Pain-Relieving Mechanisms in Neuromodulation

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Introduction

Since its inception more than 50 years ago, the forms and applications of modern neuromodulation have undergone tremendous expansion. The International Neuromodulation Society defines neuromodulation as "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body," most commonly to reduce pain or improve neurologic function. All forms of neuromodulation are reversible. Neurostimulation is the most common form of neuromodulation technology used today, and it refers to the use of electrical or electromagnetic stimuli upon target tissues to elicit a therapeutic response. Although the focus of this chapter will be on neurostimulation, other non-electrical therapies, such as intrathecal drug delivery systems, may fall into the category of neuromodulation.

On August 10, 2017, the CDC recommended that the opioid epidemic should be declared a national emergency. In light of these circumstances, neuromodulation, which is relatively safe, effective, and validated in the treatment of chronic neuropathic pain, is emerging as an important alternative to opioid therapy. Conversely, chronic high-dose opioid therapy is not validated, is often ineffective, and carries a substantial risk of dependence, abuse, addiction, and other morbidity and mortality. High-dose medication is also theorized to induce opioid-induced hyperalgesia, and these drugs may therefore increase the perception of pain.

In this chapter, we will introduce the broad and ever-expanding panoply of neuromodulation and its applications, describing what is known of the mechanisms of action through which it works. Although similar electrical stimuli may often be delivered, the prevailing mechanism of action will vary based on the pathophysiology of the underlying painful disease state being treated. Although clinical evidence will be provided, more exhaustive summaries of the clinical data will be reserved for later chapters in Part VI, each of which is dedicated to the clinical aspects of a particular form of neuromodulation.

Background and Historical Perspective

The earliest documented use of electrical current for the treatment of pain was around 63 AD, when the Mesopotamian physician, Scribonius Largus, discovered that shocks delivered by the electrical torpedo fish could relieve bodily aches and pains. In the eleventh century, the Islamic philosopher Avicenna used cranial shocks delivered by the electric catfish to treat epilepsy. In the 1600s, the natural philosopher, William Gilbert, reported using the magnetic lodestone to treat headaches and psychiatric illness.

In 1745, Ewald Georg von Kleist and Pieter van Musschenbroek independently invented the world's first capacitor, known as the Leyden jar. Subsequently in 1747, Jean Jallabert used electrical stimulation to increase blood flow, and to provoke muscle contraction and growth, thereby restoring function to the paralyzed limb of a locksmith. Also in the mid-eighteenth century, Benjamin Franklin used his electrostatic generator to treat paralysis and various painful conditions. Some of his treatments achieved transient improvement. However, his use of high voltages caused burns and nerve injuries, leading him to abandon the practice.

The true inception of modern neurostimulation can be traced to three major developments in the mid-twentieth century: (1) the advent and success of the implantable cardiac pacemaker in the late 1950s; (2) the 1965 publication of Melzack and Wall's seminal article, *Pain Mechanisms: A New Theory*, in which they first proposed the gate control theory of pain, postulating that activation of large-diameter sensory nerve fibers could block transmission of pain signals conveyed by small diameter fibers; and (3) the first clinical application of gate control theory by the neurosurgeon

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Norman Shealy in 1967, when he implanted the first spinal cord stimulator (SCS) to successfully treat chronic neuropathic pain.

In 1958, Medtronic released the first implantable pacemaker, followed in 1958 with the first battery-operated wearable pacemaker. The revenue from these early successes was then used to subsidize research and development that repurposed pacemaker technology to meet the growing demand for devices specialized for neural applications. Indeed, the first spinal cord stimulator was a Medtronic cardiac pacemaker with leads modified for intrathecal placement.

In the decades that followed, neuromodulation blossomed into one of the most fascinating and dynamic fields of medicine, with new improvements and applications emerging every year. Monopolar platinum leads have evolved into multi-contact titanium leads. Paddle leads have been developed for insertion by surgical laminotomy. Internal pulse generator (IPG) batteries are smaller and longer-lived. Rechargeable versions are now available. Every year, programs multiply, while the list of validated and experimental applications expands.

The Gate Control Theory of Pain

In 1965, Melzack and Wall first articulated the gate control theory of pain modulation in their seminal article *Pain Mechanisms: A New Theory*, published in the journal *Science*. They hypothesized that stimulation of large myelinated Aβ sensory fibers carrying touch and vibratory information to the dorsal horn could block the transmission of nociceptive stimuli conveyed by small unmyelinated C fibers and thinly myelinated Aδ fibers, thereby closing a conceptual gate to painful afferent stimuli located in the spinal cord. Their model originated from several observations on the sensory neural circuitry located in a crescent-shaped zone capping the dorsal horn known as the substantia gelatinosa (SG).

Pseudounipolar neurons of the dorsal root ganglion (DRG) conveyed painful stimuli along Aδ and C fibers from the periphery into the SG where they formed (1) excitatory synapses with secondary sensory neurons of the spinothalamic tract known as tract cells (TCs) and (2) inhibitory synapses with SG interneurons (INs) that in turn formed inhibitory synapses with TCs. These fibers therefore promoted transmission of painful signals via TCs by way of (1) direct excitation and (2) disinhibition.

Meanwhile, Aβ fibers carrying non-nociceptive signals bound for the dorsal columns (DC) were also observed to send collateral projections into the SG where they formed excitatory synapses with TCs and INs, both of them excitatory. It had been empirically demonstrated that early direct excitation of TCs at the Aβ-TC synapse was quickly overdriven by TC inhibition caused by excitatory signaling at the Aβ-IN synapse. Hence, the net effect of Aβ signaling in the dorsal horn was to block nociceptive transmission to secondary sensory neurons (TCs) of the spinothalamic tract through a mechanism of interneuron (IN)-mediated inhibition, thereby "closing the gate."

On the basis of these observations, Melzack and Wall speculated that by administering exogenous electrical stimulation to Aβ fibers, the spinothalamic gate could be closed as therapy for neuropathic pain. Figure 10.1 depicts a schematic of the gate control circuit similar to the one presented in the original article by Melzack and Wall.

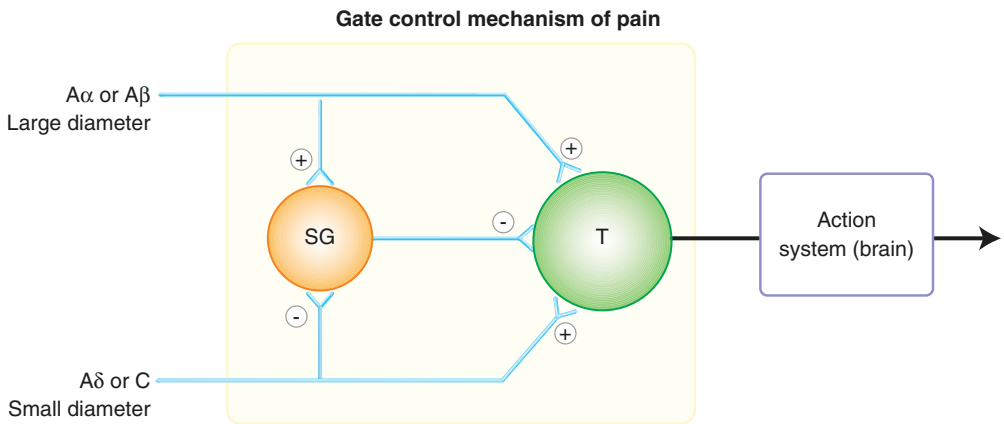

Fig. 10.1 Gate control schematic depicting large-diameter mechanoreceptive Aα and Aβ fibers and small-diameter Aδ and C fibers carrying pain and temperature signals, all entering the dorsal horn from the periphery in parallel, each synapsing on inhibitory interneurons of the substantia gelatinosa (SG) and secondary sensory spinothalamic neuron known as the tract cells (TCs) to form the gate circuitry. The net effect of input from the large fiber afferents is tract cell inhibition, which closes the gate to painful signals. The net effect of the small fiber afferents is TC excitation, which opens the gate to painful signals bound for the brain

Central Neuromodulation and Mechanisms of Action

Deep Brain Stimulation (DBS)

Deep brain stimulation (DBS) is a form of neuromodulation in which current is delivered through electrodes stereotactically implanted into the parenchyma of subcortical brain structures. DBS was first introduced by Benabid et al. when in 1985 they successfully treated symptoms of Parkinson's disease (PD) by combining thalamotomy with neurostimulation of the bilateral ventral intermediate (VIM) thalamic nuclei. In addition to PD, DBS has subsequently been used to control symptoms of dystonia, epilepsy, depression, obsessive-compulsive disorder (OCD), and cluster headaches.

Although the exact mechanism of action remains elusive, DBS is thought to act via three mechanisms: (1) by inhibition, (2) by depolarization blockade, and (3) by adjustment of neural activity. In the first model, neurostimulation depolarizes axons in the target brain structure, thereby causing the release of inhibitory neurotransmitters. In the second model, neurostimulation depresses activity in the target tissue by hyperpolarizing neurons and therefore the electrical threshold needed to produce an action potential. Finally, DBS may induce a more regular and consistent firing in target tissue where electrical activity has become disordered by disease.

DBS has been used to effectively treat a wide swath of neuropsychiatric diseases with varying and often unknown cellular pathophysiology. For each clinical entity, a constellation of functionally linked neuroanatomic loci has been identified. Many single structures, however, have been shown to play crucial roles in multiple diseases. Although there is not yet FDA approval for the treatment of pain, research in DBS has shown it to be effective in the treatment of several types of centrally mediated pain syndromes. For example, the hypothalamus was a promising target for treatment of cluster headaches. Indeed, vigorous hypothalamic activation is known to occur during cluster headache, short lasting unilateral neuralgiform headache with conjunctival injection and tearing, hemicrania continua, and paroxysmal hemicranias. Although all of these entities have been treated successfully with DBS, the hypothalamus has been largely abandoned as a target due to the high rate of morbidity associated with hypothalamic lead deployment.

Motor Cortex Stimulation (MCS)

Electrical stimulation of the cerebral motor cortex via overlying electrodes is known as motor cortex stimulation (MCS). MCS has been used in the treatment of burning central pain by removing the contralateral postcentral gyrus and the ipsilateral precentral gyrus when the pain returned, leading to the conclusion that both gyri were involved in mediating the pain. Although the exact mechanism of action is unclear, MCS is known to inhibit pain signal transmission in patients with central neuropathic pain. Positron-emission tomography (PET) scans using radiolabeled glucose as an index of cerebral blood flow have implicated the ventral, lateral, and medial thalamus as key structures. Other locations that experience increased blood flow under MCS are the anterior cingulate, the orbitofrontal cortices, the anterior insula, and the upper brainstem. It has therefore been hypothesized that MCS diminishes the perception of pain both by modulating the affective-emotional component of chronic pain and by activating descending inhibition of pain impulses through the brainstem.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is the use of the electromagnetic field generated by an electrical current to generate an electrical current in the target area of the brain by the physical process of electromagnetic induction. A coil placed over the scalp induces an electrical field, which can then be manipulated either to excite or inhibit the target tissue. Theoretical mechanisms of action for TMS on chronic pain include modulation of descending inhibition circuits in addition to effects on limbic circuitry. One significant limitation for TMS is the transient duration of analgesia; it is currently unclear whether TMS results in any permanent neuroplastic changes in pain processing.

Spinal Cord Stimulation (SCS)

Overview

Spinal cord stimulation is neurostimulation via electrodes placed into the epidural space, either percutaneously or by surgical laminotomy, and positioned to overlie the dorsal columns of the spinal cord. SCS is FDA approved for use in chronic intractable pain of the trunk and/or limbs, postlaminectomy syndrome, complex regional pain syndrome I and II (CRPS), chronic radiculopathy, painful neuropathies, chronic refractory angina, and peripheral ischemic limb pain, but it has been used to successfully treat many other pain entities. A more comprehensive list of the indications can be found in Table 10.1. SCS is thought to act via three broad classes of mechanisms, (1) neurophysiological, (2) neurochemical, and (3) vascular.

Neurophysiologic mechanisms are generally attributed to inhibitory control at the level of the dorsal horn and to supraspinal brainstem or thalamocortical mechanisms. Neurochemical mechanisms are thought to restore the

Table 10.1 Uses and indications for neurostimulation

Modality	Common indications	Other indications
Deep brain stimulation (DBS)	Parkinson's disease *Δ Essential tremor *Δ Obsessive-compulsive disorder *Δ Dystonia *Δ	Epilepsy Δ Depression Headaches Addiction disorder Severe obesity
Vagal nerve stimulation (VNS)	Drug-refractory epilepsy * Unipolar and bipolar depression * Cluster headache *	Migraine Δ Hemicrania continua Δ Medication-overuse headache Δ
Spinal cord stimulation (SCS)	Chronic intractable pain of the trunk and/or limbs, including post-laminectomy syndrome * Complex regional pain syndrome I and II * Chronic radicular pain * Painful neuropathies Refractory angina Δ Peripheral ischemic limb pain, refractory or not amenable to surgical bypass Δ	Intercostal neuralgia Spinal cord injury Arachnoiditis Central pain Nerve root avulsion Postherpetic neuralgia Phantom limb pain Abdominal pain Pelvic pain
Dorsal root ganglion (DRG) stimulation	Lower extremity pain secondary to complex regional pain syndrome I and II *Δ Chronic radicular pain	Perineal pain Phantom limb pain Chronic postsurgical knee pain Chronic visceral pain Upper limb neuropathic pain Painful diabetic neuropathy
Peripheral nerve stimulation (PNS)	Chronic pain of peripheral nerve etiology *Δ, including occipital neuralgia	Craniofacial pain Cluster headache Postherpetic neuralgia
Peripheral nerve field stimulation (PNFS)		Axial back pain Abdominal pain Pelvic pain Atypical facial pain

Single asterisk denotes current US Food and Drug Administration (FDA)-approved indications
Single triangle denotes an indication which has received Conformité Européenne (CE) mark

balance of inhibitory and excitatory neurotransmitters both at the segmental level as in the case of gamma-aminobutyric acid (GABA) and glutamate and via descending inhibitory pathways that release serotonin, substance P, and norepinephrine into the dorsal horn. Finally, vascular mechanisms are most pertinent in vascular diseases such as peripheral arterial disease and chronic refractory angina where SCS is thought to relieve pain by restoring the supply of oxygen through vasodilation and by reducing sympathetic tone.

Neurophysiologic Mechanisms of SCS

Stimulation of large myelinated primary sensory neurons in the dorsal cord provokes action potentials that originate at a node of Ranvier and propagate bidirectionally away from the stimulus. Antidromic impulses travel in the opposite direction of natural physiologic impulses. Orthodromic impulses travel in the same direction as natural physiologic impulses. In the case of SCS, orthodromic impulses are those that travel in a rostral direction toward supraspinal structures where Aβ fibers from the dorsal column synapse in the cuneate and gracile nuclei of the medulla, with subsequent impulses traveling to the thalamus and periaqueductal gray (PAG) (Figs. 10.2 and 10.3).

In the case of SCS, antidromic impulses travel in a caudad direction, back into the dorsal horn where they act in a spinal segmental manner by activating inhibitory neurons which then block transmission of nociceptive signals from C and Aδ fibers to secondary neurons known as tract cells. This spinal segmental mechanism is thought to be the primary mechanism by which classical SCS causes relief of neuropathic pain.

Orthodromic impulses are responsible for modulating supraspinal neurophysiologic mechanisms responsible for SCS-mediated pain control. These impulses are also responsible for the paresthesia experienced by patients undergoing SCS.

It is important to note that the paresthesias in and of themselves are not likely causing pain relief. In light of recent computational models conceptualizing the thalamus as a parallel processor for ascending sensory signals, one might speculate that the paresthesia generated in classic SCS causes a profusion of neutral sensory signals that "drown out" the perception of painful stimuli through lateral inhibition and direct signal competition in the thalamus. This, however, is unlikely because classic tonic stimulation typically produces mostly subthreshold presynaptic potentials in the thalamus,

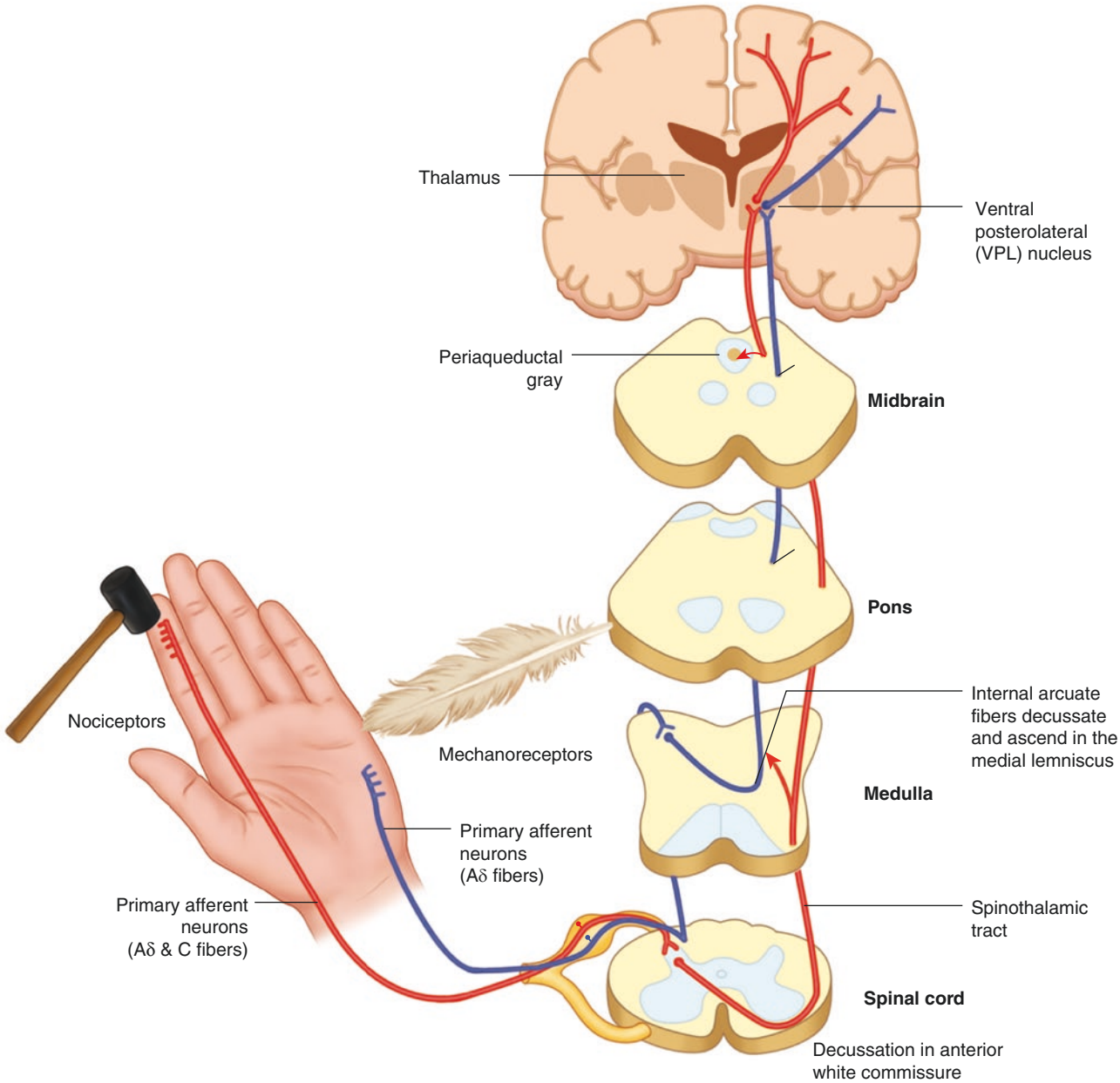

Fig. 10.2 Ascending sensory pathways: the dorsal column and spinothalamic tract. *Dorsal column (blue)*: the axons of pseudounipolar neurons of the DRG carrying fine touch, vibration, pressure, and proprioception along from the periphery along Aα and Aβ fibers enter the white matter tracts of the ipsilateral dorsal column and travel to the medulla where they synapse on second-order neurons in the gracile and cuneate nuclei. These secondary neurons then decussate as internal arcuate fibers to form the medial lemniscus and travel through the pons and form synapses with third-order sensory neurons in the thalamus. Axons coming from the body synapse in the ventral posterolateral nucleus and those from the head synapse in the ventral posteromedial nucleus. Axons of thalamic third-order neurons then travel to the primary somatosensory cortex. *Spinothalamic tract (red)*: the axons of pseudounipolar sensory neurons of the dorsal root ganglion carrying pain and temperature stimuli along Aδ and C fibers project into the dorsal horn and typically rise one to two spinal segments via Lissauer's tract where they synapse on secondary neurons known as tract cells in the substantia gelatinosa or the nucleus proprius. These tract cells give off axons which decussate via the anterior white commissure and then travel to the anterolateral quadrant of the spinal cord where fibers carrying pain and temperature enter the lateral spinothalamic tract and fibers carrying crude touch and firm pressure enter the anterior spinothalamic tract. These axons then travel up the spinal cord, through the rostral ventromedial medulla, and into the thalamus where they synapse with third-order neurons in several thalamic nuclei, including the medial dorsal, ventral posterior lateral, and ventral posterior medial nuclei. These signals are then conveyed to the cingulate cortex, the primary somatosensory cortex, and the insular cortex, respectively. These thalamocortical projections are functionally divided into two subsystems known as the direct system, for the conscious appreciation of pain, and the indirect system, which is responsible unconscious processing of pain. The indirect system is divided into spino-reticulo-thalamo-cortical circuits responsible for arousal and the spino-mesencephalic-limbic circuits responsible for the affective impact of pain

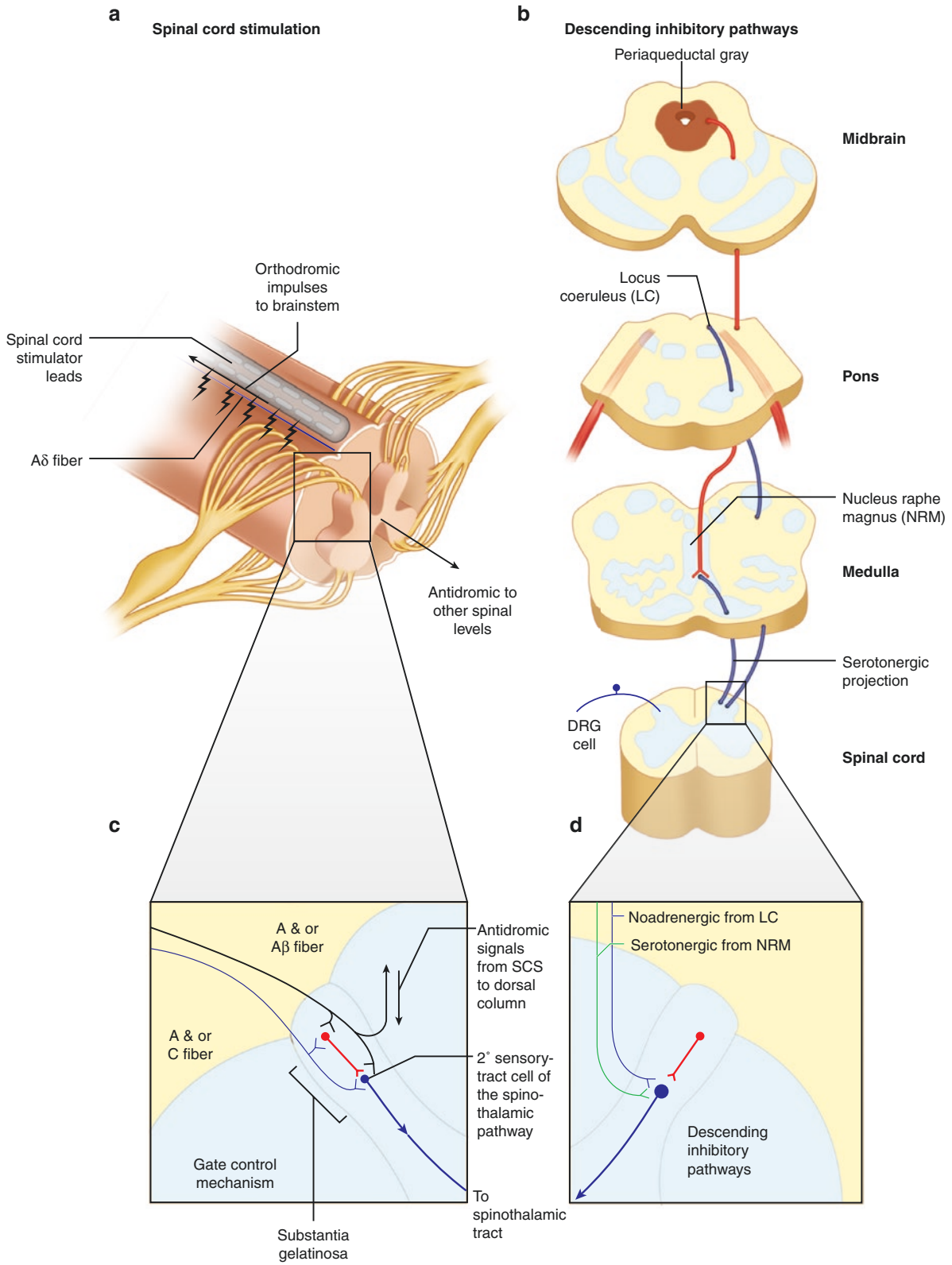

Fig. 10.3 (**a**) Spinal cord section with SCS leads overlying the dorsal columns triggering an ascending orthodromic impulse bound for the medulla and a descending antidromic impulse descending along the same Aβ fiber and into the dorsal horn, thereby closing the gate. (**b**) Gate control neurocircuitry in situ. (**c**) Descending supraspinal inhibitory pathways originating in the periaqueductal gray (PAG) and the medulla where noradrenergic and serotonergic neurons of the locus ceruleus (LC) and the nucleus raphe magnus (NRM) are located, respectively. Through caudad projections that descend along the dorsal columns and terminate in the dorsal horn, these nuclei exert supraspinal neurochemical pain control by secreting inhibitory substance P, norepinephrine, and serotonin into the SG, thereby stabilizing the gate. (**d**) Inhibitory fibers synapsing on a tract cell in the dorsal horn

suggesting that the need for overlap is more of an incidental phenomenon which at most can serve as a perceptual marker that the antidromic signals closing the gate in the dorsal horn have been correctly mapped to the affected dermatomal distribution. Indeed, in order to close the gate on a particular distribution of aberrant nociceptive C and Aδ fibers, Aβ fibers that directly form circuits with those neurons in the dorsal horn and therefore originate in the same dermatome must be stimulated.

However, there are supraspinal mechanisms through which classical SCS is thought to achieve pain relief. One experimental study performed by El-Khoury achieved pain relief by stimulation of sites rostral to various spinal cord lesions, thereby preventing the contribution of an antidromic process to analgesia. This finding implicates higher-order pain relief caused by modulation of sensory-discriminatory elements of pain at the level of the brainstem and also modulation of affective-emotional elements of pain at the level of thalamocortical circuits.

Ultimately, the experimental and clinical data suggest that classical SCS relieves neuropathic pain predominantly through modulation of gating mechanisms at the spinal segmental level. Indeed, one experimental pain model found that DC SCS at the level where an injured sciatic nerve entered the spinal cord was more effective than more rostral stimulation. This notion has been empirically supported through the mapping of the most effective sites for electrode placement.

Neurophysiologic Mechanisms of SCS: Subthreshold Versus Suprathreshold Stimulation

In the context of this topic, any neurostimulation delivered at amplitude that fails to create paresthesia is considered to be *subthreshold*. Likewise, any electrical stimulus with an amplitude sufficient to generate paresthesia is considered to be *suprathreshold*.

Subthreshold SCS at high frequency (10 kHz) has been shown to reduce the excitability of lamina I pain projection neurons when compared to sham in an in vivo model, but its exact mode of action remains unclear. Although this form of SCS has performed well in several large prospective clinical trials, as of the writing of this chapter, the PROCO trial has just released data suggesting there is no clinical benefit conferred by high-frequency stimulation.

In addition to the mechanisms described above, suprathreshold SCS may also work through orthodromic signals that activate frank motor activity in peripheral motor nerves in patients with low-thoracic SCS systems. Efferent motor traffic has been observed even with low-intensity stimulation and is thought to be mediated by monosynaptic facilitation of spinal motor reflexes strong enough to generate orthodromic action potentials.

Neurophysiologic Mechanisms of SCS: Tonic Versus Burst Stimulation Patterns

Classical SCS utilizes tonic stimulation with single pulses in sequence, each with the same pulse width, pulse rate, and amplitude. However, single action potentials do not typically trigger enough central neurons to cause modulation at the level of the thalamus. Indeed, these central neurons must integrate the input from multiple presynaptic neurons in a process known as spatial summation in order to reach threshold. In this context, *threshold* is defined as the membrane voltage required to elicit an action potential. Hence, tonic pulse stimulation is most likely filtered out at the level of the thalamus as noise, only rising to thalamocortical circuits as isolated somatosensory signals. Therefore, classical SCS most likely exerts its main effects by affecting gating in the dorsal horn.

In contrast, it has been observed that through a process known as temporal summation or facilitation, short clusters of action potentials known as "bursts" can lead to the stacking of intracellular calcium concentration in a single presynaptic bouton causing sufficient neurotransmitter release to monosynaptically trigger a postsynaptic central neuron, thereby leading to meaningful signaling either through long-term potentiation (LTP) or long-term depression (LTD). One large prospective, RCT known as the SUNBURST trial found that burst stimulation as described by DeRidder is generally more effective than tonic stimulation and is associated with higher patient satisfaction. Burst stimulation received FDA approval in October 2016. Although its long-term efficacy has yet to be established, burst stimulation is a promising form of SCS which may lead to a new generation of paresthesia-free spinal cord stimulators acting both through pre-existing mechanisms and by a novel supraspinal mechanism, possibly at the level of the thalamus.

Neurochemical Mechanisms of SCS

In addition to the neurocircuitry-mediated gating mechanism described above, antidromic and orthodromic impulses from SCS also relieve neuropathic pain by spinal segmental and supraspinal mechanisms by restoring the balance of inhibitory and excitatory molecules in the neurochemical milieu of the dorsal horn to stabilize the gate via suppression of hyperexcitable nociceptive neurons.

At a spinal segmental level, antidromic impulses propagating along Aβ fibers enter the dorsal horn provoking release of inhibitory GABA, and reducing the release of glutamate, thereby restoring a neurochemical balance that more effectively suppresses the hyperexcitability of wide dynamic range (WDR) neurons that is thought to contribute substantially to central sensitization. These findings have been corroborated by a number of biochemical and anatomical studies of the dorsal horn.

SCS impulses propagated orthodromically along rostral dorsal column projections activate descending supraspinal inhibitory pathways originating in the periaqueductal gray (PAG) and medulla where aminergic neurons of the locus ceruleus (LC) and the nucleus raphe magnus (NRM). Through caudad projections that descend along the dorsal columns and terminate in the dorsal horn, these nuclei exert supraspinal neurochemical pain control by secreting inhibitory norepinephrine, serotonin, and substance P into the SG, thereby further stabilizing the gate.

Vascular Mechanisms of SCS

In the case of vascular diseases such as chronic refractory angina and peripheral artery disease, SCS acts by peripheral vasodilation and downregulation of efferent sympathetic activity. SCS has been shown to increase blood flow in dermatomes corresponding to the spinal segmental level of stimulation. This observation by Cook et al. was subsequently applied in the treatment of peripheral vascular disease and chronic refractory angina. Furthermore, Linderoth and Meyerson found that these effects were mediated both by antidromic activation of small-diameter fibers and by inhibition of sympathetic outflow. Later studies revealed that low-intensity SCS triggers antidromic action potentials along Aβ fibers which, acting indirectly through interneurons, trigger antidromic action potentials in unmyelinated afferent fibers that then migrate to the periphery where they cause the release of a powerful vasodilator known as calcitonin gene-related protein (CGRP) at peripheral nerve terminals. CGRP then activates endothelial nitric oxide synthesis and release, resulting in vascular smooth muscle relaxation and an increase in blood flow to the affected limb.

In the treatment of angina pectoris, SCS reduces anginal pain by redistributing coronary blood flow and by decreasing myocyte oxygen demand. Clinically, this is observed as an increase in the time to angina during exercise, an increased resistance to critical ischemia, and an anti-arrhythmic effect achieved through modulation of cardiac neurons. Notably, SCS does not mask the perception of true myocardial infarction. SCS has been shown to reduce cardiac nociceptive pain transmission, stabilize the cardiac conduction system, reduce infarct size through coronary flow redistribution, and reduce sympathetic outflow. In addition to reduced infarct size, the beneficial effect of SCS manifests as a reduced magnitude of ST segment changes during active ischemia and fewer atrial arrhythmias.

Higher-Order Supraspinal Mechanisms: The Pain Matrix

In addition to the brainstem and subcortical structures discussed above, SCS is thought to interact with and modulate a broader constellation of higher-order structures implicated in the modulation of pain. This group of functionally related, reciprocally interacting brain structures is known as the "pain matrix." The pain matrix consists of the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), prefrontal cortex (PFC), parietal somatosensory cortex, insula, thalamus, hypothalamus, amygdala, hippocampus, and periaqueductal gray (PAG). It is involved both in modulating the sensory-discriminatory element of pain at the level of the brainstem and in modulating the affective-emotional elements of pain at cortical and subcortical levels.

SCS has been shown to influence the activity of neurons in many of these structures, including the thalamus and somatosensory cortices. One PET study of nine patients with chronic neuropathic lower extremity pain revealed increases in cerebral blood flow to the contralateral thalamus, bilateral parietal association cortices, the anterior cingulate gyrus, and the prefrontal cortex, all components of the pain matrix. In the thalamus and parietal association cortices, SCS is thought to affect pain threshold. In the ACC and prefrontal areas, it may regulate the affective-emotional aspects of pain.

Another study used fMRI to examine the cortical and subcortical effects of SCS on ten patients with chronic pain, concluding that SCS reduces the affective component of pain by reducing the connectivity between somatosensory and limbic structures of the pain matrix, thereby disconnecting the purely sensory signals from structures known to attach affective-emotional salience to the pain.

SCS for Chronic Visceral Abdominal Pain

Chronic visceral abdominal pain evolves by similar mechanisms to those involved in peripheral sensitization in which tonic nociceptive stimulation leads to enlargement of receptive fields, increased recruitment of peripheral fibers, increase in the number of suprathreshold responses to sensory inputs, and spontaneous activation of neurons that are typically silent in response to nociceptive stimuli. The dorsal column has also been shown to transmit some visceral nociceptive afferents and can also amplify visceral pain.

Overall, the mechanism by which SCS achieves visceral abdominal pain relief is quite similar to that in somatic pain control. One unique mechanism, however, is that SCS suppresses the visceromotor response caused by colonic distention, thereby reducing the discomfort caused by gastrointestinal hypermotility and dysmotility. Both thoracic and lumbar lead placement in rat models have been shown to ablate the visceromotor response.

Clinically, SCS has been used to successfully treat mesenteric ischemic pain, esophageal dysmotility, gastroparesis, IBS, chronic pancreatitis, familial Mediterranean fever, posttraumatic splenectomy, generalized chronic abdominal pain, and chronic pelvic pain. However, there is a paucity of prospective, randomized controlled trial data to support widespread use at this time.

Mechanisms of SCS Non-responsiveness

Non-responsiveness to SCS in neuropathic pain is poorly understood. In the setting of CRPS, it occurs in roughly 1/3 of patients and has been reliably connected to the severity of allodynia. It is thought that severe allodynia arises from extreme depletion of the inhibitory neurotransmitter GABA in the dorsal horn. This has been demonstrated in a rat model where experimental depletion of inhibitory neurotransmitters caused severe allodynia that could not be alleviated by SCS. In another experimental study, the intrathecal delivery of the GABA-B agonist baclofen was shown to convert SCS non-responders into SCS responders.

The timing of SCS placement also appears to play a crucial role in its chances of success. Indeed, it has been clinically observed that SCS is most effective when started 7 months to 1 year after the onset of neuropathic pain. Central sensitization appears to play a role in the evolution of SCS non-responsiveness, as it is likely a progressive process mediated in part by the depletion of neurotransmitters essential to SCS responsiveness. One study found that SCS works in part by reversing GABA depletion and glutamate excess known to occur during early central sensitization. Another found that GABA supplementation soon after central cord injury could reverse hyperalgesia but could not do so later in the process. This model of central sensitization as a progressive disease process is borne out in the natural history of neuropathic pain syndromes. For example, after a period of rapid progression lasting around 1 year, the symptoms of CRPS I typically stabilize, thereafter progressing quite slowly or not at all.

The level of mechanical allodynia is a clinical predictor of SCS non-responsiveness. This observation may be related to the fact that mechanical allodynia is conveyed not by C or Aδ fibers, but by large myelinated Aβ fibers, only a small fraction of which are activated by SCS.

Finally, SCS failure may be attributable to suboptimal physical and technical factors, including but not limited to the inaccurate placement of electrodes and excessive thickness of the highly conductive intervening dorsal CSF layer, which can cause dorsal root fiber activation through lateral dispersion of the SCS current. The target site for stimulation depends on the neuroanatomy. Caudally, the dorsal column afferents are located at the surface of the cord, but more rostrally, they course ventrally, which typically makes caudal sites more sensible locations for electrode placement.

Dorsal Root Ganglion (DRG) Stimulation

With dorsal root ganglion (DRG) stimulation, pain control is achieved by placing an electrode, typically by an anterograde percutaneous approach, into the lateral recess of the neural foramen directly over the dorsal root ganglion. These leads are slim and flexible, allowing their placement without compression of the DRG itself.

Neuroanatomically, there are a number of factors that make the DRG an apt target for the neuromodulation of pain. First, it is a site where the bulk of ascending pain inputs, most of them bound for the spinothalamic tract, as well as neutral mechanoreceptive stimuli bound for the dorsal column, converge before somatotopically diverging to ventral and dorsal zones of the spinal cord. Its superficial dorsal location along a relatively thin overlying layer of dura mater and CSF and low surrounding tissue impedances render the DRG more susceptible to stimulation with lower energy levels that average around 15% of the power output required for dorsal column stimulation. The convergence of all sensory pathways at this point allows the stimulation of spinothalamic fibers that are typically inaccessible because they travel in close proximity to the descending motor neurons of the corticospinal tract. Targeting a single nerve root permits greater anatomic specificity for pain control, allowing the stimulator to focus on a foot or toe rather than an entire limb. Finally, paresthesia fields in DRG tend not to vary with position, a benefit that occurs because the lead is deployed into a bony vertebral foramen that is oriented at a 90-degree angle to the spinal cord.

DRG stimulation is thought to actively reduce the net nociceptive activity to the spinal cord by restoring the neural filtration function served by the normal DRG. Notably, this mechanism is distinct from the gate control mechanism by which activation of large-diameter sensory fibers blocks transmission of pain signals in small-diameter fibers at the level of the dorsal horn. Indeed, DRG stimulation appears to normalize peripheral input before it arrives at the gate.

DRG stimulation has demonstrated 1-year efficacy in the treatment of a number of clinical entities, including radicular pain, failed back surgery syndrome, complex regional pain syndrome of the lower extremities, and chronic postsurgical pain. The targeted nature of DRG stimulation allows the treatment of pain in subdermatomal distributions with precisely sculpted paresthesia fields. Examples include the treatment of foot and post-herniorrhaphy groin pain. Other case reports have described DRG stimulation as therapy for low back pain, postherpetic neuralgia, phantom limb pain, visceral pain, somatic body wall pain, upper extremity pain, complex regional pain syndrome of the knee, and postsurgical knee pain.

Peripheral Neuromodulation and Its Mechanisms of Action

Peripheral neuromodulation is possibly the most diverse and rapidly expanding area of neuromodulation. It is comprised of a variety of techniques including peripheral nerve stimulation, peripheral nerve field stimulation, transcutaneous electrical

nerve stimulation, and functional electrical stimulation. Since the first percutaneous stimulator was used for chronic headaches in 1999, peripheral neuromodulation has been used to treat an ever-expanding variety of nerves and nerve plexuses to treat neuropathic, visceral, cardiac, abdominal, low back, and facial pain.

Peripheral Nerve Stimulation (PNS)

Peripheral nerve stimulation is a neuromodulation technique in which electrodes are placed percutaneously directly along the course of peripheral nerves and electrical current is applied to alleviate chronic pain. The prevailing hypothesis for the mechanism of pain-relieving action by PNS is via dorsal horn gate closure provoked by orthodromic action potentials that travel along Aβ fibers, entering the dorsal horn from the periphery. Just as with central neuromodulation, however, the mechanism likely varies based on the clinical entity being treated and its unique underlying physiology. PNS may also cause analgesia by neurochemical mechanisms by influencing the local concentration of neurotransmitters, neuromodulators, and inflammatory molecules that mediate the pain response. Animal studies have revealed that repeated stimulation of peripheral nerves results in decreased C-fiber response to pain at the level of the spinal cord.

At low-frequency stimulation, PNS is believed both to modulate downstream nociceptors and to promote favorable central pain processing upstream. Low-frequency stimulation of Aδ fibers in a rat model caused long-term depression of monosynaptic and polysynaptic excitatory postsynaptic potentials in the substantia gelatinosa. In a cat model, stimulation of the posterior tibial and sciatic nerves resulted in decreased C-fiber response to pain at the level of the spinal cord, thereby implicating a spinal pathway. At ultrahigh stimulation frequencies, PNS is thought to cause direct blockade of the peripheral nerve.

A promising development in the field of PNS has been the discovery that, unlike SCS, it may have antinociceptive properties extending beyond ischemic pain. Ellrich and Lamp used laser infrared stimuli to activate Aδ and C fibers in the superficial radial nerves of human subjects. Laser stimulation provoked painful prickling sensations, and associated cortical evoked potentials were observed. However, when peripheral stimulation was applied, the same painful stimulus provoked a diminished perception of pain and was associated with reduced evoked potentials and latencies.

Headache: Occipital Nerve Stimulation for Occipital Neuralgia, Chronic Migraine, and Cluster Headache

The mechanism of action of ONS in occipital neuralgia and chronic migraine relies on the anatomic convergence of trigeminal, dural, and cervical afferents in the brainstem. Experimentally, it has been shown that activation of afferents from the caudal trigeminal nucleus at the level of C2 can induce pain in the trigeminal and cervical distributions. Therefore, electrical stimulation of the occipital nerves, which is superficial and easily accessed branch of C2, can be used to modulate pain in those distributions. A PET study of eight patients with chronic migraines treated with ONS demonstrated changes in regional blood flow to the dorsal rostral pons, the anterior cingulate cortex, and the cuneus, all structures involved in central pain processing. The clinical efficacy of ONS has been evaluated by three large controlled studies, the ONSTIM and PRISM trials, and another randomized study with mixed results.

Sphenopalatine Ganglion (SPG) Stimulation for Cluster Headaches

Another target of interest for PNS in the treatment of refractory cluster headaches is the sphenopalatine ganglion (SPG), which lies in the pterygopalatine fossa providing postganglionic innervation and sensation to the facial, meningeal, and cerebral blood vessels. Local ischemia caused by vasospasm of these vessels is thought to underlie the pain caused by cluster headaches. Furthermore, cluster headaches have been successfully treated by SPG blockade and radioablation, and animal models have shown that SPG stimulation can increase regional blood flow, thereby reversing vasospastic ischemia.

Trigeminal, Facial, and Mandibular Nerve Stimulation for Facial Pain

PNS has been used to treat facial pain in a variety of conditions and involves stimulation of the peripheral nerves that provide sensory innervation to the painful area. Electrodes have also been placed in the V1, V2, and V3 trigeminal distributions to achieve pain relief in trigeminal neuralgia. Direct stimulation of the trigeminal ganglion has also been performed for trigeminal neuralgia, poststroke pain, peripheral nerve injury, and postherpetic neuralgia.

One case series studied PNS for poststroke facial pain and postherpetic neuralgia with five of seven in the poststroke group experiencing relief and none of those in the postherpetic neuralgia group experiencing pain relief.

Single Nerve and Nerve Plexus Pain

Through the use of motor stimulation, ultrasound, and anatomical landmarks, percutaneous electrodes can now safely be placed along any number of painful peripheral nerves or nerve plexuses. The first reports included supraorbital implantation, but an expanding variety of single peripheral nerves have now been reported including median, ulnar, sciatic, genitofemoral, and ilioinguinal.

Peripheral Nerve Field Stimulation (PNFS)

Many patients have neuropathic pain occurring in non-dermatomal distributions, instead of occurring in areas that either span multiple dermatomes or where the receptive fields

of several peripheral nerves overlap. In such cases, SCS and PNS can fail to capture the irregular pain patterns, while PNFS can at times provide relief. PNFS does not target a specific nerve or sensory distribution. Instead, the lead is positioned within the tissue in order to stimulate the network of cutaneous afferents that delineate an area of pain. PNFS is thought to cause analgesia either by orthodromic Aβ-mediated gating mechanisms in the dorsal horn or by provoking the release of endorphins. By placing the electrode at the epicenter of pain, relief can often be provided to an entire painful area.

Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is a form of neuromodulation in which electrical stimulation is delivered by adhesive leads placed on the skin over painful areas. More recently, TENS has emerged as a moderately effective treatment for pain. TENS is thought to act via local, spinal, and supraspinal pathways. Low-frequency TENS (<10 Hz) appears to promote signaling via u-opioid, GABA, serotonin, M1, and M3 receptors. The evolution of tolerance to TENS suggests the involvement of descending inhibitory pathways as well.

Functional Electrical Stimulation (FES)

Functional electrical stimulation (FES) is the transcutaneous application of controlled electrical stimulation to generate contractions and functional movement in paralyzed muscles, thereby facilitating and improving the mobility of limbs, and other body functions lost due to injury, including respiratory, sexual, bladder, and bowel function. This is an emerging technology recently improved with brain-computer interfacing that is thought to reduce pain and improve function by work by restoring the activity of deconditioned and unused muscles.

Vagal Nerve Stimulation (VNS)

Vagal nerve stimulation (VNS) is electrical stimulation of the left vagal nerve. VNS has a well-established role in the treatment of epilepsy, but a possible application in the treatment of pain has emerged more recently. Its mechanism of action is unknown, but is thought to be related to synchronization and desynchronization of vagal sensory afferents with cerebral activity.

Medial Branch of the Dorsal Rami of Spinal Nerves

The medial branches of the dorsal rami of spinal nerves provide sensation to the facet joints and motor innervation of the multifidi, small deep spinal muscles known to play a role in local segmental spinal stability and proprioception. Ultrasound and EMG studies have shown that multifidi atrophy and fail to fire appropriately after back injuries. These changes are thought to cause instability that renders subjects more susceptible to repeated back injuries and chronic pain. A new device is being developed to electrically stimulate these muscles with the hope of treating axial back pain by restoring dynamic spinal stability.

Key Points

- The use of electrical stimulation to treat pain is a century-old practice.
- To understand the mechanisms of neuromodulation, it is crucial to first understand the neurophysiological, neurochemical, and vascular processes and the neuroanatomy pertinent to the transmission of pain, both in disease and in health.
- Spinal cord stimulation and other forms of neuromodulation work through multiple mechanisms which can be categorized by type of process (neurophysiological, neurochemical, and vascular) and also by anatomy (local, spinal segmental, and supraspinal).
- The prevailing mechanism of action leading to neurostimulation-mediated pain relief often varies based on the pathophysiology of the underlying painful disease state.
- Gate control theory postulates that activation of large-diameter sensory fibers could block the transmission of pain signals conveyed by small-diameter fibers and is the target of action for multiple forms of central and peripheral neurostimulation.
- There is a preponderance of data to support the efficacy of neurostimulation and to corroborate its underlying mechanisms of action, but much investigation still needs to be done. The most well-validated form of neuromodulation is spinal cord stimulation.
- Neurostimulation is likely to continue to expand in importance over the coming years.

Recommended Reading

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