Zona Incerta: Target of Electrical Neurostimulation for Neuropathic Pain

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Abstract

Neuropathic pain is a neurological condition caused by damage or disease affecting the central nervous system, which includes the brain, brainstem, and spinal cord. Neuropathic pain commonly manifests as spontaneous, ongoing pain and has various causes including stroke, multiple sclerosis, tumors, epilepsy, brain or spinal cord trauma, and Parkinson’s disease. Because of the limitations and side effects associated with the pharmacological treatment of neuropathic pain, neuroscientists have suggested electrical neurostimulation for pain relief. Electrical neurostimulation procedures such as deep brain stimulation and motor cortex stimulation can regulate neuropathic symptoms in movement disorders, psychiatric diseases, and central pain disorders. However, identifying the appropriate target is necessary to maximize the effectiveness of electrical stimulation. Previous studies have described the incertothalamic pathway for the regulation of nociceptive processing in the thalamus. In this pathway, the inhibitory nucleus zona incerta, a GABAergic nucleus located in the diencephalon, suppresses responses in the posterior medial thalamus. This article will review regulation of neuropathic pain with electrical neurostimulation, focusing on the antinociceptive effects of zona incerta activation.

Introduction

Neuropathic pain can be caused by primary lesions or malfunctions in the central nervous system. These include trauma, tumors, stroke, immune system disorders, multiple sclerosis, and injury to the brain or spinal cord [1-4]. Chronic neuropathic pain can be disabling. Although medications can decrease neuropathic pain, they are often inadequate; therefore, electrical neurostimulation has been used to treat chronic neuropathic pain.

Neurostimulation techniques for pain therapy include transcutaneous electrical nerve stimulation, peripheral nerve stimulation, nerve root stimulation, spinal cord stimulation, Deep Brain Stimulation (DBS), epidural Motor Cortex Stimulation (MCS), and repetitive transcranial magnetic stimulation [5]. Among the numerous studies on pain control with electrical neurostimulation, Masri and colleagues have demonstrated that MCS activates the incertothalamic pathway in an animal model of spinal cord injury, suggesting that pain is reduced by MCS through activation of the Zona Incerta (ZI) [4,6,7]. In this review of electrical neurostimulation we focused on the ZI as a target for pain control.

Neuropathic Pain

Neuropathic pain has been defined by the International Association for the Study of Pain (IASP) Task Force as “pain initiated or caused by a primary lesion or dysfunction of the somatosensory nervous system”.

Causes of neuropathic pain

Although neuropathic pain is typically the result of tissue injury, the injury may not clearly involve the nervous system. Causes and specific etiologies associated with neuropathic pain are listed in Table 1. Neuropathic pain can also occur without an obvious injury or after the apparent healing of damaged tissues, resulting in pain that persists for months or years after the initial insult [8].

<table>
<thead>
<tr>
<th>Type of neuropathic pain</th>
<th>Causes</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral</td>
<td></td>
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<tr>
<td>Inflammation</td>
<td></td>
<td></td>
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<tr>
<td>Infections</td>
<td></td>
<td></td>
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<tr>
<td>Trauma</td>
<td></td>
<td>Traumatic and surgical nerve injury</td>
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<tr>
<td>Postherpetic neuralgia</td>
<td></td>
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<tr>
<td>HIV sensory neuropathy</td>
<td></td>
<td></td>
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<tr>
<td>Lightning pains of tertiary syphilis (tabes dorsalis)</td>
<td></td>
<td></td>
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<tr>
<td>Vasculitic neuropathy due to:</td>
<td></td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
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<tr>
<td>Rheumatoid arthritis</td>
<td></td>
<td></td>
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<tr>
<td>Systemic vasculitis (e.g. polyarteritis nodosa)</td>
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<td></td>
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<tr>
<td>Neoplasms</td>
<td></td>
<td>Direct infiltration of nerves, plexuses, and nerve roots</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td>Vasculitic neuropathy (see above)</td>
</tr>
<tr>
<td>Peripheral nerve compression</td>
<td>Lumbosacral and cervical radiculopathy</td>
<td></td>
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<tr>
<td>Thoracic outlet syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Carpal tunnel syndrome</td>
<td></td>
<td></td>
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<tr>
<td>Trigeminal neuralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic diseases</td>
<td></td>
<td>Peripheral neuropathy caused by:</td>
</tr>
</tbody>
</table>
Symptoms of neuropathic pain

The pain signal to a noxious stimulus. There are some cases where the nociceptive stimulus. Allodynia is described as burning, coldness, amplification is thought to occur in higher brain centers as well. This hypersensitivity. A common characteristic of neuropathic pain is can happen, for instance, after a stroke.

Another feature of pain is hyperesthesia, which is a condition that involves an abnormal increase in sensitivity to non-noxious stimulus of the sense. The major symptoms of hyperesthesia include the 3 types; perception of pain to a light touches sensation of touch in the absence of stimuli and increased sensitivity to a painful stimulus.

Diagnosing neuropathic pain

The general diagnosis of neuropathic pain relies on a medical history, review of systems, physical and neurological examination. Pain is a subjective experience described with patient’s specific symptom therefore it is important to know the specific medical history of neuropathic pain in the patient. And it is important to have standardized diagnostic tools, such as the neuropathic pain questionnaire, PainDetect, ID-Pain, and DN4, have been developed to classify neuropathic pain on the basis of patient reports.

Generally, laboratory tests are not required to diagnosis of neuropathic pain, even though ancillary laboratory diagnostic tests including blood and serologic tests, nerve or skin punch biopsy, magnetic resonance imaging and electrophysiological studies are useful.

Ancillary studies can confirm or exclusive underlying causes and suggests disease-specific treatment method.

Management of neuropathic pain

Treatments for neuropathic pain include massage, physical, relaxation therapy, and acupuncture. Pain medications often decrease symptoms, and some studies have suggested the use of non-steroidal anti-inflammatory drugs for neuropathic pain. In addition, anticonvulsant and antidepressant drugs appear to ease the pain in some patients [9-11]. However, patients affected by central pain syndrome require stronger painkillers, such as morphine and other opioids. Unfortunately, chronic neuropathic pain often does not respond sufficiently to pharmacological treatments and may worsen, sometimes leading to serious disability. A multidisciplinary approach that combines therapies can be an effective way to provide relief from neuropathic pain [12,13]. In cases that are difficult to treat, a pain specialist may suggest the use of an invasive or implantable device to manage the pain. Electrical stimulation of the nerves involved in neuropathic pain may significantly control symptoms.

Neurostimulation as Regulation of Neuropathic Pain

Several types of electrotherapy use an electric current to stimulate a neuron or neural network through direct or indirect excitation of the cell membrane. For example, transcutaneous electrical nerve stimulation and spinal cord stimulation can provide long-term relief, however, these methods are used in only a few types of central neuropathic pain. Several studies have reported excellent results using intracranial neurostimulation, including DBS and MCS, to treat neuropathic pain [14-18]. DBS and MCS are typically used in cases of neuropathic pain refractory to medical treatment but amenable to neurostimulation (Table 2).

Deep brain stimulation

Several researchers have reported long-term benefits after thalamic stimulation. In addition to the somatosensory thalamus (ventral posterolateral nucleus), deep brain targets include periventricular and periaqueductal gray matter, contralateral to the pain if unilateral or bilaterally if indicated. Both locations have been targeted in the treatment of pain with DBS for three decades [5,18,26].

Table 1: Causes and specific etiologies of neuropathic pain.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drugs and toxins</th>
<th>Genetic</th>
<th>Idiopathic</th>
<th>Central</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs and toxins</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>Nutritional deficiencies (e.g. niacin, pyridoxine, thiamine)</td>
<td>Pernicious anemia</td>
<td>Amyloidosis</td>
<td>Peripheral neuropathy caused by</td>
</tr>
<tr>
<td>Genetic</td>
<td>Fabry disease</td>
<td>Familial amyloid polyneuropathy</td>
<td></td>
<td></td>
<td>Trigeminal neuralgia</td>
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<tr>
<td>Idiopathic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>Trauma</td>
<td>Spinal cord injury</td>
<td></td>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neoplasms</td>
</tr>
</tbody>
</table>

Symptoms of neuropathic pain

Many patients with neuropathic pain have stimulus-induced pain and hypersensitivity. It can be divided into two types of sensory hypersensitivity. A common characteristic of neuropathic pain is chronic allodynia. Allodynia is defined as pain in response to a non-nociceptive stimulus. Allodynia is described as burning, coldness, tingling, “pins and needles” sensations, numbness, or severe pain is caused by a gentle mechanical stimulus that does not ordinarily elicit a painful response (e.g., light touch). It can be continuous or paroxysmal in presentation. Second, hyperalgesia is defined as an amplification of painful response (e.g., light touch). It can be continuous or paroxysmal in presentation. Several researchers have reported long-term benefits after thalamic stimulation. In addition to the somatosensory thalamus (ventral posterolateral nucleus), deep brain targets include periventricular and periaqueductal gray matter, contralateral to the pain if unilateral or bilaterally if indicated. Both locations have been targeted in the treatment of pain with DBS for three decades [5,18,26].
### Causes of Pain

<table>
<thead>
<tr>
<th>Causes of Pain</th>
<th>Stimulation Target</th>
<th>Long-term Success (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPSP</td>
<td>VPL or PAG/PVG</td>
<td>&gt;30</td>
<td>[19]</td>
</tr>
<tr>
<td>Various neuropathic pain conditions</td>
<td>Vc and PAG/PVG</td>
<td>24</td>
<td>[20]</td>
</tr>
<tr>
<td>DBS</td>
<td>VPL</td>
<td>92</td>
<td>[21]</td>
</tr>
<tr>
<td>Surgery</td>
<td>PAG/PVG</td>
<td>62</td>
<td>[22]</td>
</tr>
<tr>
<td>Various neuropathic pain conditions</td>
<td>VPL/VPM</td>
<td>83</td>
<td>[20]</td>
</tr>
<tr>
<td>Various neuropathic pain conditions</td>
<td>VPL/VPM</td>
<td>14</td>
<td>[23]</td>
</tr>
<tr>
<td>Facial neuropathic pain</td>
<td>M1</td>
<td>76</td>
<td>[24]</td>
</tr>
<tr>
<td>Various neuropathic pain conditions</td>
<td>M1</td>
<td>83.3</td>
<td>[20]</td>
</tr>
<tr>
<td>Facial neuropathic pain</td>
<td>M1</td>
<td>75</td>
<td>[15]</td>
</tr>
<tr>
<td>Facial neuropathic pain</td>
<td>M1</td>
<td>&gt;50</td>
<td>[16]</td>
</tr>
<tr>
<td>Various neuropathic pain conditions</td>
<td>M1</td>
<td>50</td>
<td>[25]</td>
</tr>
</tbody>
</table>

**DBS:** Chronic Post-Surgical Pain; **Vc:** Ventrocaudalis thalamic nucleus; **M1:** primary motor cortex; **VPL/VPM:** Ventroposterolateral and Ventroposteromedial Thalamic Nuclei.

### Motor cortex stimulation

MCS is another technique for the management of neuropathic pain [28-35]. Compared with DBS, MCS is currently more frequently used, mainly because it is more easily performed and has a wider range of indications. In addition, MCS is thought to have a lower complication rate than DBS. Chronic neuropathic pain has been treated with electrical stimulation of the primary motor cortex since the 1990s. Electrical stimulation of the motor cortex enhances activity of the ZI and restores inhibition of the posterior nucleus of the thalamus (PO), thereby reducing the flow of pain information to the cortex.

In particular, MCS has been useful in the treatment of trigeminal neuropathic pain and central pain syndromes such as thalamic pain syndrome. Numerous studies have demonstrated the benefits of MCS for treating trigeminal neuropathic pain [14-16]. Post-stroke pain responds nearly as well to MCS, with almost two-thirds of patients obtaining at least adequate relief [15,27]. Proposed MCS protocols include electrical neurostimulation with implanted electrodes, repetitive transcranial magnetic stimulation, and transcranial direct current stimulation [36-38]. Pain relief is achieved at the beginning of MCS and persists after the stimulation has ended [6,39]. This post-stimulation effect can last from minutes to hours and even weeks [40-43]. Although MCS is used to treat a number of complex pain conditions, outcomes have been variable. Therefore, randomized controlled clinical trials are needed to optimize treatment parameters and provide a better understanding of the mechanisms underlying MCS-induced analgesia [44-46].

### Inhibitory Nucleus Zona Incerta

The ZI is a thin, flat band of gray matter located in the subthalamicus. The ZI can be subdivided into the following sectors according to cytoarchitecture and neurochemical function in rats: rostral (visceral), dorsal (attention), ventral (posture/locomotion), and caudal (arousal) [47]. Each of these sectors has distinct connections with other regions of the central nervous system, from the cerebral cortex to the spinal cord. In particular, the ventral area of the ZI has a rich network of GABAergic cells with widespread connections, receiving inputs from the cerebral cortex, basal ganglia, and cerebellum [48,49].

Although the precise function of the ZI remains unclear, a number of studies have indicated that it is related to limbic–motor integration, which includes controlling instinct and pain, gating sensory input, and synchronizing cortical and subcortical brain rhythms [50-55]. Recent research suggests that the development and maintenance of neuropathic pain is linked to abnormal inhibitory regulation of the PO by the ZI [1]. Animals with central pain syndrome show significant suppression of both spontaneous and evoked activity of inhibitory neurons in the ZI and abnormally high spontaneous and evoked activity of neurons in the PO. The positive association between behavioral and neurophysiological thresholds in rats with central pain syndrome is consistent with a causal role for suppressed incertothalamic inputs in this condition.
Figure 1: Schematic diagram of the major anatomical pathways affected by deep brain stimulation and motor cortex stimulation. Left: Both the Subthalamic Nucleus (STN) and Zona Incerta (ZI) receive heavy projections from a subgroup of layer V neurons in the cerebral cortex. The external pallidal segment (GPe) receives inputs from the neostriatum (caudate nucleus and putamen) and the STN. The internal pallidal segment (GPi) is the main output structure of the basal ganglia (the other being the substantia nigra reticulata) and projects to the nuclei of the motor thalamus (ventral anterior nucleus and ventral lateral nucleus). The subthalamic region is a white matter area abutting the STN and encompassing the ZI. Right: Epidural electrodes are targeted to the primary motor cortex contralateral to the site of the defect and connected to a stimulus. Stimulation intensity ranges from 0 to 75 \(\mu\text{A}\), frequency from 0 to 75 Hz, and duration from 0 to 90 minutes [6]. In a neuropathic pain model, MCS enhanced the activity of inhibitory nucleus ZI neurons and suppressed the activity of posterior thalamic nucleus (PO) neurons. Activity is decreased in the somatosensory cortex, a major projection target of the PO, diminishing pain. Excitatory (glutamatergic) pathways are shown as red lines, inhibitory (GABAergic) connections as blue lines. Abbreviation: Put: putamen.

The ZI can exert strong inhibition on the relay cells of the PO and has strong GABAergic output to several brain regions including the PO, higher-order thalamic nuclei, superior colliculus, pontine nuclei, and lower brainstem [56]. Trageser and Keller demonstrated that inactivating the ZI has a profound effect on posteromedial nucleus (POm) responses [48]. Median spontaneous activity rates of neurons were eight-fold higher after electrolytic lesions were created in the ZI, suggesting that the ZI exerts tonic inhibition on POm neurons [6,57].

Barthó and Masri demonstrated that the development and maintenance of chronic pain syndrome can result from abnormal inhibitory inputs from the ZI to the PO (i.e., the incertothalamic pathway) [4,6,7,56].

Park and colleagues recently reported that ZI regulation of the PO is mediated by the GABAA and GABAB receptors. These receptors differ in their binding kinetics and electrophysiological properties, suggesting distinct roles in incertothalamic regulation. Their findings indicate that regulation of the incertothalamic circuit may be achieved by modulating the ZI firing rate and synaptic GABA concentrations, suggesting potential interventions for sensory processing disorders [58].

Activation of the Incertothalamic Pathway by MCS

Transcranial magnetic stimulation of the primary motor cortex (M1) increases electrical activity in the ZI [46], providing evidence for the incertothalamic pathway in rats. Under normal conditions, nociceptive and somatosensory information processed in the PO is regulated by inhibitory inputs from the ZI. However, in neuropathic pain such as Spinal Cord Injury (SCI) pain, ZI activity is suppressed, and pain is therefore enhanced. Masri and colleagues reported that spontaneous pain-like behaviors were reduced by MCS in animal models of SCI. Inactivation of the ZI blocks the effects of MCS, suggesting that SCI pain is associated with abnormal inhibitory regulation by the ZI [4,6,7,56,59,60]. The findings indicate that MCS enhances spontaneous activity in ZI neurons but suppresses spontaneous activity in PO neurons.

Conclusion

Neuropathic pain is one of the most difficult conditions to treat [61,62]. Electrical neurostimulation applied to precise sites in the central nervous system has been shown to relieve pain and is now considered to be a useful therapeutic approach for chronic pain [29,62]. In this review we focused on the role of the ZI in mediating the effects of electrical neurostimulation in treating neuropathic pain. Previous studies have shown that pain relief is achieved with the initiation of MCS and persists after the stimulation has ended. However, the outcomes of MCS are variable, making it difficult to predict which patient groups will benefit from treatment. Therefore, a better understanding of the mechanisms underlying the effects of MCS are needed, along with characterization of the morphology and firing patterns of ZI cells and the relationship between firing patterns and cortical activity.

Previous studies have indicated that enhancing activity in the ZI and restoring inhibition in the PO may prove effective in the treatment of neuropathic pain.
Acknowledgments

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