Mechanisms of peripheral neuropathic pain: implications for musculoskeletal physiotherapy

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Physiotherapy has long been part of the overall intervention for the attempted rehabilitation of patients with pain and disability following peripheral (and central) nerve damage. In musculoskeletal physiotherapy (a subspecialty), a movement-based assessment and treatment protocol has been devised that is guided by, among other things, therapists' perceptions of patients' responses to mechanical stimuli, including various tests of 'neural tension'. Recently, this process together with provocative tests of sensation has been employed to identify, and predict outcomes for, patients suspected of having a 'neural tissue' component to their pain and consequent disability (either fascicular damage or 'neuritis'). However, some of the syndromes involved are controversial, and uncertainty still surrounds the diagnosis, mechanisms and, therefore, effective treatment of the highly complex symptom, true neuropathic pain. In this review, the current basic scientific evidence for the proposed cause, and often intractable nature, of neuropathic pain is presented and discussed with reference to musculoskeletal therapy. It will be seen that peripheral nerve damage has the potential to create potentially irreversible changes in (peripheral and) central nervous system structure and function that have, to date, largely defied effective medical treatment. For musculoskeletal physiotherapy to discriminate accurately and, where appropriate, intervene (or not) responsibly, it would seem constructive to incorporate this (and other) mechanisms-related evidence into its clinical reasoning and decision-making process.

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Introduction

The fundamental basis for neuropathic pain is nerve damage.[1–3] Possible causes of peripheral nerve damage include trauma, bacterial and viral infections, vascular and metabolic disease, neurotoxins, autoimmune insult, ionising radiation, and genetic abnormalities.[2]

Pain which may develop following damage to the peripheral nervous system for any reason has the potential to be an extremely serious clinical problem. This is primarily because the resulting damage alters the structure and function of peripheral nerves, providing at least the initial basis for spontaneous neuropathic pain.[2,4] Importantly, these peripheral events create potentially permanent 'pain-maintaining' changes in both the physiology and anatomy of the central nervous system (CNS).[1] The central changes are believed to be the basis for chronic spontaneous and (in particular) evoked neuropathic pain.[5] It is also acknowledged that effective management of neuropathic pain has not yet caught up with insight into likely mechanisms, which itself is still a 'work in progress'.[6–8]

Nonetheless, this does not mean that pain is an automatic consequence of peripheral nerve pathology. Even with the most common painful neuropathies, diabetic and postherpetic neuralgia, pain is present in only some 20 and 50% of cases,

respectively.[9] As for the role of sudden or gradual onset *traumatic* peripheral nerve injury, this requires considerable qualification given that less than 10% of all such cases are said to develop clinically relevant pain.[10] In this regard, Campbell and Meyer[1] point out that deliberately severing dorsal nerve roots in order to relieve spasticity or remove tumours, for example, is not known to result in neuropathic pain in humans. It is not known for sure why such a large proportion of individuals with seemingly identical pathologies escape pain. Genetic predisposition and psychosocial influences probably play a part.[2,6,11,12] Whatever the case, clearly, there is more to the development of severe, chronically disabling neuropathic pain than just some patent or purported traumatic peripheral neuropathy, major or 'minor'.[6,10,13–15]

The following presents information from acknowledged authorities concerning currently understood mechanisms for the production and maintenance (hence, potentially optimal management) of peripheral neuropathic pain. This information has been selected on the basis of its presumed relevance to the prevailing philosophical, investigative and therapeutic approach adopted by a sub-speciality of the physiotherapy profession (now) known as musculoskeletal physiotherapy (MP)[16–18] (see also *Grieve's Modern Manual Therapy*[19]).

The less than conclusive, at times seemingly contradictory, nature of some of the evidence clearly indicates the need for ongoing scientific research into this refractory and disabling form of chronic pain. The currently unsatisfactory 'state-of-the-art' should not, however, be viewed as simply another orthodox medical 'void' into which various alternative and enterprising ancillary professions feel safe to opportunistically leap.[20]

Diagnosis
Pain

It is significant that the most common sensory complaint by patients with peripheral nerve damage is reported to be tingling (or buzzing) paraesthesia and numbness, not pain.[8,10,21] These, of course, are symptoms initiated peripherally by (loss of) activity in large diameter cutaneous mechanoreceptive (Aβ) fibres, and not small diameter nociceptors.

Though potentially unpleasant, Marchettini *et al.*[10] caution against automatically recording such 'abnormal' large diameter afferent-mediated sensations as pain. They further assert that where these abnormal sensations present with a decided 'pain quality', this

is usually accompanied by some loss of small-diameter afferent-mediated sensation (warmth, cold).[10,14] This is in line with Klein *et al.*[3] and Abrahams[6] who maintain that (small-diameter afferent) sensory loss plays a major role in the identification of true neuropathic pain. If this is so, then these sensory 'signs' have a reasonable chance of being detectable with standard bedside examination.[22] Where practical, this can be extended using a choice of modern 'screening tools' and Quantitative Sensory Testing (QST).[23,24] It is important to remember, however, that these measures are entirely subjective, hence, potentially misleading.[25,26] Nevertheless, while the converse is not nearly as sound, where small diameter afferent sensation tests as normal, this alone should cast considerable doubt on a diagnosis of true neuropathic pain.

Large diameter afferents

Notably, animal models indicate that, at least initially, neuropathic pain (hyperalgesia/'neuropathic behaviour') is the result of spontaneous 'ectopically' produced activity in large-diameter peripheral afferents, not small diameter nociceptors.[4,27] Moreover, studies employing the L5 spinal nerve ligation-and-transection model (SNL) have identified deep-tissue large-diameter joint (group II) and muscle (Ia, II) afferents as conveying this pain-producing and 'central sensitising' input.[28] Normally, such input is concerned with sensations of movement and posture (proprioception), and has no role in the production of pain. This is clearly an issue of interest to purveyors of (passive–active) movement-based treatments such as MP. For one thing, at least during the first few weeks following pain onset, positive responses to provocative tests of 'neural tension' are probably being signalled by superficial and deep large-diameter tissue afferents, and not 'sensitised' nociceptors. Moreover, movement-based treatment would need to be undertaken with great care and specificity to avoid aggravating peripheral neuropathic pain and help sustain central sensitisation.

In some case, this large diameter afferent-produced neuropathic pain may be facilitated by a change in the afferents' phenotype. This is a genetically mediated 'switch' that can occur following peripheral nerve damage. Namely, it is the ability of superficial and deep-tissue large-diameter peripheral afferents to acquire the abnormal capability to produce and release peptides such as substance P (along with their usual transmitter glutamate) from their central terminals.[29,30] This would allow inputs along these fibres to initiate and perhaps maintain central

sensitisation, a role normally reserved for unmyelinated small-diameter nociceptors. However, some studies have failed to convincingly demonstrate Aβ-mediated substance P release in the dorsal horn of the spinal cord following peripheral nerve damage.[31] This suggests that the situation with respect to this proposed mechanism is still unclear.[1] Whatever the case, large-diameter afferent-mediated neuropathic pain is generally acknowledged to be a product of central (sensitisation) and not peripheral nervous system mechanisms.[32,33] Interestingly, Sun *et al.*[34] showed that sectioning the ipsilateral dorsal column can eliminate mechanical allodynia (but not heat hyperalgesia, which travels in the contralateral spinothalamic tracts). This suggests that the source of mechanical allodynia (pain to a normally painless stimulus) is 'higher' than (just) sensitised dorsal horn neurones, possibly in the thalamus or other forebrain centre.[1]

Evidence such as this is of interest to MP which tends to base 'diagnostic' and therapeutic clinical decisions on patients' subjective responses to, and therapists' psychophysical perceptions of, provocative mechanical stimuli ('manual diagnosis').[18,35,36] When it comes to spatial diagnosis by provocation (i.e. attempting to determine a 'peripheral' versus 'central' source of symptoms), it is cautionary to consider Hansson's[8] list of possible biological mechanisms for the evoked symptom, dynamic mechanical allodynia: i) peripheral sensitisation of cutaneous Aδ/C fibre afferents, ii) 'awakening' of cutaneous silent nociceptors, iii) a switch in phenotype of peripheral Aβ afferents, iv) loss of Aβ-mediated inhibitions centrally, v) central sensitisation (for 'heterosynaptic/topic' inputs), vi) sprouting of large diameter mechanoreceptive afferents onto central 'pain' transmission neurones, and vi) tonically active descending facilitation of spinal cord neurones (detailed descriptions of individual items on this list may be found in Campbell and Meyer[1] and Woolf[33]). It might also be kept in mind that a significant proportion of neuropathic pain patients do not present with mechanical allodynia (their most common complaint being continuous pain).[8,37]

The deeper significance of ectopically initiated neuropathic pain lies with the observation that the large-diameter (or for that matter any other) spontaneous activity has virtually disappeared by around two months after onset.[5,38] Mechanically evocable pain, however, persists. Assuming this (myelinated afferent) mechanically evoked pain is still being mediated centrally, what then is the *peripheral* 'driver' for ongoing central sensitisation?

Small diameter afferents

The possibility that continuous inputs in unmyelinated nociceptive (C, group IV fibre) afferents might also contribute to spontaneous neuropathic pain is complex and evidently requires particular circumstances. To begin with, such low-level discharges as may develop in *damaged* unmyelinated fibres would seem insufficient for this purpose.[27] Nevertheless, Serra[39] asserts that discharges from unmyelinated nociceptors are probably the basis for spontaneous burning pain. The necessary requirements appear to be both axonal damage and an independent and adequate source of inflammation. Under these circumstances, continuous comparatively high-frequency unmyelinated afferent activity has been shown experimentally to develop in nearby *intact* small-diameter nociceptive afferents. This is likely to be due to a genetically instigated redistribution of $Na_v1{\cdot}8$ sodium ion channels to their terminals.[40] However, discharges only occurred when the intact afferents were exposed to an artificial source of inflammation (experimentally: loose chromic gut ligature, complete Freund's adjuvant – CFA).[41] It is currently unclear whether nearby naturally occurring Wallerian (damaged nerve) degeneration would always be an adequate physiological substitute.[42] If it is not, then it becomes necessary to propose realistic circumstances under which a suitable inflammatory environment might exist. Presumably an (undamaged) unmyelinated nociceptive afferent contribution to *chronic* neuropathic pain would require a continuous source of inflammation. Whatever the case, it is questionable whether the proposed 'neuritis' model (see below) would qualify since axonal damage is said to be absent or insignificant in these cases.[43]

The role of inflammation in the development, and subsequent duration, of neuropathic pain raises an issue that appears to be of considerable clinical concern to MP. Namely, the ability to discriminate trauma-induced neuropathic and inflammatory ('neural tissue') pain, in part using the process known as 'manual diagnosis'.[44,45] Why a movement-based intervention such as MP should have a selectively valid role in the treatment of pain owing to inflammation (as opposed to frank nerve damage) is not clear. The presence of inflammation is generally considered to be a contraindication to direct mechanical perturbation, passive or active.[35,44,45] Furthermore, inflammatory (nociceptive) pain might evolve to become neuropathic or perhaps a mixture

of both, for example, sciatic radiculopathy.[46–51] Definitively discriminating clinical presentations such as this would be a daunting task[14,51] especially for an empirical movement-based 'diagnostic' process such as MP.[13,18,36]

Assisting in the physical rehabilitation of individuals who have adequate (pharmacological) pain cover is, of course, another issue. In this case, drug aided restoration of optimal function, not (necessarily) direct pain relief, is the primary therapeutic goal of physical treatments.[49,50] Evidence that MP is capable of effectively engaging endogenous pain inhibitory mechanisms under clinical inflammatory conditions is still somewhat sparse.[46] The possibility that MP might selectively suppress, rather than evoke, pain-reinforcing peripheral afferent input has not been investigated (see Zusman[47,48]).

Neuritis

Bennett[9] offers an interesting clinical classification in this regard which might be of interest to MP. This involves the albeit largely experimental 'neuritis' model proposed by various authors.[43,52–56] With this model, pain of 'neural tissue' origin is proposed to occur in the *absence of any (or completely insignificant) axon damage* (therefore, no accompanying negative symptoms).[43] Exposure of its connective tissue nerve supply (nervi nervorum) to some superficial source of inflammation is said to give rise to and be diagnosable symptomatically as nociceptive inflammatory pain. In other words, this is essentially the same pain (and mechanism) as that arising from acutely damaged muscle or joint tissue. However, should the inflammatory medium penetrate to, or for some reason arise exclusively within, the deeper fascicular axons and generate ectopic discharges, the (solitary symptom) pain is likely to resemble that which can occur following nerve damage. In any event, in the absence of evidence of nerve damage, both pain presentations should probably be classified as inflammatory and not neuropathic.[10]

As Bennett[9] acknowledges, how realistic it is to expect either perineural or endoneural inflammation to present in complete isolation under clinical circumstances further highlights the problem of definitive diagnosis ('manual' or any other). Recently, Freynhagen *et al.*[51] reported the 'unexpected [sic] similarity' with relative lack of definitive discriminatory sensory evidence, between samples of 'pseudoradicular' and radicular low back pain patients. The origin and definitive nature of ('work-onset') cervical neck/arm pain is likely to be even more obscure. This is because a) the unique uncovertebral joints are thought to largely screen cervical nerve roots from contact with (products of) the intervertebral disc and b) foraminal narrowing as a basis for root irritation is a common, and mostly asymptomatic, age-related change (Hall, personal communication). As for posttraumatic cervical radicular pain (e.g. 'whiplash'), the problem is exemplified by Schwartzman and Grothusen.[14] These authors appear to have difficulty in deciding whether this (and other sensory perceptions) is due to fascicular damage, inflammation or both.[14]

Sodium channels and the ectopic pacemaker hypothesis

Because of their diagnostic and therapeutic potential, considerable attention has been given to the role that voltage-gated sodium ion channels might have in neuropathic pain.[2,5,57] Their change in expression and function in the peripheral nerve membrane following damage is proposed to be a major peripheral mechanism for (at least initiating) neuropathic pain.[5] Further support comes from the (partially) favourable response some neuropathic syndromes exhibit to certain sodium channel-blocking drugs.[1,58–60] However, it needs to be acknowledged with respect to sodium channel blocking drugs in general that translating encouraging results from smaller clinical trials and animal studies to the larger trials and broad clinical practice has proved rather difficult.[58]

The clinically relevant consequence of damage-initiated change in sodium channel expression and function in the periphery is the trains of ectopically created spontaneous discharges that follow. Sustained firing of impulses is necessary for the production of clinically relevant pain.[2] It is significant that both damaged, and nearby undamaged, peripheral afferents are capable of generating ectopic discharges.[29] Experimental evidence indicates that following axon severance or dysmyelination, spontaneously produced nerve impulses may emanate from various sodium channel redistribution and accumulation sites on the nerve cell. These include the area of peripheral damage, proximally along the axon, and (particularly) from within the dorsal root ganglion.[4,29] The production of repetitive trains of impulses ectopically has been attributed to injury-induced enhancement of specific 'electrophysiologic properties' of the nerve membrane afforded by the upregulated and redistributed sodium channels: specifically, an increased capacity to display sinusoidal oscillatory membrane potentials, along with depolarising after-potentials (DAPs) (the interested reader is asked to consult Devor[2] and Amir *et al.*[5] for a detailed explanation of these phenomena).

Therefore, the major peripheral mechanism for at least initiating neuropathic pain, and central sensitisation, is damage-induced alterations in the structure and function of peripheral nerves. It is these changes that result in a 'remodelling of the intrinsic electrical properties of the nerve membrane'.[2] Therapeutically, to suppress ectopic electrogenesis and repetitive firing it is necessary to reduce the pathologically increased number of active sodium channels in the nerve membrane. By blocking a proportion of these channels, membrane stabilising drugs create a substantial rise in repetitive or rhythmic firing threshold. This will suppress ectopia while allowing normal action potential conduction to continue.[2] It would seem highly unlikely that mechanical perturbation of peripheral nerves could have any such effect.

Significant though they are, the apparent spontaneous disappearance of peripheral ectopia some two months after onset raises an important question with respect to the *maintenance* of (evoked) neuropathic pain.[5,38] Namely, what role might a profound alteration of CNS function, that is the legacy of the aforementioned peripheral events, have to play in the development and maintenance of chronic neuropathic pain?

Central mechanisms
Structural

The available evidence points to CNS mechanisms as critical for both the development and maintenance of neuropathic pain. Again, these peripherally triggered central events involve (irreversible?) changes in central physiology and anatomy, albeit with varying degrees of severity and probability.

Central structural changes observed experimentally include sprouting of large-diameter collateral afferents from lamina III in the dorsal horn to make contact with a pool of deafferented excitatory 'pain-generating' (inter)neurones in laminae II.[61,62] This would result in (yet another) mechanism for mechanical allodynia, a distressing evoked symptom that can severely limit everyday activity.[3,50,63] Similarly, a part central-part peripheral form of sprouting involving the sympathetic nervous system has been demonstrated following experimental peripheral nerve damage. Postganglionic sympathetic efferents are seen to extend basket-like sprouts on to, and tonically stimulate, the cell bodies of somatic afferents in dorsal root ganglia.[64,65] This would provide a (further) source of continuous 'pain-producing' ectopic impulses arriving centrally. Moreover, beginning, say, with spinal cord preganglionic sympathetic

neurones, the peripheral input would serve to drive a 'reflex' (hence pain) segmentally, as well as via supraspinal autonomic centres such as the hypothalamus.

While these structural changes are clearly important, the extent to which they (might) occur clinically is not certain. Routinely, however, and no less significantly, peripheral events trigger a concerted chain of physiological and anatomical changes centrally that seriously compromise the ability to inhibit pain (see next). 'In-built', naturally activated pain inhibitory mechanisms are of course targets for a variety of artificial therapeutic interventions, including the mainstream pharmacologic treatments.[6,11,12,59,66] When, as is the case with neuropathic pain, these endogenous mechanisms are physiologically and anatomically disabled, neither natural nor artificial means of pain relief are particularly effective. Hence, even the first line of attack with pain, namely the ability to create symptomatic relief, is weakened with neuropathic pain.[7,12,67] Despite extensive high-level scientific research, and an occasional encouraging breakthrough, realistic hope of actual cure for most types of neuropathic pain still appears some way off.[2,6,7,10–12,33]

Loss of inhibitions

It is well recognised that an afferent-induced increase in central excitability ('central sensitisation') can result in spontaneous or evoked pain.[32,33,68] It is important to appreciate that a reduction in endogenous inhibition(s) can have effectively the same net result.[33] If this central inhibitory loss were permanent, ongoing 'central sensitisation' could result in chronic intractable clinical pain.

One commonly observed response to peripheral nerve damage is a central decrease in the expression of receptors for inhibitory neurotransmitters/modulators. Thus, Kohno *et al.*[69] demonstrated a substantial loss of opioid/opiate receptors from both presynaptic terminals of peripheral afferents as well as the postsynaptic membrane of CNS 'pain' projection neurones. Further receptor 'disablement', hence compromise of inhibitions, would arise from a significant upregulation centrally of the opioid receptor antagonist cholecystokinin.[38,70]

Notably, a decline in the spinal cord of the inhibitory transmitter γ-aminobutyric acid (GABA), along with its receptors, has also been observed in several animal models of peripheral nerve damage. Loss of the transmitter together with its synthesising enzyme (glutamic acid decarboxylase, GAD) is

considered especially ominous since this probably signals death of the inhibitory interneurons themselves ('dark cells').[71] Such selective apoptosis of GABA-containing spinal cord cells is effectively permanent. This represents, as Campbell and Meyer[1] put it, a 'hard-wired change in [CNS] circuitry'. An impairment of this magnitude obviously has enormous clinical relevance when it comes to the attempted (physical) management of true neuropathic pain.

It is apparent that disabling GABA's central inhibitory capability permits superficial and deep large-diameter mechanoreceptive afferent input to gain abnormal access to spinal cord pain projection neurones.[72] Among other things, stimulation of these second-order neurones by 'unmodified' large diameter afferent input has been shown to cause an NMDA-dependent activation of intracellular 'signalling cascades'.[72] Physiological events such as these are usually the result of unmyelinated small-diameter afferent input ('homosynaptic facilitation'[1]). They constitute an integral part of the mechanism for creating central sensitisation, and long-term memory for pain.[33,73–75] Therefore, with or without a 'switch' in phenotype, this pathological effect of large-diameter afferent input would constitute an important mechanism for the exacerbation and maintenance of mechanical/movement-evoked pain. Such a dramatic change in large-diameter afferent function from 'good guy' (potential to shut the spinal gate) to villain helps emphasise the difficult-to-manage nature of this grave form of chronic pain. The clinical implications evidence such as this has for a movement-based intervention such as MP are obviously profound.[29,46,49]

It should also be pointed out that normal inhibitory interneuronal control of central sensory (and motor) output neurones is not necessarily unidirectional. That is, in addition to the (therapeutic) suppression of 'painful' neuronal activity, GABA/glycine mediated inhibitions can, under pathological circumstances, also contribute to its enhancement. This involves the 'focusing' of excitatory input/output from relevant pain pathway neurones by segmental, or descending inhibition of 'noisy' output from other irrelevant neuronal pools.[76] In addition, under certain circumstances it may be possible for inhibitory interneurons themselves to be inhibited.[77] This would release symptomatic outputs from disinhibited pain pathway neurones. Notably, loss of central inhibitory potential in this way would further reduce any therapeutic ability to prevent or control central sensitisation.[1,76,78]

Central sensitisation and long-term pain memory

It is significant that central sensitisation for pain in general[75] and neuropathic pain in particular,[1,79] is beginning to be conceived and described in terms of (mechanisms for) learning and memory.[73,80,81] Viewed until recently as parallel but separate lines of enquiry, pain and memory research are now joining forces.[68,74,78,82,83] While here is not the place for in-depth discussion, this is a field that could be of considerable clinical relevance to MP.[48] Two points, one therapeutic and the other 'diagnostic', might be singled out.

From a therapeutic perspective, in order for some treatment to 'erase' a pain memory (or 'mask' it so that it is no longer dominant) and thereby help restore pain free function, it needs to be capable of engaging in-built pain inhibitory mechanisms.[6,78,84,85] To be successful this would need to be accompanied by the elimination or modification of afferent sources of (pain) memory reinforcement.[48,78,86,87] The above-described concerted undermining of endogenous inhibitory systems, which is a hallmark of true neuropathic pain, is obviously a barrier to the potential success of any such therapeutic enterprise. Stimulus-based arousal of endogenous inhibitions is proposed to be a neurological basis for the clinical efficacy of MP.[46,88] The likelihood for this potential to be compromised with neuropathic pain should be recognised by MP. Where appropriate the implications ought to be included in its clinical reasoning and decision-making process. In doing so the rationale for endeavouring to minimise (homo- and hetero-topic) afferent input that might serve to reinforce and so sustain or exacerbate a disabling pain 'memory' would also be strengthened.[48]

The other point is that, in practice, (learning and) memory for pain is essentially associative.[86,89] Pain 'associations' consist of a range of extraneous sensory stimuli present in the environment at the time of (and subsequent to) injury.[89,90] They also include the various informational, cognitive and emotional items that ultimately come to bear on the experience. This being so, in addition to pain being highly demanding in its own right[91,92], such complex and persistent sensory 'overload' could place overwhelming demands on the processing capabilities of often distressed, despairing and (pain-) distracted patients. It is reasonable to assume that 'colonisation' of working memory in this fashion could compromise their ability to accurately perceive, process and report artificially delivered sensory inputs.[93–96] This further cautions against routine uncritical interpretation

of (chronic) pain patients' subjective responses to evocative clinical sensory/motor assessment procedures.[25,26]

Descending facilitation (tonic)

Ossipov and Porreca[38] are adamant that '...descending pain facilitation...is essential to maintain states of sustained and enhanced [neuropathic] pain'. Specifically, there is now abundant experimental evidence that (presumed) clinical manifestations of chronic neuropathic pain are critically dependent on descending facilitation of dorsal horn neurones by inputs arriving from the rostroventromedial medulla (RVM).[1,38,97]

Likely circumstances and means by which descending facilitation is 'turned on' centrally (to the exclusion of inhibitory pathways) should be of interest to healthcare professionals engaged in diagnosing and/or attempting to manage neuropathic pain. Defined areas of the brainstem that constitute the 'final common pathway' for potential excitation of dorsal horn pain pathway neurones are now being identified (see references in Ossipov and Porreca[38]). Given the enormous difference in size and complexity, it is hardly surprising that supraspinal centres might control the output of spinal cord sensory (and motor) neurones. It is also evident that these brainstem sites may be activated by both peripheral afferent input ascending in the spinal cord[33,38] along with that from several 'pain processing' centres further forward in the brain.[98–100] Hence, even at the spinal cord level, central sensitisation may be influenced by spino-bulbo-spinal loops as well as by cognitive emotionally driven forebrain input to relevant brainstem nuclei.[101]

Significantly, following peripheral nerve damage, descending facilitation of spinal cord pain pathway neurones appears to become tonic.[38,102,103] This then provides a means of sustaining chronic, mechanically evoked neuropathic pain long after the initial peripheral ectopic 'driver' has disappeared (see earlier[5,38]).[5,104] Descending facilitation of spinal cord pain pathway neurones is also believed to be implicated in the 'spread' of pain symptoms beyond the involved nerve's innervation territory, a pattern that is sometimes seen clinically.[1]

Gene transcription

Many of the previously described (maladaptive) alterations in CNS structure and function are effectively the end product of gene activity.

One measure of the magnitude of the clinical problem that is neuropathic pain is the growing awareness of the scale and consequences of change in gene function and expression. This occurs in both the peripheral and central nervous systems following peripheral nerve damage. The cause is believed to be a combination of afferent activity and trophic factor (e.g. NGF, BDNF) influence on transcription.[1,29,105] It entails a combination of the down regulation of certain genes and re-expression of long absent embryonic genes, as well as the induction of a complete set of 'new' or de novo genes.[106] So far, hundreds of genes have been identified as being involved, and the number is expected to grow.[29,106–108] The specific and unique contribution some of these genes make to the mechanisms of neuropathic pain, and its potential control, are beginning to be identified. The following are a few clinically relevant examples of basic sciences research into this important aspect of true neuropathic pain.

For instance, peripherally there occurs an upregulation of the presynaptic calcium channel subunit $\alpha2\delta$-1 (target for the more effective drugs, gabapentin and pregabalin). There is also reappearance of the rapidly 'repriming' (embryonic) sodium channel $Na_v1\cdot3$, and bradykinin B1 and capsaicin TRPV1 inflammatory chemical receptors are expressed on myelinated axons.[109] This is accompanied by down-regulation of some other channels and receptors, including (as mentioned earlier) the inhibitory μ-opioid receptor on central terminals of unmyelinated peripheral afferents.[69,109] Significantly, following peripheral nerve damage the nociceptor specific $Na_v1\cdot8$ sodium ion channel is downregulated from the cell body of damaged unmyelinated afferents (and is not redistributed peripherally). This is considered to be one reason why these (damaged) small diameter afferents do not make any significant contribution to the generation of symptomatic ectopic impulses or, therefore, neuropathic pain.[40,57]

The release of cytokines both peripherally and in the spinal cord is known to be associated with neuropathic pain.[67,110] Peripheral nerve damage causes a massive increase (ipsilaterally) in the number of 'activated' microglia in the dorsal horn of the spinal cord.[67] Stimulation of activated microglia releases several 'pain-relevant' chemicals, including cytokines such as interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α). Recently, Inoue[111] demonstrated that cytokine release was enhanced as a result of damage-induced upregulation in the expression of the adenosine triphosphate (ATP) receptor, P2X$_4$, on microglial cells. Pharmacological blockade and suppression of the P2X$_4$ receptor gene (hence

cytokine release) decreased neuropathic pain.[111] Nor is an increase in the presence of 'symptomatic', and potentially destructive, cytokines confined to the spinal cord: Apkarian *et al.*[112] report a correlation between neuropathic-like pain behaviour and increased expression of interleukin 1*β* (IL-1*β*) in the brainstem and prefrontal cortex following peripheral nerve damage.

Pain-induced loss of supraspinal neurones

Evidence of neuro-immune involvement in neuropathic pain together with the loss ('death') of spinal cord interneurones following peripheral nerve damage, has led to the proposal that chronic neuropathic pain and central neurodegenerative disease share (some) similar mechanisms.[113] Recent studies combined various techniques for imaging nerve cell activity, metabolism and morphology in the brains of clinical pain patients. Together, these studies demonstrated a decrease in the volume of neocortical grey matter, and regional grey matter density in the thalamus and dorsolateral prefrontal cortex (DLFC) in patients with chronic neuropathic pain (see references in Apkarian and Scholz[113]). The specific agency considered to be responsible for these striking changes in brain structure is an afferent activity-mediated form of programmed cell death known as apoptosis. Apoptosis is a complicated process, and only points appropriate to the present topic will be discussed. For a detailed description the interested reader is asked to consult Yuan and Yankner.[114]

Essentially, the process by which neurones may be (sufficiently) stimulated to 'orchestrate their own death' requires a relatively slow but sustained 'rise' in intracellular levels of calcium.[113] Calcium influx is through calcium entry receptors/channels (e.g. NMDA) on the (postsynaptic) nerve membrane. These open following receptor binding by the neurotransmitter glutamate. With peripheral nerve damage, glutamate is released at the first synapse in the spinal cord by peripherally generated ectopic impulses. Notably, ectopic discharges may be enhanced by natural or deliberate environmental stimuli. Glutamate is then released at subsequent CNS synapses by impulse activity coursing through spinal cord and supraspinal pathways. Apoptotic glutamate excitotoxicity results in nerve cell destruction, fragmentation, and ultimately phagocytosis. These, in turn, are the result of a complex process involving death genes, their protein products and receptors, ending with activation of the 'executioner' enzyme, caspase-3[113] (Maione[115] recently showed that spinal cord apoptosis may use a somewhat different set of receptors, enzymes and 'death' pathways). The presence of reactive oxygen species (ROS)[116] and IL-6 and TNF-*α*[111,112] observed in the CNS during the development of (behavioural signs of) neuropathic pain is consistent with their respective roles in neural apoptosis: namely, the over-expression of proapoptotic genes and caspase-3 activity and the activation of death receptors by cytokines.[112,117]

Importantly, it is quite likely that oxidative and metabolic stress, a well known trigger for apoptosis with neurodegenerative disease, is also implicated in (neuropathic) pain-induced loss of supraspinal neurones. Thus, cortical and thalamic cell death could simply be secondary to that seen in the spinal cord.[71,72] However, it is also possible that this is a result of the supraspinal neurones' inability (congenital, acquired?) to withstand 'intolerable' levels of excitatory sensory and affective afferent input. With susceptible individuals, suitably 'stressful' afferent input to cortical areas would have both peripheral/spinal as well as various intra-cortical sources.[6,12,79,99,113,118,119] The fact is, apoptosis is dependent on (afferent) nerve impulse activity and can be slowed if that activity is halted. However, this suppression has only been demonstrated for the duration of a (peripheral) nerve block; the destructive process resumed soon after the anaesthetic had worn off and the afferent barrage recommenced.[117] Hence, not only (further) pain, but also (permanent) loss of supraspinal neurones may be a consequence of nerve impulse activity with neuropathic pain. If so, it would seem to be in the best interests of all parties concerned for movement-based therapists to attempt to discern just which parameters of stimulus evoked afferent input could be therapeutic and which potentially harmful. Appropriately designed brain imaging studies might be helpful in this regard.

While the precise clinical implications of these 'degenerative' cortical changes may not be easy to interpret, they do indicate once again that (chronic) neuropathic pain can be associated with probably irreversible changes in CNS structure. This, in turn, implies a clinically relevant alteration in function. Indeed, afferent activity-induced loss of cortical neurones has been shown to correlate with both pain intensity and pain affect, including (levels of) trait and state anxiety.[119,120] The latter endorses the consistent finding of a relationship between the presence of psychosocial factors such as anxiety, catastrophysing, and depression and the development of chronic (neuropathic) pain.[6,12,118] Significantly,
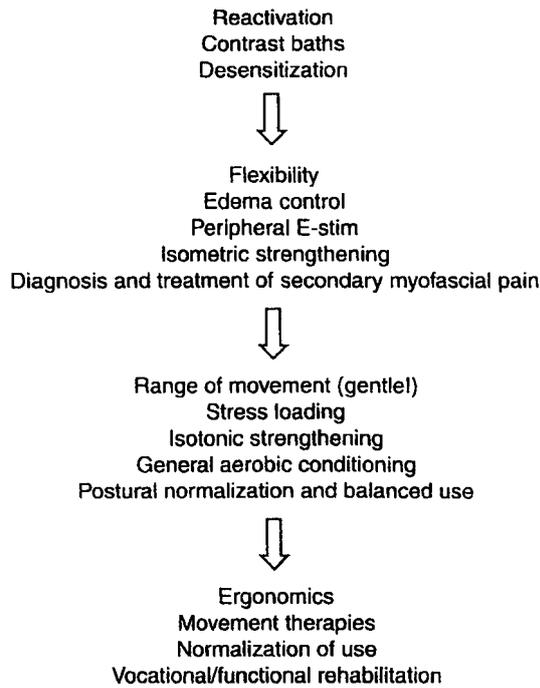
Reactivation
Contrast baths
Desensitization

⇩

Flexibility
Edema control
Peripheral E-stim
Isometric strengthening
Diagnosis and treatment of secondary myofascial pain

⇩

Range of movement (gentle)
Stress loading
Isotonic strengthening
General aerobic conditioning
Postural normalization and balanced use

⇩

Ergonomics
Movement therapies
Normalization of use
Vocational/functional rehabilitation

Figure 1   Example of physical treatment component of functional rehabilitation programme for patients with peripheral neuropathic pain (from Chong and Bajwa[49])

such cognitive-emotional variables, together with an exaggerated response to experimental/environmental(?) stimuli, are recognised as being potent risk factors for the development of chronic pain following (nerve damage with) surgery.[12,121]

Conclusion

From what is known to date it should be apparent that neuropathic pain is a multi-impairment-based symptom that is not easily assessed subjectively, and remains less than satisfactorily managed. For these reasons, and because it can be readily mimicked, to even begin to diagnose true neuropathic pain demands a broad information base, and, in order to intervene, the competence is required to deliver highly specialised mechanisms-validated care.

The fundamental intervention for neuropathic pain remains pharmacotherapy.[66,122] The goal of pharmacotherapy is to selectively block the production and/or transmission of pain-producing afferent activity in the periphery, and to engage mechanisms of endogenous inhibition in the CNS. Though often included in the rehabilitation process, therapeutic expectations for physical treatments are less specific. Chong and Bajwa[49] offer a non-invasive, non-pharmacological 'functional restoration' algorithm that is more or less in keeping with the physical competencies of a movement-based intervention such as MP (Fig. 1);

the authors do, however, add a rider for the referring medical practitioner:

'if [patients] cannot perform any step due to pain, then consider [nerve] block and/or change of drug therapy; in the case of inconsistencies or inordinate pain behavior, step up psychologic assessment and/or drug therapy' (p. S8).

It is important for MP to have a realistic appreciation of the reasons behind, and implications of, this statement.

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