials. The interstimulus interval was about 10 s.

Data analysis

For each skin site, the absolute 2PDT value was defined as the midpoint between the region of trials in which the person always indicated that one point was felt and the region in which two points were always reported. For example, if the person gave one point responses for esthesiometer settings from 10 to 32 mm, inconsistent responses from 33 to 44 mm, and consistent two-point responses from 44 to 59 mm, the 2PDT would be the midpoint between 33 and 43 mm or 38 mm. The BMDP statistical package was used for all statistical analyses. Pertinent SCI characteristics of the SCI-PAIN and SCI-NoPAIN groups were compared with *t* tests. The 2PDTs were compared at each skin site by using one-way analyses of variance (ANOVA). Pearson product moment correlations were used to evaluate the relationship between the 2PDT at each site and degree of pain (VAS) in the SCI-PAIN group and the relationship between the 2PDTs and age.

Results

We excluded data from one SCI-PAIN patient and one CONTROL subject because they responded incorrectly on more than four catch trials. Members of the SCI-PAIN group made a total of 11 incorrect responses on catch trials (1.8% of all catch trials); members of the SCI-NoPAIN group had eight incorrect responses (1.3%); while the CONTROL group members had 18 incorrect responses (3%). The injury level for the SCI-PAIN group ranged from T1–L4 and T1–L3 for the SCI-NoPAIN group. A *t* test revealed no significant difference in injury level between the two SCI groups. The average age was 50 years (range 32–70) for the SCI-PAIN group, 57 years (range 33–73) for the SCI-NoPAIN group and 50.0 years (range 30–73) for the CONTROL group. A one way ANOVA displayed no significant age differences among the three

groups, $F(2,42) = 1.32$, $p > 0.05$. The left forearm data from one SCI-PAIN patient was omitted from the analysis because the patient suffered from left ulnar neuritis. The data from the spine skin areas of 5 SCI-PAIN patients were not used because cordectomies had been performed.

Group means and standard errors of the means for 2PDTs are presented for each site in Figure 2. For the CONTROL group, the neck was most sensitive and the spine least sensitive. Both SCI groups, however, showed greater 2PDT sensitivity over the spinal region compared to the forearms. Figure 2 also reveals that the SCI-PAIN group had the smallest 2PDTs at all sites tested. One way ANOVA showed that significant differences existed among the groups over all skin areas (Table I). Tukey HSD tests further indicated that the SCI-PAIN group had significantly lower 2PDTs in the skin areas of the spine and neck then either the SCI-NoPAIN or CONTROL groups. *T*-tests disclosed no differences between the forearm of the dominant hand and nondominant hand.

As reported by several other investigators, we found strong positive correlations between age and 2PDTs over all skin areas (all $ps < 0.05$) signifying that older subjects had larger threshold values. The SCI-PAIN group had a significant inverse correlation between degree of pain (VAS) and 2PDT in the spinal skin area ($r = -0.54$) and a moderate, nonsignificant inverse correlation at the neck site ($r = -0.25$). That is, the higher the patient's perceived level of pain, the better his 2PDT. Correlations between VAS and 2PDT for the forearms were low positive. Correlations between level of SCI and 2PDT over the neck area were negative and very low for the SCI-PAIN group, $r = -0.15$ but positive and moderate for the SCI-NoPAIN group, $r = 0.29$.

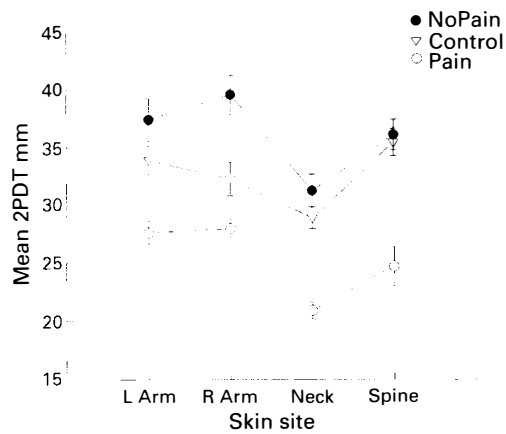

Figure 2 Two-point discrimination thresholds by groups at each skin site. Error-bars are standard errors of the mean.

Discussion

Of interest, is the observation that the SCI-PAIN group was more sensitive to 2PDT, particularly in the neck and spine skin areas, than either the SCI-NoPAIN or CONTROL groups. Also, the SCI-PAIN group had an inverse relationship between perceived degree of pain and 2PDT in the skin of the neck and spine. The findings indicate that SCI patients with DPS have greater sensitivity to somatosensory stimuli, particularly in skin areas with projections to

Table I Analyses of variance for 2PDT among groups over all skin areas

Source of variance	SS	df	Mean square	F	Significance *p*
Left forearm	709	2	354.5	11.73	0.0001
Error		41	30.2		
Right forearm	1026.4	2	513.2	18.02	0.0000
Error		42	28.5		
Neck	889.6	2	444.8	26.05	0.0000
Error		42	17.2		
Spine	919.1	2	459.5	18.45	0.0000
Error		37	24.9		

the primary somatosensory cortex near deafferentated areas. Equal size skin surfaces over different areas of the body are represented by widely varying cortical areas dependent on functional importance. Areas capable of the lowest 2PDTs have the largest cortical representations. The increase in somatic sensitivity seen in the SCI-PAIN group may be due to an increase in the cortical areas dedicated to the corresponding skin surfaces.

The high levels of somatosensory stimulation from DPS could encourage greater reorganization and/or regeneration in deafferentated somatosensory regions. It is well known that the organization of the central nervous system (CNS) is strongly influenced by stimulation and experience. The types of spinal cord injuries that lead to DPS and the types of injuries that cause phantom limb pain (crush injuries, gunshot wounds), produce long-lasting, high levels of stimulation and pain. In fact, how much time passes before a crushed limb is amputated is related to the probability of developing phantom limb pain. Our results are consistent with the theory of neuronal hyperexcitability and plasticity after tissue injury, stimulation,[42,43] or deafferentation[26,44] and also conform to findings that the reorganization of the cerebral cortex after amputation or deafferentation depends on the patterns of activation of sensory elements and is 'use dependent'.[44,45]

We suggest that the cortical maps of deafferentated areas following SCI change similarly to the experimental demonstrations of reorganization following amputation and deafferentation in monkeys.[29,44] The degree and quality of the reorganization progressively changes over time and is influenced by pain and/or tactual stimulation.[46,47] The cortical representations of normally innervated skin surfaces, adjacent to the injured areas, slowly expand and occupy cortical territories that had previously represented the injured area. According to this view, it is reasonable to assume that innervated cortical regions in close proximity to deafferentated regions receive increased levels of stimulation causing more extensive reorganization. Our findings support this hypothesis. The SCI-PAIN group had small 2PDT in skin regions proximal to the deafferentated cortex and the higher the patients' perceived levels of pain the smaller the 2PDTs.

It could be argued that the application of the esthesiometer activated pain receptors, though no subject reported feeling pain during 2PDT testing. An increase in tactual discrimination ability in the somatosensory cortex implies that pain perception increases, because projections of tactual and pain afferent fibers run parallel and terminate in the same areas of the somatosensory cortex. There may also be a reorganization of the pain and tactual afferent neurons and their related sensory ascending paths. However, it appears that the reorganization of these neurons and their synaptic circuits may not be entirely functional leading to high levels of spontaneous abnormal electrical activity and pain. Lenz *et al*[3] reported that thalamic cells which normally responded only to stimulation below the level of an SCI, responded to stimulation of the head and neck following SCI with central pain. This finding of expanded areas of responding in thalamic neurons is very supportive of our finding of small 2PDT in the spine and neck of SCI pain patients.

We favor a hypothesis that DPS below the level of the injury is substantially CNS memory for pain. High levels of pain and stimulation, following injury, produce remapping and regeneration of somatosensory cortical areas along the borders of the newly deafferentated regions. The reorganization of cortex may also induce somatosensory (pain or touch) memories that were experienced before SCI.[48]

An alternative explanation is that collateral sprouting and regeneration occur at the spinal cord and at the site of injury. The spinal cord's capability for substantial plasticity and vigorous sprouting in SCI animal preparations has been demonstrated.[49] While sprouting or changes in receptor sensitivity may account, in part, for the increased 2PDT sensitivity just above the site of injury, SCI plasticity is an unlikely explanation for the significantly smaller 2PDT for the neck area of the SCI-PAIN group. The level of SCI ranged from T1 to L4 with no significant difference in SCI level

between the SCI-PAIN and SCI-NoPAIN groups. Also, the 2PDT was uncorrelated with level of injury. Individuals with injuries a few centimeters to over 50 centimeters from the neck area had similar 2PDT over the neck. On the somatosensory cortex, the entire spinal skin area is smaller than the area allotted for representation of the thumb. The anatomical distance between the spine and neck areas is relatively small on the cortex but large at the skin sites.

Our results are dissimilar from those of Peters and Schmidt[40] who reported no significant difference in 2PDT between chronic low back pain patients and controls. The mechanism of typical chronic low back pain is fundamentally different from the cause of DPS following SCI. Most chronic low back pain results from musculoskeletal and joint disorders which do not involve deafferentation, but do provide for increased activity in peripheral receptors, spinal cord, and somatosensory cortex. There is no evidence that low back pain causes cortical reorganization and regeneration, and there is no reason to assume that the cortical regions representing the back expand. We would not expect low back pain patients to have smaller 2PDT compared to a control group.

The present findings may have important implications for the treatment and prevention of DPS. If use-dependent cortical reorganization is a major cause of DPS, then appropriate surgical and medical interventions performed soon after SCI could reduce or eliminate the high levels of tactual and pain stimulation. The outcome should be less cortical reorganization of tactual and pain circuits and reduced memory for pain, perhaps reducing or eliminating the subsequent DPS. In addition, an appropriate, effective program of rehabilitation may be able to modify the deafferentated cerebral cortex of recent SCI patients and mold a more suitable remapping of the cortex.

Acknowledgements

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