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Neuropathic pain in cancer

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ABSTRACT

Neuropathic pain in cancer arises following injury to peripheral or central neurons, in a similar manner to such pain arising from a non-cancer injury. Much of our knowledge of neuropathic pain is based on peripheral originating events with little known about central neuropathic pain. This article explores some of the similarities and differences between cancer and non-cancer-related neuropathic pain. The neural pathways, ion channels, receptors and neurotransmitters that potentially can be altered in both neuropathies are the same; however the nature of the injury, the timing, repeated injuries and the co-existence of simultaneous non-neuropathic pain states lead to potential unique constellations of neuroreceptor and neurotransmitter expression in the context of cancer pain. This in turn may lead to different clinical presentation of pain sensations and potentially lead to specific treatment options.

1. Introduction

Neuropathic pain, defined as pain initiated or caused by a primary lesion or dysfunction (although major doubts exist about the utility of the term dysfunction since it could apply to many if not all pain states) in the nervous system is often difficult to manage and poses significant clinical challenges.[1] As with all intractable pains, it can have a detrimental impact on the overall quality of life; it impairs the patient's ability to perform daily functions as well as their ability to cope with the disease, further adding to the anxiety, worry and stress of the afflicted patient and family.[2,3]

Cancer pain is often referred to as a mixed mechanism pain, as it rarely presents as a pure neuropathic, visceral or somatic pain syndrome, but rather a complex syndrome with components of inflammatory, neuropathic and/or ischaemic mechanisms often in multiple sites.[4] Even within neuropathic pain syndromes, the presentation and evolution of the pain is affected by pre-existing non-cancer damage, as well as subsequent interventions and cancer relapse. An absolute distinction between cancer and non-cancer-related neuropathic pain is perhaps artificial. The pathophysiology of cancer-related neuropathic pain fundamentally remains similar to non-cancer-related neuropathy and cross-referencing between the two states is frequent.[1] Work on cancer-related neuropathic pain (chemotherapy induced, or direct invasion) has identified distinct differences in the signature of neuroreceptor/transmitter alterations, unique damage and disruption to neuronal function and may yet reveal differences in initiation and maintenance. This evidence would suggest unique features of cancer-related neuropathy, giving a unique molecular signature, whilst acknowledging some similarity to non-cancer-related neuropathies.[5,6] Related to this issue, the ability of drugs used to treat neuropathic pain, such as gabapentin to reduce both behavioural and neuronal measures in certain animal models of cancer induced bone pain (CIBP) may indicate neuropathic mechanisms. The broad actions of this drug do not allow for drug efficacy to be used as a diagnosis.[7]

Clinically, the comparison between cancer and non-cancer-related neuropathic pain continues, with a similar language and description of pains, overlapping signs and

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similar array of drugs used. These include a combination of positive and negative signs such as sensory loss (numbness), spontaneous pain, allodynia, hyperalgesia and paresthaesia.[8–10] Descriptors such as burning, tingling, shooting, 'pins and needles-like', electric, itch can vary immensely between patients, and do not identify the aetiology reliably. In both cancer- and non-cancer-related neuropathic pain, signs and symptoms occur as the dominant feature.[4] The concept of neuropathy as being more or less predominant in the overall pain state has been suggested as a means of reflecting the complex clinical state. There is clinical evidence that drugs effective in non-cancer pain states, such as opioids, are effective in cancer pain states,[11,12] the efficacy determined rather by the underlying balance of neuronal excitation (inflammatory versus somatic versus neuropathic) rather than the clinical diagnosis. For example opioids have greater efficacy in inflammatory pain as compared to neuropathic pain, regardless of whether the latter is caused by viral, surgical or cancer destruction,[13–15] but still retain clinical efficacy. It could be argued that as cancer and the attendant treatments result in mixed pain mechanisms, the resulting neuronal and higher centre stimulation induces a complexity and 'chaos' and so produces a unique signature, on a familiar background.

2. Non-cancer-related neuropathic pain

Some of these potential mechanisms have been best studied in animal models involving nerve injuries (e.g. partial or full sciatic nerve ligation, infra-orbital nerve injury), viral infection (varicella zoster virus-induced PHN), systemic chemical injection (streptozocin-induced diabetic neuropathy).[16,17] Neuropathic pain arises from initiating changes in the damaged nerves which then alter function in the spinal cord and the brain and lead to plasticity at a number of sites. (see Fig. 1).

Nerve damage increases the excitability of both the damaged and undamaged nerve fibres, neuromas and the cell

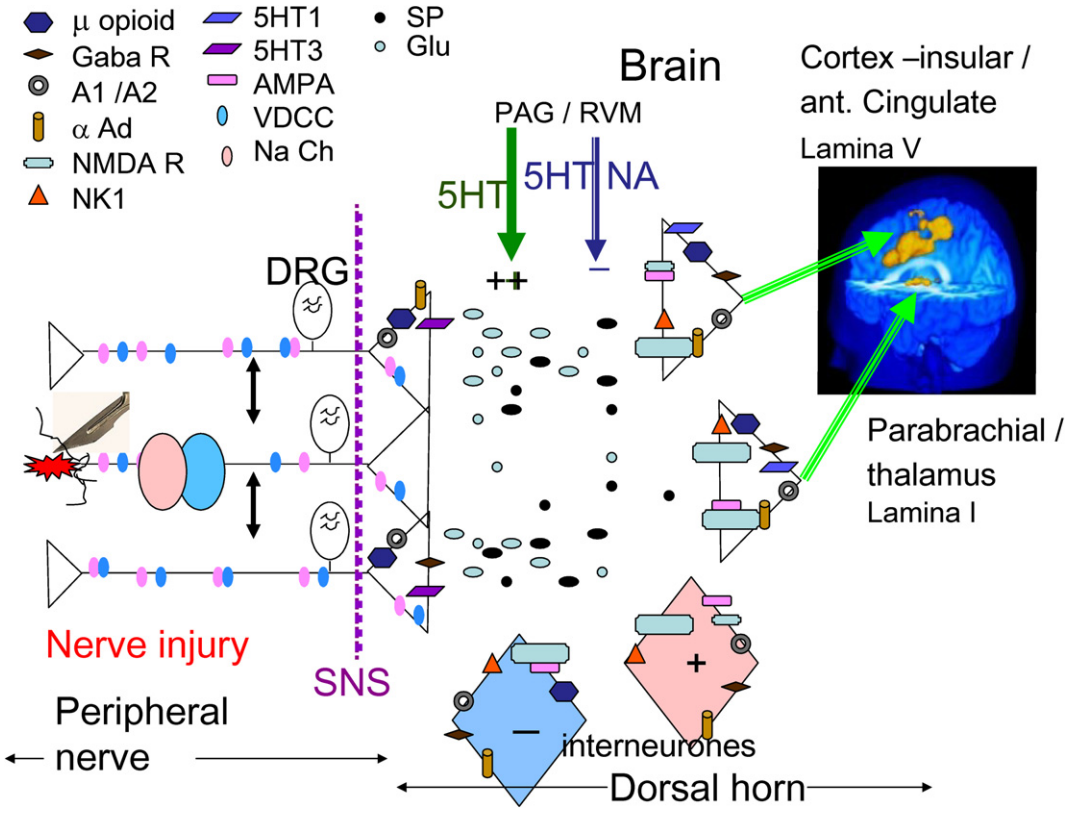

Fig. 1 – A diagram to summarise the changes that occur in the peripheral and central neuronal pathways following a peripheral nerve injury (nerve transection shown), resulting in chronic neuropathy. In the periphery, the nerve distal to the injury dies to regenerate in an abnormal manner. The sodium (NaCh) and calcium (VDCC) channels alter in expression (to be more responsive) and number (increase particularly around the area of damage). Aberrant transmission in the damaged nerve leads to spontaneous discharge and epiphatic cross-talk between damaged and undamaged neurones, and between DRG and sympathetic nervous system (SNS). This results in an increase in the receptive field size, spontaneous and lower threshold discharge of neurones, and can lead to the aberrant excitation of the sympathetic nervous system. Within the dorsal horn, glutamate (Glu) and substance P (SP) are released in increased and irregular amounts (not necessarily in response to a threshold stimulus), although there may be reduced or absent release in the damaged neurone termination. Increased excitatory amino acid release results in an overall excitation of the inter-neurones and increased transmission to the brain. This is further enhanced by the overall reduction in inhibition, both by the loss of GABAergic neurones, the relative inactivation of μ opioid receptors and facilitation of descending serotonin – 5HT3 excitation pathways.

bodies in the dorsal root ganglion. The spontaneous and erratic discharge of the damaged neurone in turn cross-talks to surrounding normal neurons, causing further spread of abnormally reacting neurons. These peripheral changes are substrates for the ongoing pain and the efficacy of sodium channel excitability blockers.[18] Within the spinal cord, increases are seen in the activity of calcium channels on peripheral fibres and the receptors for glutamate, especially the NMDA receptor that trigger wind-up and central hyperexcitability.[19] Increases in transmitter release, neuronal excitability and receptive field size ensue. Ketamine acts on central spinal mechanisms of excitability, whereas gabapentin and pregabalin act on a subunit of calcium channels that are responsible for the release of pain transmitters into the spinal cord.[20,21]

In addition to these peripheral and spinal mechanisms of hyperexcitability, recent fMRI studies have suggested a re-wiring and hyperexcitation of cortical and afferent areas in patients with persistent neuropathic pain.[22] Parts of the brain involved in affective responses to pain alter and engage descending excitatory systems[23], thus a long term pathological state of central sensitization can be maintained via central feed-forward loops, with or without continued peripheral input. Opioids act to control the activity of peripheral nerve fibres, spinal excitability and also regulate brainstem mechanisms, thus acting at three of the major sites of generation of neuropathic pain, whilst anti-depressants act centrally.[24,25]

These multiple mechanisms of neuropathic pain are the basis for the use of combinations of agents that attack more than one site, so providing the possibility of synergy in the control of these difficult pain states.

3. Cancer-related neuropathic pain

Although the exact prevalence of neuropathic pain in cancer patients remains unknown, it is predicted that at least 15-20% of patients are likely to suffer from neuropathic pain during the course of the disease, and an even higher proportion at advanced stages of the disease.[26]

Neuropathic pain in cancer patients may arise from several different mechanisms, some but not all have been investigated in animal models, however in clinical practice all of the following causes may arise simultaneously or sequentially in patients, adding new complexity to neuronal signatures. Neuropathic pain may be considered the result of a multi-step process, each contributing to neuronal sensitization. The final event that triggers initiation or maintenance of neuropathy will differ between individuals. This may in some way explain the diversity of clinical presentations. Cancer-induced neuropathic pain may result from compression of the nerve or direct infiltration by the growing tumour, or secondarily from changes in the neuronal milieu resulting from cancer growth or from the resulting inflammatory response such as tissue pH (acidosis), release of tumour algogens or circulating chemokines and cytokines.[27] These inflammatory events in cancer-neuropathy are likely to be more common and important than in other neuropathies; in these an acute tissue response subsides leaving restricted neuropathic mechanisms within peripheral nerve and the central nervous system. In addition to cancer-induced inflammation, debilitated patients are more likely to succumb to secondary infections such as Herpes-Zoster, bacterial or fungal infections, which may lead directly to neuropathic damage, or additional hypersensitivity.

Neuropathic pain can also arise as a consequence of cancer-directed therapy, such as surgery, radiotherapy and chemotherapy.[28] Drugs such as paclitaxel, vincristine, cisplatin and bortezomib have been widely reported to produce sensory neuropathies, evoking tingling sensations, paraesthesias or numbness in the distal extremities consistent with a glove-and-stocking distribution.[29,30] Neurophysiological examination and nerve biopsies often reveal evidence for axonal degeneration, nerve fibre loss and demyelination.[31] In a phase I trial, patients receiving paclitaxel (Taxol) developed symptoms of neuropathy as early as 1–3 days following treatment.[29] Surgical interventions such as mastectomy, or debulking tumours often results in deafferentation pain. Patients post-mastectomy report a constellation of symptoms including pain or discomfort in the chest wall, surgical scar, upper arm and shoulder, which may be suggestive of intercostobrachial nerve damage and phantom breast sensations.[32] Finally, radiation-induced fibrosis can injure peripheral nerves (e.g. fibrosis of brachial plexus) causing chronic neuropathic pain that begins months to years following treatment.[28]

4. Models of cancer-related neuropathic pain

There are an increasing number of cancer-related neuropathic animal models, although still far fewer than non-cancer-related. These include an array of chemotherapy agents which have clinical neurotoxic effects, such as taxols, platins and the newer bortezomib, and innoculation with tumour cells. Models may vary depending on the species and strains used, tumour types (carcinomas, sarcoma, myelomas) and the methods of innoculation. One limitation is the difficulty in achieving reproducible tumour growth and preventing its spread to multiple organs, which may otherwise result in a severely ill animal precluding the quantitative assessment of pain. In part this is achieved by localized intra-muscular, hind-paw, or nerve roots innoculation. The methods of measuring pain behaviour are taken from validated non-cancer models, which may or may not be appropriate. Although the originating source of pain may differ between malignant (e.g. tumour compression) and non-malignant neuropathic pains (diabetic neuropathy), the mechanisms and neural pathways involved in the generation of the pain state are essentially similar and, as such, much of the underlying pathology is inferred from mechanisms operating in non-malignant neuropathic pain.

5. Direct tumour damage

Murine models of direct inoculation or compatible murine cancer cells have been developed, such as squamous cell carcinoma into the hind paw and heptocellular carcinoma into thigh muscle,[33,34] which result in spontaneous pain behaviour, heat hyperalgesia and mechanical allodynia over varying time courses. Early onset pain behaviour was noted,

1-3 days after innoculation of squamous cell carcinoma cells into the mouse hind paw. However, over 60% of mice died within 16 days post-surgery and metastasis to the lung was apparent.[33] There was no sign of tumour infiltration into the nerve, although plantar nerves were clearly encapsulated by tumour cells, producing substantial compression of nerves and a degree of nerve damage.[33] Direct innoculation of tumour cells close to a nerve results in neuropathy in a well animal. Meth-A sarcoma cells injected around mouse sciatic nerve resulted in the growth of a tumour mass surrounding the nerve and maximum pain behaviours by day 21 post-innoculation, when histological signs of nerve damage were identified.[35] In addition markers of neuronal activation were described with enhanced spinal expression of c-fos and neuropeptides (e.g. Substance P, CGRP, dynorphin A), consistent with behavioural findings.[5] The implantation of mammary adenocarcinoma cells adjacent to the sciatic nerve produced similar pain behaviours in mice for seven days.[36] Some evidence suggests immune infiltration and mild oedema adding inflammatory hypersensitivity to direct cancer nerve damage. In both these sciatic nerve models there is progressive decline in hypersensitivity behaviours, which may be secondary to motor nerve damage. Persistent underlying neuronal hyperexcitability has not been reported.

6. Chemotherapy-related neuropathy

The last decade has seen the introduction of a growing number of animal models of sensory neuropathies induced by antineoplastic agents such as Taxol, used to treat a range of solid tumours. Side effects include myelosuppression (which can be and is treated) and peripheral neuropathy, which to date cannot be prevented and often becomes dose limiting.[37] A pre-sensitization through previous chemotherapy, co-existing diabetic or alcoholic neuropathy (not necessarily painful) have high susceptibility to chemotherapy-related neurotoxicity. The majority of patients receiving Taxol developed signs of neuropathy by three weeks, which preferentially affects the sensory, rather than motor or autonomic nervous system.[38,39] Classically, neurological examination reveals slower sensory conduction velocities, reduced nerve action potential amplitudes and altered H reflexes.[31] Axonal micro-tubule disruption appears to be the primary site of action of Taxol. In a rat model of Taxol-induced neuropathy morphological analysis of the rat sciatic nerves revealed evidence for marked microtubular aggregation.[40,41] By binding to the mitotic spindle tublin, Taxol interferes with microtubule dynamics, arresting cellular division and engaging apoptosis,[42] although whether this triggers painful neuropathy directly is open to debate.

The evidence of degeneration of peripheral nerve axons or dorsal root ganglia (DRG) is contradictory, with some models showing sciatic oedema, no DRG damage with progressive allodynia, while others demonstrate severe damage but no alteration in heat sensitivity.[43,44] Vincristine-induced painful peripheral neuropathies have been shown to be accompanied by nociceptor hyper-responsiveness and alterations within the dorsal horn.[45–47] Both have been shown to penetrate the peripheral nerves and accumulate in the DRG[41], whilst taxol also initiates neuroimmune pro-inflammatory cytokine release (e.g. TNF-alpha). In breast cancer patients, Taxol treatment was accompanied by transient increases in cytokines including IL-8, IL10 and IL-6.[48] These neuroimmune responses may underlie the flu-like symptoms patients experience following therapy with Taxol and additionally could contribute to the development of sensory neuropathy.

With the emergence of Taxol and vincristine-induced models of neuropathy, there has been a growing interest in the molecular, histological and pharmacological analysis of these models.[49] A confounding factor in the animal models of chemotherapy-induced neuropathy is the detrimental effect of the drugs on the animals' general health (e.g. pronounced weight loss, increased mortality). Increasing doses of vincristine (1 – 100mcg/kg/day) were shown to produce increased weight loss in rats, with respiratory complications at higher doses leading to a progressive increase in mortality rate,[49] although subsequent protocols deliver neuropathy with minimal effect on health.[44] The various pathologies observed in animal models: altered pain sensory thresholds, anatomical changes in nerve structure, disruption in nerve conduction, loss of sensory or motor function, represent different stages of chemotherapy-induced neuropathy, which may be considered to be a graded phenomenon.

7. Pharmacological attenuation

There is still limited evidence from animal models regarding the efficacy of different therapeutic agents to treat or prevent chemotherapy-induced cancer pain. Drugs from non-cancer models that suggest an ability to attenuate hyperexcitable neurons may be effective in cancer-related neuropathy. In both Taxol-induced and traumatic nerve injury neuropathies, immunohistochemical observations of an upregulation of the alpha-2 delta subunit of calcium channels has been reported, correlating with allodynia and reversed by gabapentin.[50–52] The efficacy of drugs has been studied extensively in vincristine-induced neuropathy. Some drugs such as ibuprofen, aspirin, celecoxib, desipramine and an NMDA receptor antagonist were ineffective at attenuating allodynia, however venlafaxine, ethosuxamide, lidocaine, pregabalin, lamotrigine, dextromethorphan, gabapentin, acetaminophen, carbamazepine, clonidine and morphine were effective. Morphine exerted dose-dependent reversal of mechanical allodynia with varying efficacies and therapeutic indices. Clonidine and morphine were the most potent and safest.[53–55] Thus, despite differing aetiology, agents used currently for the treatment of peripheral neuropathic pain may have the potential to show demonstrable efficacies in chemotherapy-induced neuropathy.

8. Conclusion

Whilst not strictly a neuropathic injury, cancer induced bone pain (CIBP) is a unique state with features or neuropathy and inflammation. Recent work has demonstrated that osteoclasts damage peripheral nerves (peptidergic C fibres and SNS) within trabeculated bone leading to deafferentation.[56] In addition glia cell activation and neuronal hyperexcitablity within the dorsal horn, are all similar to a neuropathy.[57,58] Gabapentin and carbamazepine (both anti-convulsants that modulate neuropathy) are effective at attenuating dorsal horn

neuronal excitability and normalizing pain like behaviours in a rat model of CIBP.[7] However alterations in neuroreceptors in the dorsal horn do not mimick neuropathy, rather only dynorphin is upregulated, glia cells are active and hypertrophic and c-fos expression is increased post-noxious behavioural stimulus.[57,59] CIBP perhaps best illustrates the complexity of cancer pains. Rarely are they purely neuropathic, inflammatory, ischaemic or visceral rather a combination. Clinically CIBP also demonstrates a hallmark of cancer pain, the presence of disease with no pain at some sites and severe pain at others. It is as yet unclear as to why some areas of cancer growth and destruction induce pain, whilst others do not, and why some become painful with no apparent alteration in the level of damage or tumour load. Loss of central inhibition, neuronal sensitization by circulating cytokines, interleukins, the accumulation of multiple sub-threshold triggers may all contribute. Models of cancer or treatment induced neuropathy are adding to the understanding of the triggers, maintenance and potential role of inflammation (or inflammatory mediators) in these pain states. Interestingly despite the complexity and notable differences between cancer-induced pain states drugs used in non-cancer neuropathy appear to be effective.

Conflict of interest statement

None declared.

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