Review

OPEN

PAIN REPORTS®

Rethinking the causes of pain in herpes zoster and postherpetic neuralgia: the ectopic pacemaker hypothesis

Marshall Devor

Abstract

Introduction: Pain in herpes zoster (HZ) and postherpetic neuralgia (PHN) is traditionally explained in terms of 2 processes: irritable nociceptors in the rash-inflamed skin and, later, deafferentation due to destruction of sensory neurons in one virally infected dorsal root ganglion.

Objectives and methods: Consideration of the evidence supporting this explanation in light of contemporary understanding of the pain system finds it wanting. An alternative hypothesis is proposed as a replacement.

Results: This model, the ectopic pacemaker hypothesis of HZ and PHN, proposes that pain in both conditions is driven by hyperexcitable ectopic pacemaker sites at various locations in primary sensory neurons affected by the causative varicella zoster virus infection. This peripheral input is exacerbated by central sensitization induced and maintained by the ectopic activity.

Conclusions: The shift in perspective regarding the pain mechanism in HZ/PHN has specific implications for clinical management.

Keywords: Deafferentation, Dorsal root ganglion, Dying-back, Ectopic discharge, Herpes zoster, Pain mechanism, Postherpetic neuralgia

1. Introduction

Herpes zoster (HZ, "shingles") is caused by resurgence of a long-standing varicella zoster virus (VZV) infection in a single dorsal root ganglion (DRG). This induces a severe painful skin rash in the corresponding dermatome, most often on the face or chest wall. In some patients, the dermatomal pain persists long after the rash has cleared, giving rise to a chronic painful condition known as postherpetic neuralgia (PHN). Herpes zoster is much more common in older people than young, with the likelihood that HZ pain will transition into PHN increasing sharply with advancing age. Both HZ and PHN feature intense unilateral spontaneous pain in the skin, usually described as burning or stinging in quality, but sometimes also including itch, aching, and pain paroxysms. The ongoing (spontaneous) pain is almost always accompanied by extreme tenderness to the touch (tactile allodynia). Frequently, there is also "hyperpathia," the explosive appearance of pain often accompanied by aftersensation, as stimulus intensity in increased stepwise. These positive symptoms are accompanied by sensory deficits (negative signs) especially dulling of sensation in response to warming or cooling of the skin.[59,83,84]

The traditional explanation of pain in HZ and PHN is cutaneous inflammation in the herpetic rash, and deafferentation due to necrosis of the infected DRG. Both elements, inflammation and deafferentation, were proposed to be causative more than a century ago on the basis of clinical observation and concepts about the pain system that were current at the time.[56] In this article, I will reconsider this explanation in the light of more recent clinical experience and progress made in the understanding of the neurobiological processes that underlie chronic neuropathic pain conditions in general.

2. Consideration of the traditional hypothesis

2.1. Viral infection causes herpes zoster

Epidemiological and virological research in the 1950s and since established convincingly that HZ is a late complication of varicella, childhood chickenpox. Briefly, after the systemic infection with VZV has cleared a low titer of this neurotropic virus persists in sensory cell somata and satellite glial cells in all sensory ganglia of the body, including the trigeminal ganglion (TRG). There, it hides in a latent form for the remainder of the individual's life, evading the immune system. As VZV is highly infectious, and chickenpox has until recently been a nearly universal childhood disease,

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Department of Cell and Developmental Biology, Institute of Life Sciences, and Center for Research on Pain, The Hebrew University of Jerusalem, Jerusalem, Israel

Corresponding author. Address: Department of Cell and Developmental Biology, Institute of Life Sciences 3-533, The Hebrew University of Jerusalem, Jerusalem 91904, Israel. Tel.: +972 2 658-5085; fax: +972 2 658-4480. E-mail address: marshlu@mail.huji.ac.il (M. Devor).

PR9 3 (2018) e702

http://dx.doi.org/10.1097/PR9.0000000000000702

virtually all adults have latent ganglionic infection. The onset of HZ in adulthood is believed to result from resurgence of the latent VZV infection in a single DRG or division of the TRG. That is, in unfortunate individuals, the latent VZV reactivates decades after the initial chickenpox infection. The reasons for reactivation are not yet known. The viral load in the affected ganglion skyrockets and some virus particles track down the associated nerve and cause painful HZ eruptions in the corresponding dermatome.[48,67,84,91] Lack of spread to additional ganglia is usually attributed to efficient immune response, although it might simply be that reactivation in any given ganglion is so rare an event that most people do not live long enough to suffer a second hit. Either way, emergence of a VZV-related rash elsewhere in the body is uncommon except in individuals with a compromised immune system.

The idea that HZ/PHN results from VZV reactivation in a single DRG is based on 2 related observations: the unilateral dermatomal distribution of symptoms and pathological observations of inflammation and loss of nerve fibers and sensory cell somata in DRGs.[84] The viral etiology of HZ/PHN seems solid. Questions arise, however, when it comes to the presumed causes of pain in HZ and PHN.

2.2. Cutaneous inflammation as a cause of pain in herpes zoster and postherpetic neuralgia

The 2 processes currently believed to cause pain in HZ and PHN are virally induced inflammation, which sensitizes nociceptors in the infected skin, and deafferentation due to destruction of sensory neurons in a single virally infected DRG.[25] Spontaneous burning pain and tactile allodynia in HZ are felt in the area of the herpetic rash. This, and their disappearance in most patients with the clearance of the rash, strongly implicates inflammation as the cause of the pain. Because pain in PHN is qualitatively similar to pain in HZ, is felt in the same location, and follows HZ with no pain-free gap, it is generally considered to be a late phase of HZ rather than an independent condition. Note, however, that in PHN the spontaneous pain and allodynia persist after the rash has crusted over and the inflammation cleared. This is obviously at odds with inflammation being the cause of the pain, at least in PHN. Also at odds is the fact that pain fades over the ensuing months in most PHN patients, persisting for more than a year in only ~20% and indefinitely in still fewer, with no obvious correlation with cutaneous inflammation. These inconsistencies suggest a different pain mechanism. Indeed, although it is rarely stated explicitly, there is a tendency to think that inflammation drives pain in HZ with deafferentation later taking over as the predominant pain driver in PHN.

2.2.1. Spontaneous pain

As noted above, ongoing burning pain, in HZ at least, is universally and not unreasonably attributed to the herpetic rash and associated inflammation-induced sensitization of cutaneous nociceptor endings ("irritable nociceptors"). Indeed, in experimental preparations, peripheral sensitization is known to lower the threshold for heat activation of C nociceptors in the skin at least partially due to changes in thermal gating of heat-sensitive transducer channels including TRPV1.[49] This results in enhanced impulse discharge upon moderate elevation of skin temperatures and hence heat allodynia, a common symptom in inflamed skin. If firing threshold falls below ambient skin temperature (~34°C), the afferents fire "spontaneously," with no intentionally applied stimulus. The result is spontaneous burning pain. Ongoing burning pain is a prominent symptom in HZ consistent with inflammation being the cause. However, as noted, response to warming tends to be blunted in HZ, not exaggerated as in inflammation. Other observations that do not fit the inflammation hypothesis are that pain frequently appears a few days before the rash begins and in a few patients occurs although a prominent rash never develops (zoster sine herpete). I will return to these inconsistencies below.

2.2.2. Tactile allodynia

In contrast to ongoing burning pain, tactile allodynia is probably not a direct result of peripheral (receptor) sensitization in inflamed skin. Direct microneurographic recordings in HZ/PHN patients have not yet been reported. However, recordings of afferent fiber sensitivity have been made in other conditions in humans who feature tactile allodynia and in animal models of tactile allodynia triggered by experimentally induced inflammation and neuropathy. These studies reveal increased nociceptor response to strong mechanical stimuli, but response of C fibers to very light touch is rare (references below). Other compelling inconsistencies with the irritable nociceptor hypothesis include response latency and effects of selective nerve block. Specifically, pain is felt rapidly after light touch in HZ (and PHN). C fibers conduct at ~1 m/s, and therefore, in humans, it takes ~1 to 2 seconds for impulses carried in C fiber nociceptors to reach the spinal cord from the hand or foot and even longer to reach levels of conscious perception. And yet pain is felt almost immediately upon touch, certainly not after a delay of seconds. Aδ nociceptors conduct quickly enough. However, they are rare in comparison with C fibers, and touching allodynic skin in HZ/PHN does not trigger 2 painful hits, one sharp and rapid ("first pain" due to Aδ fibers) and the other dull and delayed ("second pain," due to C fibers.) This 2-hit sensation is very distinct in response to sudden brief heat stimuli applied to healthy skin. Likewise, selective block of C fiber conduction attenuates heat allodynia, but not tactile allodynia. By contrast, blocking touch-responsive Aβ fibers eliminates tactile allodynia without affecting heat allodynia.[1–3,9,43,44,65,72,73,77]

Together these observations have convinced most investigators that rather than being due to irritable nociceptors, tactile allodynia is signaled by impulses in normal, fast-conducting, touch-responsive Aβ fibers. The appearance of pain rather than touch sensation upon activation of touch afferents is a consequence of "central sensitization." It is "Aβ pain."[15,18,32,86,87] Within the framework of the inflammation/deafferentation hypothesis, the revised explanation of tactile allodynia in patients with HZ (and PHN) is therefore as follows: Ongoing discharge, at least partly generated in heat-sensitive afferent C fiber endings in the inflamed skin, initiates and maintains central sensitization in associated spinal segments. Because of the central sensitization, otherwise innocuous activity in low-threshold Aβ touch afferents evokes a sensation of pain upon gentle stroking of the skin.

2.2.3. Conclusion—does cutaneous inflammation drive pain in herpes zoster/postherpetic neuralgia?

The conventional irritable nociceptor hypothesis of pain in HZ[25] seems to make sense a priori. However, even with the modified explanation of tactile allodynia being an instance of Aβ pain, too many details in the clinical picture of HZ (and PHN) are inconsistent with inflammation being the major driver of pain. Prominent inconsistencies include the following:

(1) Ongoing burning pain in HZ is accompanied by reduced response to warm stimuli while, in inflamed skin, the response is typically enhanced.
(2) Ongoing pain and tactile allodynia may appear before or without zoster rash.
(3) In HZ patients who go on to have PHN, the transition is apparently seamless. Both the ongoing pain and the tactile allodynia continue unchanged despite clearance of the rash and disappearance of cutaneous inflammation.
(4) Pain in PHN tends to fade over time in most patients, although it persists in some. But the fading and the persistence do not appear to be associated with corresponding changes in cutaneous inflammation.
(5) Likewise, the increased chance of HZ transitioning into PHN with increasing age, severity of the HZ, and other risk factors[26,38] is not obviously correlated with the degree of inflammation present in the skin.
(6) The dominant sensory symptom in chickenpox, which is also caused by VZV infection of the skin, is itch, not pain as in HZ/PHN. Indeed, dermatologists report that, in general, itch is a more common symptom than pain in inflamed skin. Prominent examples are eczema, allergies, psoriasis, and contact dermatitis. Inflammatory lesions in leishmaniasis are generally painless.
(7) Given disruption of skin barriers due to the rash, topical anti-inflammatory drugs are expected to reach epidermal nerve endings and provide effective relief. But systemic and topical NSAIDs, and corticosteroids, are at best only moderately effective in HZ and largely ineffective in PHN.[22,28,51,62] Anti-inflammatory creams dispensed by compounding pharmacists may help, but such remedies usually contain local anesthetics and/or other membrane stabilizers such as amitriptyline and ketamine that are known to act on ectopic pacemaker sites.[10,16]

2.3. Spinal deafferentation as a cause of pain in herpes zoster and postherpetic neuralgia

The striking inconsistencies with inflammation being a prime cause of pain, in PHN in particular, call out for an alternative explanation. This was provided by a number of early postmortem pathological studies. Most notable was the seminal 19th century study of Head and Campbell,[33] which reported in a series of patients, severe haemorrhagic and inflammatory necrosis in one DRG, the one most closely associated with the painful dermatome. All the neighboring DRGs were relatively spared. This observation formed the basis of the current belief that spontaneous pain, in PHN at least, is caused by spinal cord deafferentation. That is, pain in PHN is an instance of "anesthesia dolorosa."

In this context, the terms "deafferentation" and "denervation" need to be clarified because they are often confused. Nerve injury (distal to the DRG) denervates peripheral tissue, but it does not massively deafferent (ie, destroy afferent input to) the spinal cord. Many DRG neurons survive axotomy and continue to maintain their central connectivity. It they did not, there would be no Tinel sign (pain upon percussion of a cut nerve end, eg, in amputees). Indeed, nerve injury per se often increases afferent input to the spinal cord by generating ectopic discharge. This makes a major contribution to (peripheral) neuropathic pain.[16] Dorsal rhizotomy or ganglionectomy, on the other hand, does reduce afferent drive by preventing peripheral impulse activity from reaching the dorsal horn and the trigeminal brainstem. The central synaptic terminals of the affected afferent neurons degenerate. To implicate processes playing out in the central nervous system (CNS) as the primary generators of the ectopic discharge that underlies ongoing pain sensation, it is necessary to document that pain persists despite true deafferentation.

After both nerve injury and true deafferentation, the quality of spontaneous pain (burning, cramping, tingling, paroxysmal, and electric shock-like) is a reflection of the specific type(s) of neurons that contribute to the "ectopic" discharge, and their firing rate, pattern, and degree of synchrony (esp. for pain paroxysms). But the location of the ectopic electrogenesis differs. Note that the term "ectopic" refers to the location of electrogenesis, not to the abnormal firing itself or whether it is spontaneous or evoked. The normal location of impulse generation is the specialized sensory ending in the skin (or other tissues). All other generators, the nerve-injury site, outgrowing sprouts or dying-back axon ends, the DRG, or the CNS, are ectopic.

Ongoing pain felt in a numb body part, anesthesia dolorosa, is most commonly associated with deafferentation due to brachial plexus avulsion injury. In this condition, dorsal roots are traumatically wrenched from the spinal cord.[88] Although this undoubtedly causes deafferentation, there is also direct damage to the CNS raising the possibility that this is an instance of central neuropathic pain. However, anesthesia dolorosa can also occur after clean deafferentation. For example, for several decades, severe chronic pain in the periphery was treated with surgical rhizotomy or ganglionectomy. This left the limb numb as expected, and it usually eliminated ongoing pain. The approach was ultimately abandoned; however, as in a fraction of patients, a new ongoing pain eventually emerged in the area of numbness.[85] This iatrogenic form of anesthesia dolorosa does not involve direct CNS injury proving that deafferentation per se can be a cause of pain. The "false" sensation felt in the numb area is presumed to be generated within the CNS. In HZ/PHN, the progressive loss of response to heat with persistent spontaneous pain recalls the numbness of anesthesia dolorosa and supports the deafferentation hypothesis. However, the presence of exquisite tactile allodynia in the area of ongoing pain, rather than numbness, is inconsistent with this explanation. Other caveats also undermine the hypothesis that pain in PHN (or HZ) results from deafferentation.

2.3.1 Caveat 1—pathological findings

Uncertainty begins with the underlying pathological observations themselves and the associated diagnosis. As pointed out by Oaklander on the basis of close reading of the original publication,[56] it is likely that most of Head and Campbell's patients had (or had recently recovered from) HZ at the time of death and did not actually have PHN. The terminal nature of their medical condition and their hospitalization in a "lunatic" (psychiatric) asylum suggests that most had dementia and suffered from serious diseases other than HZ/PHN, which is not normally lethal. For this reason, although the location of the rash may have been well defined, there is uncertainty about the HZ/PHN diagnosis, the quality and distribution of pain, and even whether pain was in fact present at the time of death.

As for the pathology, modern DRG specimens affirm prominent inflammation, but DRGs are not described as being bloody. Reported demyelination and fiber loss in peripheral nerves are also consistent with more recent studies of HZ, although its extent in recent studies is much less than would be expected from the near-total necrosis of the ganglion described by Head and Campbell (1900). The 1900 study, like modern studies, included histological examination of the spinal cord, but it did not mention

ipsilateral atrophy of the dorsal horn. This is a prominent feature in long-standing PHN specimens (2–18 years) in contemporary studies, but not in acute HZ.[82,83,90] This again suggests that Head and Campbell were not dealing with PHN but with HZ, probably complicated by the presence of another disease(s), that affects DRGs. Tertiary syphilis, for example, is well known to cause dementia and to compromise sensory neurons in the DRG (tabes dorsalis). Perhaps reactivated VZV in acute HZ, on the background of syphilis, formed the basis of the pathological observations reported by Head and Campbell.[33]

Finally, although modern studies do report significant cell loss in the dermatomal DRG in long-standing PHN, none to date has applied the quantitative methods considered essential for assessing the degree of cell loss in DRGs in experimental studies, including serial sectioning and unbiased sampling.[35,76] Indeed, although neuronal loss undoubtedly occurs in long-standing PHN, the published images suggest that, even in severe cases, neuronal loss is far from complete.[82,83] These considerations and others should moderate our confidence about the accuracy of the >100-year-old conclusion that rapid and massive necrosis of one DRG is a major cause of pain in HZ or PHN.

2.3.2. Caveat 2—what it takes to produce anesthesia dolorosa

Therapeutic rhizotomy of the past that occasionally triggered anesthesia dolorosa involved sectioning several adjacent dorsal roots. This was required because adjacent dermatomes overlap. Any given point on the skin is served by sensory neurons resident in multiple DRGs, usually ≥3. Cutting a single dorsal root is simply not enough to cause a patch of insensate skin.[85] Indeed, the alleged deafferentation underlying pain according to the inflammation/deafferentation hypothesis involves only a single DRG and it does not yield an anesthetic dermatome. Surgical experience shows that rhizotomy or ganglionectomy restricted to one segment almost never triggers anesthesia dolorosa. For example, single-level lumbosacral rhizotomy is routinely performed to relieve dystonia and spasticity in patients with cerebral palsy. C2 rhizotomy and/or ganglionectomy is also performed to relieve chronic headaches and occipital neuralgia, and even to facilitate procedural screw placement.[29,60,61,74] Likewise, major albeit incomplete destruction of the TRG using balloon compression, radiofrequency lesioning, or gamma-knife ablation is a routine treatment of trigeminal neuralgia. Here too, anesthesia dolorosa is a relatively rare and delayed complication.[7] If definitive single-ganglion ablation rarely if ever triggers anesthesia dolorosa, how could late and incomplete loss of neurons in one DRG due to VZV infection do so routinely?

2.3.3. Caveat 3—effects of dorsal rhizotomy and ganglionectomy on ongoing pain in herpes zoster and postherpetic neuralgia

If the impulses driving spontaneous pain in HZ or PHN originated primarily, even if not exclusively, in the deafferented spinal dorsal horn or in the brain, the pain should not be much affected by rhizotomy or ganglionectomy. In fact, multilevel procedures have been performed in patients with chronic, severe PHN usually after affirming pain relief by diagnostic root block. As in other chronic pain conditions of peripheral origin, this surgery usually produced immediate and definitive elimination of the pain. True, the approach was dropped as a therapeutic option because of the risk of delayed onset of anesthesia dolorosa.[58,85] This, however, does not undermine the conclusion based on the immediate postsurgical elimination of pain, that drivers of the original PHN pain resided in the peripheral nervous system (PNS). One might argue that the causative impulses originate in the PNS, but that what causes them to be painful is a CNS process, central sensitization. This suggestion is actually in line with the ectopic pacemaker hypothesis (see the discussion of tactile allodynia, below). However, it flies in the face of the considerable body of evidence indicating that central sensitization associated with neuropathy is itself driven by nociceptive input from the periphery. Finally, although tactile allodynia is frequently present at the boundaries of the anesthetic region generated by multilevel dorsal rhizotomy, spontaneous pain within the anesthetic zone, anesthesia dolorosa, is not dependent on residual cutaneous innervation.[42,88]

3. The ectopic pacemaker hypothesis of pain in herpes zoster and postherpetic neuralgia

The take-home message from the previous section is that the evidence of inflammation and deafferentation being the causes of pain in HZ/PHN is not secure. Given the clinical significance of the condition, the subject merits a fresh look.

The ectopic pacemaker hypothesis of pain in HZ and PHN attempts to interpret the clinical facts surrounding HZ/PHN in light of recent advances in our understanding on the biology of neuropathic pain.[17] In a nutshell, the hypothesis has 2 elements: (1) spontaneous pain in both HZ and PHN is proposed to be due to spontaneous impulse discharge arising at ectopic pacemaker sites in the PNS, sites associated with the dying-back of axons ends and pathology in sensory somata in the VZV-infected DRG. Dying-back neuropathy also explains the dulling of response to warm stimuli as C fiber sensory endings are lost in the epidermis. (2) Tactile allodynia is proposed to result from intensification of the sensory effects of normal cutaneous Aβ touch afferents by central sensitization. The central sensitization, in turn, is maintained by the spontaneous ectopic discharge. Spontaneous discharge in both Aβ afferents and nociceptors is presumably also "amplified" (ie, rendered painful and more intense) by central sensitization. This factor augments spontaneous pain. Both elements deserve elaboration.

3.1. Ectopic pacemakers as peripheral nervous system generators of spontaneous pain and tactile allodynia

3.1.1. Ectopic impulse initiation in compromised nerve fibers

Sensory nerve fibers are designed to generate impulses at specialized transducer endings. Pressing on healthy axons at mid-nerve does not evoke impulses or sensation in the territory served by the nerve (try applying pressure to your median nerve at the wrist). However, in the event of focal nerve trauma or compression, or injury such as occurs after amputation (Tinel sign) and carpal tunnel entrapment, mid-nerve axons change their properties and become responsive to locally applied stimuli. They may also begin to fire spontaneously. The anatomical structures associated with such ectopic pacemaker sites in the PNS are swollen endbulbs (formed by axotomy or axonal dying-back), axon sprouts, and patches of demyelination.[16,27] With time, mechanosensitive hotspots may migrate distally, although injured C fibers have limited regenerative capacity.[12,30] Ectopic pacemaker sites may be disseminated in the nerve, giving rise to a Tinel-like response evocable over long expanses of nerve, such as in painful diabetic polyneuropathy.

Histopathological studies based on skin punch biopsies taken from patients with HZ and PHN are consistent with a dying-back process. Specifically, these studies reveal substantial, progressive small-fiber loss in the epidermis where most nociceptors end, the loss being roughly proportional to the blunting of sensation. In advanced PHN, it can reach a stage of near-total denervation.[6,37,57,63] Pathological changes are also seen in axon bundles in deeper dermal layers and in distal nerve trunks. The reduction of cutaneous flare in response to focal application of histamine is a functional indicator of the loss of nociceptive C fibers.[4] Oddly, published reports of epidermal fiber loss in small-fiber neuropathy tend to attribute the loss to the death of afferent cell bodies. This is almost universally the case in HZ/PHN where the withdrawal of fine epidermal endings is explained in terms of VZV-induced loss of somata in the infected DRG followed by anterograde (Wallerian) degeneration of the axon. But this explanation is based on the questionable beliefs that there is heavy loss of DRG neurons already during the acute rash stage of HZ, and that ongoing pain is caused by deafferentation. As noted above, neither is likely. Anterograde degeneration from the DRG also fails to account for the proportional increase in spontaneous pain with increasing epidermal fiber loss.[57] This is the opposite of what is expected.

The ectopic pacemaker hypothesis adopts a very different explanation. Rather than reflecting neuronal degeneration, the loss of epidermal endings is supposed to represent "dying-back" of the distal end of the axon because of metabolic stress in infected DRG neurons. There may also be dying-back of axon ends of noninfected neurons compromised by the toxic inflammatory milieu of the infected DRG. The retracted axon end then becomes an ectopic pacemaker, a generator of abnormal afferent discharge much like experimental neuroma endings. Greater loss of fibers from the epidermis (without death of the DRG neuron itself) means more dying-back axon ends and hence more ongoing firing and pain.

The process of dying-back is well established in peripheral polyneuropathies (eg, diabetic polyneuropathy or CMT-2) and usually manifests with sensory loss, sometimes accompanied by ongoing pain in a stocking-glove pattern. In both instances, the DRG neurons themselves, at least most of them, are preserved along with more proximal parts of the axons and central connectivity. Because in HZ/PHN major pathology is limited to a single ganglion, the distribution pattern of ongoing pain and allodynia is dermatomal rather than stocking glove. The retracted distal C fiber ends form endbulbs and/or sprout(s) in the dermal plexus and distal nerve trunk, essentially forming disseminated microneuromas. Endbulbs of larger diameter fibers and axons that have shed myelin segments near the axon end, probably also contribute to ectopic spontaneous and evoked discharge. As noted, pathological changes consistent with this scenario have been documented in nerve samples taken from patients with HZ and PHN. Also consistent with this model are a number of reports that infiltrating the skin with a local anesthetics in HZ and PHN, skin resection, or blocking cutaneous nerves relieves pain for the duration of the block (up to hours and sometimes longer).[14,64,70] This would not be expected if the pain-provoking impulses were generated in the CNS.

3.1.2. Selective block of ectopia

The abnormal hyperexcitability of peripheral ectopic pacemaker sites, and the resulting ongoing discharge and mechanosensitivity, is probably due to a number of processes that play out at the axon end, in patches of demyelination, or in the cell soma. These include the upregulation and/or accumulation of voltage-gated Na^+ channels, or other ion channels and receptors (eg, hyperpolarization-activated cyclic nucleotide–gated [HCN] channel, acid sensing ion channel, piezos, and transient receptor potential channels), the depletion of voltage-gated or background K^+ channels and/or the buildup of inflammatory mediators.

Such neuroplastic changes can be visualized by immunolabeling with appropriate antibodies,[19,24,71] a method that ought to be applied to biopsy samples from HZ/PHN patients. The local anesthetics used in topical patches, therapeutic skin infiltration, and nerve block, of course, are Na^+-channel blockers. High concentrations are used, typically 2% lidocaine, because such concentrations are required to block impulse propagation along axons. Far lower concentrations, however, are sufficient to suppress the initiation of impulse discharge at ectopic pacemaker sites.[16,40,45] Suppression of ectopia is also the presumed mechanism of action of transdermal lidocaine patches.[8,52,81] Although the patch depot contains 5% lidocaine, skin penetration is poor and the concentration in the skin is far lower, much too low to block impulses propagating along dermal axon bundles. This explains why the skin itself is not numbed. But intradermal concentrations achieved are apparently enough to at least partly suppress ectopic impulse initiation. Together, these observations suggest that hyperexcitable nerve fibers in the skin make a significant contribution to pain in HZ and PHN. However they do not, on their own, indicate whether the impulse generator sites are irritable nociceptor endings or ectopic pacemakers in dying-back axon ends.

3.1.3. The dorsal root ganglion as a driver of spontaneous pain in herpes zoster and postherpetic neuralgia

Animal studies have identified the DRG as a second major locus of ectopic spontaneous and evoked electrogenesis in peripheral neuropathy, and there is indirect evidence of this also in humans.[13,41,45,47,54,79,80,89] Indeed, the DRG may be a more important source of ectopic discharge than neuroma endbulbs.[50] Because DRG infection is the root cause of HZ/PHN, involvement of the DRG as an impulse generator in this condition seems likely a priori. The DRG is located paraspinally, within the intervertebral foramen. Thus, if the DRG contributes a significant fraction of the impulses responsible for ongoing pain in a particular patient, diagnostic nerve block distal to the ganglion will not stop the pain, but block of the DRG itself (intraforaminal block), or centrally (dorsal root or spinal block), will.[17] If the reports on lidocaine patches, skin infiltration, and nerve block are to be taken at face value (section 3.1.2 and below), the signal in most patients originates distal to the DRG. However, there are also reports to the contrary. For example, while infiltration or excision of painful skin in PHN often relieves the pain at least temporarily, in a fraction of cases, pain persists and, in others, it returns.[55,64,66,68] Likewise, an unpublished PhD thesis reported that intercostal blocks in 28 patients with acute zoster (<12 weeks) relieved the pain transiently (6–8 hours) in 25% of the cases, but in 32% there was no effect. In 18 patients with PHN, pain was relieved in only 2 patients (11%). There was no effect in 9 patients (50%, Christoph Maier, personal communication). The DRG is a likely driver of pain in cases in which skin infiltration and nerve block distal to the ganglion are ineffective or only partly effective. To know this for sure, however, will require targeted research such as observation of effects of intraforaminal application of dilute lidocaine (non-blocking concentration) in patients with HZ/PHN.[45,79]

Transient silencing of DRGs in an animal neuropathy model and in human amputees has been shown to yield transient pain

relief, with the duration of effect lasting up to 12 days with repeated drug application. These observations implicate the DRG as a pain generator.[75,79] Nor has the DRG been overlooked as a potential target for pain control in HZ and PHN. Going back as far as the 1930s, there have been therapeutic trials of intraganglionic, epidural, and intrathecal injection of lidocaine, procaine, or bupivacaine, usually together with depot-form (particulate) corticosteroids including large randomized controlled trials.[11,46,69,78] Variable therapeutic benefit was reported. Unfortunately, these trials say little about the DRG (or the CNS) as a pain source because the key information was not reported. The authors failed to report (and apparently failed to record) changes in pain sensation during the first hour or 2 after injection, the time when the local anesthetic drug was active.

Most valuable for determining the contribution of the DRG to pain in HZ/PHN would be information on the acute effect of depositing lidocaine on the spinal nerve just distal to the DRG vs on the surface of the DRG itself within the intervertebral foramen. I have not found any published reports on this. However, a colleague offered the following comment (Shane Brogan, personal communication): "Anecdotally, I have done selective nerve root blocks (and presumably blocking the DRG) on PHN patients and the response is always interesting. Some patients describe pain relief (seldom with long-term benefit) and others describe an anesthesia dolorosa situation where they are anesthetic to exam, but their pain is somewhat disturbingly unchanged." The obvious interpretation is that block on or central to the DRG eliminates both evoked and spontaneous pain, while block just distal to the DRG eliminates sensation evoked from the skin, but not ongoing pain (hence "an anesthesia dolorosa situation"). This result, if reliable, points to the DRG as a prime generator of ongoing pain in HZ/PHN.

Although the evidence is strong for DRG somata being a major source of ectopic afferent discharge, few studies have been devoted to defining the types of afferents involved. In a rat study in which nerves were transected distally and impulses originating in the DRG monitored 6 to 12 days later, spontaneous discharge was prominent in muscle nerve, but not cutaneous nerve afferents. Follow-up studies confirmed intense ectopia in muscle, but also in skin afferents after nerve crush.[39,40,53] The relevance to HZ/PHN of ectopic input on muscle afferents is uncertain. This observation needs to be repeated when an adequate rodent model of HZ/PHN is developed, and/or using microneurographic recordings from skin vs muscle afferents in patients with HZ/PHN. From symptoms alone, pain in HZ/PHN seems to arise mostly in the skin, but this may not be the last word on the matter. The infrequent mention of pain in deep tissues in patients with HZ/PHN might reflect "delivered wisdom" rather than results of unbiased clinical observation. The matter deserves focused study.

3.1.4. Tactile allodynia

The explanation of tactile allodynia according to the ectopic pacemaker hypothesis is like other neuropathies and not much different from inflammatory pain as laid out above (section 2.2.2). Both attribute the allodynia to touch-evoked activity in low-threshold Aβ afferents rendered painful by central sensitization. The major difference is that, under the ectopic pacemaker hypothesis, central sensitization is presumed to be maintained by afferent discharge arising at ectopic pacemaker sites in dying-back nerve fibers and/or the VZV-infected DRG. Even in patients with dense epidermal denervation, numerous Aβ touch-sensitive afferent endings remain in the skin as evidenced by the very presence of tactile allodynia.[63] These presumably belong to residual large-diameter neurons in the infected DRG and corresponding neurons in neighboring, mostly intact DRGs whose dermatomes overlap with that of the infected DRG. Note that central sensitization does not apply only to stimulus-evoked activity in low-threshold touch afferents innervating the painful dermatome (Aβ pain). It also applies to ongoing ectopic discharge originating in myelinated dying-back axons, somata of Aβ afferents in VZV-infected DRGs, and perhaps ongoing discharge in afferents from adjacent segments. Thus, both evoked and spontaneous pain in HZ/PHN might be due as much to the abundant ectopia generated in low-threshold mechanoreceptive Aβ afferents as in Aδ and C nociceptors.[15]

3.2. Remission of spontaneous pain and tactile allodynia in herpes zoster and postherpetic neuralgia

Punch biopsies show very little if any recovery from epidermal fiber loss even years after the onset of HZ and PHN.[63] C fibers regenerate poorly.[30] Why, then, does pain in acute zoster usually fade in a matter of weeks and in PHN within a year in most cases? A number of factors probably contribute. An obvious one is resolution of the herpetic rash and presumably also of the decline of inflammation in the VZV-infected DRG. For reasons elaborated above, the ectopic pacemaker hypothesis de-emphasizes the role of irritable nociceptor endings in the skin. However, it is well established that discharge of injured nociceptor endbulbs at ectopic pacemaker sites is exacerbated by inflammatory mediators as is ectopic electrogenesis in DRGs.[5,16,20,23,31]

The ectopic pacemaker hypothesis posits that, in HZ patients who do not go on to develop PHN, inflammation is the principal factor that exacerbates ectopic discharge. This is why ongoing pain subsides as the herpetic rash and inflammatory foci in the DRG clear. Tactile allodynia is also expected to resolve as the discharge that maintains central sensitization fades. For HZ patients in whom pain persists, the ectopic discharge is presumably more autonomous than in those in whom it does not and relatively independent of inflammatory mediators. Because the cause of pain and allodynia in these individuals is the same during the early (HZ) and late (PHN) phases of the disease, with ectopic firing only moderately exacerbated by inflammatory mediators, symptoms remain much as they were as inflammation clears. The transition from HZ to PHN is seamless. The various risk factors for developing PHN, most notably advanced age,[26,38] suggest that ectopia in older individuals tends to be more independent of inflammatory mediators than in younger individuals. If so, response to the topical application of inflammatory mediators to the herpetic rash, and to anti-inflammatory agents, might serve as a prognostic indicator of the likelihood of an HZ patient developing PHN.

Be that as it may, even PHN pain eventually resolves in most patients. Resolution probably reflects reestablishment of normal cellular control over neuronal excitability including the waning of hyperexcitability with decline of the excess delivery of Na^+ (and other) channels to dying-back endbulbs and the somatic membrane. In addition, over months and years, there is likely to be progressive death of the DRG neurons that drive the pain. Loss of neuronal somata and consequent Wallerian degeneration of the distal axon might transiently release proinflammatory mediators in the distal nerve capable of enhancing discharge in surviving afferents. Ultimately, however, the net effect of cell loss in the ganglion is depletion of ectopic pacemakers in the skin, the nerve, and the DRG itself. This is expected to lead to a decline in both spontaneous and tactile-evoked pain. In the relatively few patients in whom PHN persists indefinitely, a population of active DRG neurons presumably persists indefinitely.

4. Pain management in light of the ectopic pacemaker hypothesis

Some of the therapeutic modalities available for HZ and PHN have measurable efficacy, but none is considered adequate.[34,84] Prevention, eg, through effective immunization, is clearly the optimal way forward. But in the meanwhile, a revised understanding of mechanism can point to therapeutic options that have not been tried yet, but deserve trying. Specifically, knowledge of the source of pain drivers, of where the causative impulses are coming from, can shed light on the mechanism of action of effective treatment modalities and foster the design of new ones. This is particularly so for PHN.

4.1. Systemic drugs

The classical hypothesis of pain in PHN stresses degenerative loss of infected DRG neurons resulting in deafferentation pain. The impulses that cause the pain are generated in neurons in the CNS; PHN is a type of "central pain." The ectopic pacemaker hypothesis, by contrast, presumes that many (most?) DRG neurons survive and that continuing pain is driven by generators in the PNS. The (limited) efficacy of the systemic drugs in current clinical use is consistent with both hypotheses. Most of these drugs, which include systemic local anesthetics, membrane-acting antidepressants (tricyclics and SNRIs, but not SSRIs), and anticonvulsants (carbamazepine and gabapentin, but not barbiturates), are membrane-stabilizing drugs, ie, they are drugs that suppress neuronal hyperexcitability.[10,16,40] As noted (section 3.1.2), this action occurs at drug concentrations far below those required to block impulse propagation in nerves. Blocking nerve conduction on a systemic basis, of course, would be lethal.

The major difference between the classical and the new hypothesis is the proposed site of drug action: CNS vs PNS. This difference is important. Essentially all systemic drugs currently in use share a common set of dose-limiting side effects: drowsiness, reduced cognitive focus, dizziness, and nausea. These are all CNS effects. If pain is indeed due to ectopic pacemaker activity in the PNS as proposed by the ectopic pacemaker hypothesis, the usefulness of our standard drugs might be much enhanced by preventing their access to the CNS. This would reduce central side effects and make tolerable the use of increased, more effective drug concentrations. Cardiology exploited this strategy long ago by peripheralizing β blockers so that they are unable to cross the blood–brain barrier. This strategy ought to work also for PHN and other for neuropathic pain conditions. A related approach, currently being pursued, is the development of membrane stabilizers that act selectively on Na^+-channel subtypes present in PNS neurons, but not in the CNS.[21]

4.2. Drug targeting

Another therapeutic strategy for enhancing the usefulness of existing membrane stabilizing drugs is to deliver them specifically to the site of electrogenesis. The strategy would begin with diagnostic blocks needed to determine whether the primary driver in a given patient is in the skin, nerve trunk, or DRG.[17] Useful conclusions, of course, depend on the technical adequacy of the block. If incomplete, there is a risk of false-negative conclusions. In addition, one needs to pay attention to the possible redistribution of drug from the site of focal administration to the systemic circulation. If systemic levels creep high enough, there is a risk of false-positive conclusions due to systemic actions of the drug.

Knowing the principle location of the pain driver(s) can directly guide therapy. Thus, if pain in a particular patient is driven by impulse electrogenesis in the skin, topical transdermal modalities might be tried. If the key driver is the DRG, the drug should be delivered intraforaminally. After verification with a diagnostic bolus injection, it should be possible to extend pain relief indefinitely by repeated drug delivery through a port, or through a catheter attached to an implantable pump system.[79] If dilute concentrations of the membrane stabilizer are used, only local DRG electrogenesis will be affected and not conduction along en passage sensory and motor axons.[45] Sensation from the periphery should remain intact, and there will be no motor blockade. Filling the pump reservoir with a high concentration of the drug and using a very slow pumping rate should allow a low, nontoxic concentration of drug to permeate the ganglion for long periods. The time between reservoir refills would be very long, easing problems of compliance. Finally, according to the ectopic pacemaker hypothesis, pain in PHN might be eliminated without risk of anesthesia dolorosa by single-level ablation of the infected DRG. The classical inflammation/deafferentation model in any event presumes that, for all practical purposes, the ganglion no longer exists.

Intraforaminal block of the infected DRG using full-strength lidocaine should eliminate pain signals originating distally in the nerve as well as in the ganglion itself. If a focal site of electrogenesis were identified in a peripheral nerve, the site could be targeted directly by slow pump delivery of dilute lidocaine through a flexible catheter. Indeed, pump delivery of anesthetics to injured nerves is a part of current clinical practice, but the underlying concept is nerve block rather than selective suppression of focal electrogenesis.[36] Failure of intraforaminal block using full-strength lidocaine would indicate that the pain source is in the CNS.

The ectopic pacemaker hypothesis of pain in HZ and PHN stresses 3 principles: (1) diagnostic identification, in the individual patient, of where the pain-provoking impulses are coming from, (2) targeting the primary source(s), and (3) focusing on suppression of ectopic electrogenesis using nonblocking concentrations of membrane-stabilizing drugs. Incorporating these principles could benefit clinical outcomes.

Disclosures

The author has no conflict of interest to declare.

Acknowledgements

The author thanks Shane Brogan and Christoph Maier for permitting him to cite their unpublished observations and Peter Watson for his helpful responses to numerous queries about clinical aspects of HZ and PHN. The author's research on neuropathic pain mechanisms is funded by the Israel Science Foundation, the National Network of Excellence in Neuroscience (NNE) program initiated by Teva Pharmaceuticals, the Seymour and Cecile Alpert Chair in Pain Research, and the Hebrew University Center for Research on Pain.

Article history:
Received 7 June 2018
Accepted 10 October 2018

References

[1] Andrew D, Greenspan JD. Mechanical and heat sensitization of cutaneous nociceptors after peripheral inflammation in the rat. J Neurophysiol 1999;82:2649–56.
[2] Banik RK, Brennan TJ. Spontaneous discharge and increased heat sensitivity of rat C-fiber nociceptors are present in vitro after plantar incision. PAIN 2004;112:204–13.

[3] Banik RK, Brennan TJ. Sensitization of primary afferents to mechanical and heat stimuli after incision in a novel in vitro mouse glabrous skin-nerve preparation. PAIN 2008;138:380–91.
[4] Baron R, Saguer M. Postherpetic neuralgia. Are C-nociceptors involved in signalling and maintenance of tactile allodynia? Brain 1993;116(pt 6): 1477–96.
[5] Bove GM, Ransil BJ, Lin HC, Leem JG. Inflammation induces ectopic mechanical sensitivity in axons of nociceptors innervating deep tissues. J Neurophysiol 2003;90:1949–55.
[6] Buonocore M, Gatti AM, Amato G, Aloisi AM, Bonezzi C. Allodynic skin in post-herpetic neuralgia: histological correlates. J Cell Physiol 2012;227: 934–8.
[7] Burchiel KJ, ed. Surgical Management of Pain. 2nd ed. New York: Thieme, 2015.
[8] Campbell BJ, Rowbotham M, Davies PS, Jacob P III, Benowitz NL. Systemic absorption of topical lidocaine in normal volunteers, patients with post-herpetic neuralgia, and patients with acute herpes zoster. J Pharm Sci 2002;91:1343–50.
[9] Campbell JN, Raja SN, Meyer RA, MacKinnon SE. Myelinated afferents signal the hyperalgesia associated with nerve injury. PAIN 1988;32: 89–94.
[10] Catterall WA. Common modes of drug action on Na+ channels: local anaesthetics, antiarrhythmics and anticonvulsants. Trends Pharmacol Sci 1987;8:57–65.
[11] Chen N, Yang M, He L, Zhang D, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2010; CD005582.
[12] Chen Y, Devor M. Ectopic mechanosensitivity in injured sensory axons arises from the site of spontaneous electrogenesis. Eur J Pain 1998;2: 165–78.
[13] Defrin R, Devor M, Brill S. Tactile allodynia in patients with lumbar radicular pain (sciatica). PAIN 2014;155:2551–9.
[14] Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. Cochrane Database Syst Rev 2014;CD010958.
[15] Devor M. Ectopic discharge in Abeta afferents as a source of neuropathic pain. Exp Brain Res 2009;196:115–28.
[16] Devor M. Neuropathic pain: pathophysiological response of nerves to injury. Chapter 61. In: SL McMahon, M Koltzenburg, I Tracey, DC Turk, editors. Wall and Melzack's textbook of pain. London: Churchill Livingstone, 2013. p. 861–88.
[17] Devor M. Neural basis of pain in herpes zoster and postherpetic neuralgia: the ectopic pacemaker hypothesis. Chapter 13. In: CPN Watson, AA Gershon, MN Oman, editors. Herpes zoster: postherpetic neuralgia and other complications focus on treatment and prevention. Cham: Adis (Springer Nature), 2017. p. 157–87.
[18] Devor M, Basbaum A, Bennett G, Blumberg H, Campbell J, Dembowsky K, Guilbaud G, Janig W, Koltzenberg M, Levine J, Otten U, Portenoy R. Mechanisms of neuropathic pain following peripheral injury. In: A Basbaum, JM Besson, editors. Towards a new pharmacology of pain. Chichester:Dahlem Konferenzen: Wiley, 1991. p. 417–40.
[19] Devor M, Govrin-Lippmann R, Angelides K. Na^+ channel immuno-localization in peripheral mammalian axons and changes following nerve injury and neuroma formation. J Neurosci 1993;13:1976–92.
[20] Devor M, White DM, Goetzl EJ, Levine JD. Eicosanoids, but not tachykinins, excite C-fiber endings in rat sciatic nerve-end neuromas. Neuroreport 1992;3:21–4.
[21] Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. Annu Rev Neurosci 2010;33:325–47.
[22] Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, Betts RF, Gershon AA, Haanpaa ML, McKendrick MW, Nurmikko TJ, Oaklander AL, Oxman MN, Pavan-Langston D, Petersen KL, Rowbotham MC, Schmader KE, Stacey BR, Tyring SK, van Wijck AJ, Wallace MS, Wassilew SW, Whitley RJ. Recommendations for the management of herpes zoster. Clin Infect Dis 2007;44(suppl 1):S1–26.
[23] Eliav E, Benoliel R, Tal M. Inflammation with no axonal damage of the rat saphenous nerve trunk induces ectopic discharge and mechanosensitivity in myelinated axons. Neurosci Lett 2001;311:49–52.
[24] England JD, Happel LT, Kline DG, Gamboni F, Thouron CL, Liu ZP, Levinson SR. Sodium channel accumulation in humans with painful neuromas. Neurology 1996;47:272–6.
[25] Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis 1998;5:209–27.
[26] Forbes HJ, Thomas SL, Smeeth L, Clayton T, Farmer R, Bhaskaran K, Langan SM. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. PAIN 2016;157:30–54.
[27] Fried K, Govrin-Lippmann R, Rosenthal F, Ellisman M, Devor M. Ultra-structure of afferent axon endings in a neuroma. J Neurocytol 1991;20: 682–701.
[28] Galluzzi KE. Managing herpes zoster and postherpetic neuralgia. J Am Osteopath Assoc 2009;109:S7–12.
[29] Gande AV, Chivukula S, Moossy JJ, Rothfus W, Agarwal V, Horowitz MB, Gardner PA. Long-term outcomes of intradural cervical dorsal root rhizotomy for refractory occipital neuralgia. J Neurosurg 2016;125: 102–10.
[30] Gorodetskaya N, Grossmann L, Constantin C, Janig W. Functional properties of cutaneous A- and C-fibers 1-15 months after a nerve lesion. J Neurophysiol 2009;102:3129–41.
[31] Grossmann L, Gorodetskaya N, Baron R, Janig W. Enhancement of ectopic discharge in regenerating A- and C-fibers by inflammatory mediators. J Neurophysiol 2009;101:2762–74.
[32] Hardy JD, Wolf HG, Goodell H. Pain sensations and reactions. New York: William and Wilkins, 1952.
[33] Head H, Campbell AW. The pathology of herpes zoster and its bearing on sensory localization. Brain 1900;23:353–523.
[34] Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med 2005;2:e164.
[35] Hu P, McLachlan EM. Selective reactions of cutaneous and muscle afferent neurons to peripheral nerve transection in rats. J Neurosci 2003; 23:10559–67.
[36] Ilfeld BM. Continuous peripheral nerve blocks: a review of the published evidence. Anesth Analg 2011;113:904–25.
[37] Jensen TS, Gottrup H, Sindrup SH, Bach FW. The clinical picture of neuropathic pain. Eur J Pharmacol 2001;429:1–11.
[38] Johnson RW. Zoster-associated pain: what is known, who is at risk and how can it be managed? Herpes 2007;14(suppl 2):30–4.
[39] Kirillova I, Rausch VH, Tode J, Baron R, Janig W. Mechano- and thermosensitivity of injured muscle afferents. J Neurophysiol 2011;105: 2058–73.
[40] Kirillova I, Teliban A, Gorodetskaya N, Grossmann L, Bartsch F, Rausch VH, Struck M, Tode J, Baron R, Janig W. Effect of local and intravenous lidocaine on ongoing activity in injured afferent nerve fibers. PAIN 2011; 152:1562–71.
[41] Kirk E. Impulses in dorsal spinal nerve rootlets in cats and rabbits arising from dorsal root ganglia isolated from the periphery. J Comp Neurol 1974; 2:165–76.
[42] Kirk EJ, Denny-Brown D. Functional variation in dermatomes in the macaque monkey following dorsal root lesions. J Comp Neurol 1970; 139:307–20.
[43] Kocher L, Anton F, Reeh PW, Handwerker HO. The effect of carrageenan-induced inflammation on the sensitivity of unmyelinated skin nociceptors in the rat. PAIN 1987;29:363–73.
[44] Koltzenburg M, Kees S, Budweiser S, Ochs G, Toyka KV. The properties of unmyelinated nociceptive afferents change in a painful chronic constriction neuropathy. In: G Gebhart, D Hammond, T Jensen, editors. Progress in pain research and management. Vol. 2. Seattle: IASP Press, 1994. p. 511–21.
[45] Koplovitch P, Devor M. Dilute lidocaine suppresses ectopic neuropathic discharge in DRGs without blocking axonal propagation: a new approach to selective pain control. PAIN 2018;159:1244–56.
[46] Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka M, Yodono M, Asai M, Matsuki A. Intrathecal methylprednisolone for intractable postherpetic neuralgia. N Engl J Med 2000;343:1514–19.
[47] Kuslich S, Ulstro C, Michael C. The tissue origin of low back pain and sciatica. Orth Clin North Am 1991;22:181–7.
[48] Levin MJ, Cai GY, Manchak MD, Pizer LI. Varicella-zoster virus DNA in cells isolated from human trigeminal ganglia. J Virol 2003;77:6979–87.
[49] Levine JD, Alessandri-Haber N. TRP channels: targets for the relief of pain. Biochim Biophys Acta 2007;1772:989–1003.
[50] Liu CN, Wall PD, Ben-Dor E, Michaelis M, Amir R, Devor M. Tactile allodynia in the absence of C-fiber activation: altered firing properties of DRG neurons following spinal nerve injury. PAIN 2000;85:503–21.
[51] Max MB, Schafer SC, Culnane M, Dubner R, Gracely RH. Association of pain relief with drug side effects in postherpetic neuralgia: a single-dose study of clonidine, codeine, ibuprofen, and placebo. Clin Pharmacol Ther 1988;43:363–71.
[52] Meier T, Wasner G, Faust M, Kuntzer T, Ochsner F, Hueppe M, Bogousslavsky J, Baron R. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. PAIN 2003;106:151–8.
[53] Michaelis M, Liu XG, Janig W. Axotomized and intact muscle afferents but no skin afferents develop ongoing discharges of dorsal root ganglion origin following peripheral nerve lesion. J Neurosci 2000;20:2742–8.
[54] Nordin M, Nystrom B, Wallin U, Hagbarth KE. Ectopic sensory discharges and paresthesiae in patients with disorders of peripheral nerves, dorsal roots and dorsal columns. PAIN 1984;20:231–45.

[55] Nurmikko T, Wells C, Bowsher D. Pain and allodynia in postherpetic neuralgia: role of somatic and sympathetic nervous systems. Acta Neurol Scand 1991;84:146–52.
[56] Oaklander AL. The pathology of shingles: Head and Campbell's 1900 monograph. Arch Neurol 1999;56:1292–4.
[57] Oaklander AL. The density of remaining nerve endings in human skin with and without postherpetic neuralgia after shingles. PAIN 2001;92:139–45.
[58] Onofrio BM, Campa HK. Evaluation of rhizotomy: review of 12 years' experience. J Neurosurg 1972;36:751–5.
[59] Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, Clark MR, Raja SN. Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. Anesthesiology 2000;92: 691–8.
[60] Park TS, Johnston JM. Surgical techniques of selective dorsal rhizotomy for spastic cerebral palsy. Technical note. Neurosurg Focus 2006;21:e7.
[61] Patel AJ, Gressot LV, Boatey J, Hwang SW, Brayton A, Jea A. Routine sectioning of the C2 nerve root and ganglion for C1 lateral mass screw placement in children: surgical and functional outcomes. Childs Nerv Syst 2013;29:93–7.
[62] Peppin JF, Albrecht PJ, Argoff C, Gustorff B, Pappagallo M, Rice FL, Wallace MS. Skin matters: a review of topical treatments for chronic pain. Part two: treatments and applications. Pain Ther 2015;4:33–50.
[63] Petersen KL, Rice FL, Farhadi M, Reda H, Rowbotham MC. Natural history of cutaneous innervation following herpes zoster. PAIN 2010;150:75–82.
[64] Petersen KL, Rowbotham MC. Relief of post-herpetic neuralgia by surgical removal of painful skin: 5 years later. PAIN 2007;131:214–18.
[65] Pitcher GM, Henry JL. Governing role of primary afferent drive in increased excitation of spinal nociceptive neurons in a model of sciatic neuropathy. Exp Neurol 2008;214:219–28.
[66] Puri N. Modified Jaipur block for the treatment of post-herpetic neuralgia. Int J Dermatol 2011;50:1417–20.
[67] Reichelt M, Zerboni L, Arvin AM. Mechanisms of varicella-zoster virus neuropathogenesis in human dorsal root ganglia. J Virol 2008;82: 3971–83.
[68] Riopelle JM, Naraghi M, Grush KP. Chronic neuralgia incidence following local anesthetic therapy for herpes zoster. Arch Dermatol 1984;120:747–50.
[69] Rosenak S. Procaine injection treatment of herpes zoster. Lancet 1938; 232:1056–8.
[70] Rowbotham MC, Davies PS, Verkempinck CV, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. PAIN 1996;65:39–44.
[71] Roza C, Castillejo S, Lopez-Garcia JA. Accumulation of Kv7.2 channels in putative ectopic transduction zones of mice nerve-end neuromas. Mol Pain 2011;7:58.
[72] Serra J, Duan WR, Locke C, Sola R, Liu W, Nothaft W. Effects of a T-type calcium channel blocker, ABT-639, on spontaneous activity in C-nociceptors in patients with painful diabetic neuropathy: a randomized controlled trial. PAIN 2015;156:2175–83.
[73] Shim B, Kim DW, Kim BH, Nam TS, Leem JW, Chung JM. Mechanical and heat sensitization of cutaneous nociceptors in rats with experimental peripheral neuropathy. Neuroscience 2005;132:193–201.
[74] Sindou M, Mifsud JJ, Boisson D, Goutelle A. Selective posterior rhizotomy in the dorsal root entry zone for treatment of hyperspasticity and pain in the hemiplegic upper limb. Neurosurgery 1986;18:587–95.
[75] Sukhotinsky I, Ben-Dor E, Raber P, Devor M. Key role of the dorsal root ganglion in neuropathic tactile hypersensibility. Eur J Pain 2004;8: 135–43.
[76] Tandrup T. Unbiased estimates of number and size of rat dorsal root ganglion cells in studies of structure and cell survival. J Neurocytol 2004; 33:173–92.
[77] Tsuboi Y, Takeda M, Tanimoto T, Ikeda M, Matsumoto S, Kitagawa J, Teramoto K, Simizu K, Yamazaki Y, Shima A, Ren K, Iwata K. Alteration of the second branch of the trigeminal nerve activity following inferior alveolar nerve transection in rats. PAIN 2004;111:323–34.
[78] van Wijck AJ, Opstelten W, Moons KG, van Essen GA, Stolker RJ, Kalkman CJ, Verheij TJ. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. Lancet 2006;367:219–24.
[79] Vaso A, Adahan HM, Gjika A, Zahaj S, Zhurda T, Vyshka G, Devor M. Peripheral nervous system origin of phantom limb pain. PAIN 2014;155: 1384–91.
[80] Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve injured rats. PAIN 1983;17:321–39.
[81] Wasner G, Kleinert A, Binder A, Schattschneider J, Baron R. Postherpetic neuralgia: topical lidocaine is effective in nociceptor-deprived skin. J Neurol 2005;252:677–86.
[82] Watson CP, Deck JH, Morshead C, Van der Kooy D, Evans RJ. Post-herpetic neuralgia: further post-mortem studies of cases with and without pain. PAIN 1991;44:105–17.
[83] Watson CP, Evans RJ, Watt VR, Birkett N. Post-herpetic neuralgia: 208 cases. PAIN 1988;35:289–97.
[84] Watson CPN, Gershon AA, Oman MN. Herpes zoster: postherpetic neuralgia and other complications focus on treatment and prevention. Cham: Adis (Springer Nature), 2017. p. 431.
[85] White J, Sweet W. Pain and the neurosurgeon. Springfield: Thomas, 1969.
[86] Woolf CJ. Evidence for a central component of postinjury pain hypersensitivity. Nature 1983;306:686–8.
[87] Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. PAIN 2011;152(3 suppl):S2–15.
[88] Wynn-Parry CB. Pain in avulsion lesions of the brachial plexus. PAIN 1980;9:41–53.
[89] Yang Q, Wu Z, Hadden JK, Odem MA, Zuo Y, Crook RJ, Frost JA, Walters ET. Persistent pain after spinal cord injury is maintained by primary afferent activity. J Neurosci 2014;34:10765–9.
[90] Zacks SI, Elliott FA, Langfitt TW. Herpetic neuritis: a Light and Electron Microscopic Study. Neurology 1964;14:744–50.
[91] Zerboni L, Arvin A. Neuronal subtype and satellite cell tropism are determinants of varicella-zoster virus virulence in human dorsal root ganglia xenografts in vivo. PLoS Pathog 2015;11:e1004989.