

## Mechanisms of neuropathic pain

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Neuropathic pain is defined as ‘pain initiated or caused by a primary lesion or dysfunction in the nervous system’.<sup>94</sup> The spectrum of neuropathic pain covers a variety of disease states (Table 1) and presents in the clinic with a variety of symptoms.<sup>145</sup> Neuropathic pain is often reported as having a lancinating or continuous burning character and is often associated with the appearance of abnormal sensory signs, such as allodynia (pain as a result of a stimulus which does not normally provoke pain) or hyperalgesia (an increased response to a stimulus which is normally painful) (Figure 1). The sensory phenomena can be further characterized into static or dynamic sub-types. The mechanistic implication of allodynia is that elements of the sensory nervous system, which normally signal innocuous sensation have begun to encode painful stimuli, whilst in hyperalgesia the structures that sub-serve nociception have become hyperexcitable. Neuropathic pain is an area of largely unmet therapeutic need. The current pharmacological mainstays of clinical management are tricyclic anti-depressants and certain anti-convulsants,<sup>92 119</sup> but these only achieve clinically significant (greater than 50%) pain relief in less than 50% of patients and are associated with sub-optimal side effect profiles. Opioids are generally considered to be less effective in neuropathic pain than in inflammatory pain, with the dose response curve of opioids in neuropathic pain shifted to the right of that for inflammatory pain, although the extent of this difference is controversial.<sup>112</sup>

The majority of research into neuropathic pain mechanisms has concentrated on changes in the peripheral nerve or spinal cord after peripheral nerve injury and, therefore, most available evidence relates to changes in these parts of the nervous system and the review will, therefore, focus on these aspects. Nevertheless, it is important to recognize that

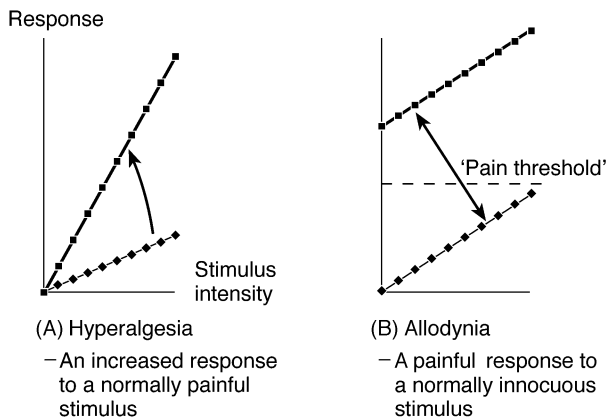
alterations in the brain have also been demonstrated following peripheral nerve injury, but much less is known about the significance of these changes. For example, phantom limb pain has been shown to be associated with re-organization of the cortex of humans.<sup>43</sup> The degree of cortical re-organization, as determined by BTi neuro-magnetic imaging, was linked in a linear fashion to the intensity of pain, with an increase in re-organization being associated with greater pain intensity.<sup>43</sup> A more recent study indicated that cortical re-organization was evident only in patients with phantom limb pain, and not in patients with non-painful phantom limb phenomena or congenital absence of the limb.<sup>44</sup>

### Animal models

In order to identify novel therapeutics for neuropathic pain and, in particular, to design compounds for clinical use in ‘mechanism based’ treatment paradigms it is important to understand the underlying pathophysiology. Unlike inflammatory pain, human volunteer models of neuropathic pain have yet to be developed and animal models are, thus, the mainstay of such research and aspects of these models will be reviewed before a discussion of neuropathic pain mechanisms. Nevertheless, there are a number of shortcomings of these animal models, which need to be considered. In common with all animal models of pain, it is difficult to know what is actually perceived by the animal. However, for neuropathic models, a further drawback is that, in general, alterations in cutaneous sensory thresholds in response to a peripheral nerve injury rather than integrated pain-related behaviour are measured. Therefore, a priority is to develop neuropathic pain models, which also

**Table 1** Traditional aetiological classification of neuropathic pain, with examples. In the future it is possible that this classification may be superseded by symptom or mechanism-based approaches to clinical management. An estimate of the prevalence, in the USA (population 270 million) is given in brackets after each example cited

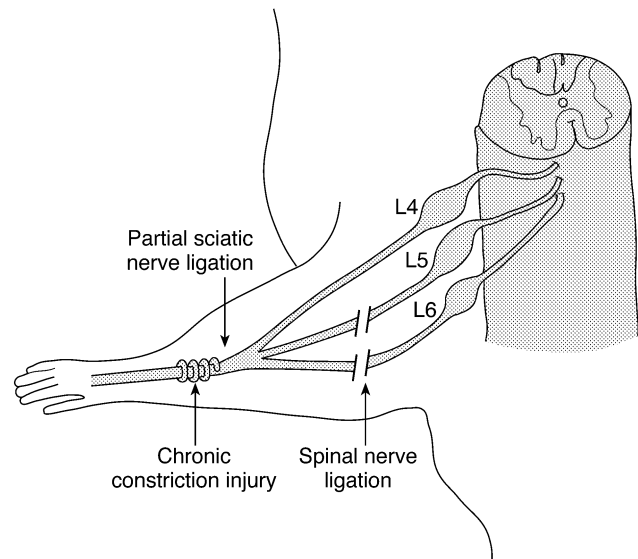
|   |
|---|
| Trauma: phantom limb (50), spinal cord injury (120).                    |
| Ischaemic injury: central pain (30), painful diabetic neuropathy (600). |
| Infection/inflammation: post-herpetic neuralgia (500), HIV (15).        |
| Cancer: invasion/compression of neural structures (200).                |
| Drugs: vinca alkaloids.   |
| Compression: sciatica (2100), trigeminal neuralgia (15).                |
| Unknown: trigeminal neuralgia, MS (51).                                 |



**Fig 1** Graphical representation of hyperalgesia and allodynia: stimulus intensity vs response relationship for noxious and innocuous stimuli.

feature a measurable and repeatable ‘integrated behavioural pain response’. Furthermore, whilst neuropathic pain is a devastating response to nerve injury, it is not the usual consequence, as most patients do not develop neuropathic pain following nerve injuries. However, animal models have been developed to result in a highly reproducible and frequent development of allodynia and hyperalgesia and this does not mirror the ‘normal’ human response to nerve injury. It is, therefore, important to identify the injury and patient factors that dictate whether a human develops pain in response to nerve injury. Finally, for good ethical reasons, most animal models of neuropathic pain study the animals for a period of weeks, whereas the clinical course of neuropathic pain presenting to a pain relief clinic is years.

With these caveats in mind, we must first survey the various animal models of neuropathic pain that have been developed, with simple axotomy being the first widely used model.<sup>138</sup> In this model, the self-mutilation of the injured foot (autotomy) was often observed and interpreted as a response to pain, the authors suggesting an afferent barrage from the neuroma as being crucial in generating autotomy behaviour. More recently, it has been suggested that autotomy occurs in response to the total motor and sensory denervation of the hind-paw rather than pain (for review see<sup>63</sup>). Ethical considerations dictate that autotomy is undesirable as an outcome measure and it is a very rare occurrence with the more recent neuropathic models.



**Fig 2** Schematic drawing of the partial sciatic nerve ligation (tight ligation of 33–50% of the sciatic nerve trunk), CCI (loose ligations of the sciatic nerve trunk), and SNL (tight ligation and transection of the L5 and L6 spinal nerves) animal models of neuropathic pain.

The majority of currently used neuropathic pain models share alterations in hind-limb cutaneous sensory thresholds following partial injury of a peripheral (usually sciatic) nerve as a common feature. In particular, demonstration of hyperalgesia to noxious thermal stimuli and allodynia to cold and mechanical stimuli are used as outcome measures. The three most commonly used models are the chronic constriction injury (CCI) of sciatic nerve,<sup>10</sup> the partial sciatic nerve ligation model (PNL)<sup>116</sup> and the spinal nerve ligation model (SNL)<sup>66</sup> (Figure 2).

The CCI model consists of the loose ligation of the sciatic nerve at mid-thigh level with chromic gut sutures.<sup>10</sup> An inflammatory reaction develops in response to the catgut and consequentially a loss of most A-fibres and some C-fibres, but few cell bodies.<sup>129</sup> This is associated with spontaneous pain-related behaviour, allodynia and hyperalgesia. It has been demonstrated that anti-inflammatory treatments of CCI rats decreases the associated thermal hyperalgesia<sup>135</sup> and so it is speculated that there is a significant inflammatory component in the development of the painful neuropathy. There is a degree of operator variability with this model, particularly in relation to the difference in the tightness of the ligatures. The PNL model also consists of injury to the sciatic nerve at mid-thigh level. In this model, a tight ligation is created around 33–50% of the sciatic nerve, leaving the rest of the nerve ‘uninjured’.<sup>116</sup> This is associated with the development of spontaneous pain-like behaviour, allodynia and hyperalgesia. Although this model is regarded as having less of an inflammatory component than the CCI model, there is still likely to be variability in the actual number of ligated neurones per animal. Also, it is not easy to relate the PNL injury to a

specific DRG or level of the spinal cord as it will be a random mixture of L4 and L5 spinal nerve afferents which are injured. The SNL model consists of injury to the L5 and L6 spinal nerves, which contribute to the sciatic nerve.<sup>66</sup> Once again, this is associated with the development of spontaneous pain-like behaviour as well as long lasting allodynia and hyperalgesia. The authors demonstrated that a tight ligation of the L5 spinal nerve only resulted in comparative symptoms to the L5 and L6 ligation group and hence some experimenters now use this as a modified SNL model.<sup>15</sup> This model is conducive to examination of cellular responses to the injury at the DRG level as the L5 and L6 DRGs will be affected, but the L4 DRG will not, and this allowed investigation into the importance of input from uninjured afferents in neuropathic pain.<sup>80</sup>

A direct comparison of these three models has been reported.<sup>65</sup> In this study, the authors demonstrated a similar onset of sensory threshold changes in mechanical and cold allodynia in all three models, but a greater magnitude of change in sensory thresholds in SNL. All three models demonstrated significant cold and mechanical allodynia at 3 days after injury and spontaneous pain at one day after injury. Mechanical allodynia was determined by the application of an 8.4 mN Von Frey hair. The allodynia was greatest in the SNL model with an ~80% response frequency, followed by PNL (~60% response frequency) and CCI (~45% response frequency). They also demonstrated a more significant involvement of the sympathetic nervous system component in the sensory response to SNL than following PNL or CCI.

A more recent development of the hind-limb peripheral nerve injury models has been a description of the sequelae of injury to the terminal branches of the sciatic nerve. Decosterd and Woolf described a spared nerve injury model involving tight ligation and lesion of the tibial and common peroneal nerves, leading to robust sensory threshold changes to mechanical, thermal, and cold stimuli.<sup>28</sup> Further studies investigated more closely the importance of injury to each branch in the development of behavioural signs of neuropathy, namely mechanical and cold allodynia and spontaneous pain.<sup>75</sup> This study demonstrated that the largest change in sensory thresholds was initiated by injury to the tibial and sural nerves, leaving the common peroneal nerve intact. This model allows testing of distinct regions of the hind-paw which are either innervated by injured or uninjured neurones, as well as separating degenerating neurones from uninjured neurones to a greater level. A further model exploiting injury to the sciatic nerve is a photochemical/laser irradiation model. The sciatic nerve is subjected to an ischaemic injury as a result of laser activation of a systemically administered photosensitive dye resulting in a thrombosis within the nerve because of a photochemical reaction. This model was originally described for the study of direct spinal cord injury<sup>150</sup> before being adapted to become a peripheral nerve injury model.<sup>73</sup> This model has been described as having good reproduc-

bility statistics, as well as a quantifiable degree of nerve injury. However, this model has not been widely adopted, presumably because of the expenses of lasers.

The majority of animal models of neuropathy have been based on a discrete peripheral nerve injury. However, some have been developed to more closely mimic individual disease states. An example of this is the streptozotocin model of peripheral diabetic neuropathy.<sup>85</sup> In this model, a single injection of streptozotocin induces diabetes and then hyperalgesia and allodynia. This model has been used extensively in the testing of new pharmaceuticals such as gabapentin,<sup>41</sup> however, the influence of the ill health of the rats *per se* (as opposed to neuropathy) on sensory thresholds has been questioned.<sup>45</sup> A further example, described by Idanpaan-Heikkila and Guilbaud, uses a CCI of the infraorbital branch of the trigeminal nerve as a model for trigeminal neuralgia.<sup>58</sup> A model of acute herpes zoster has been reported, which may offer some insight into the mechanism of acute zoster pain and possibly post-herpetic neuralgia.<sup>42</sup> Takasaki and colleagues have also demonstrated that, in comparison with herpes simplex in humans, herpes simplex virus type-1 induces allodynia and hyperalgesia in infected rats.<sup>128</sup>

The majority of neuropathic pain models were originally described in rats, but more recently the PNL model has been adapted to the mouse,<sup>86</sup> as has the photochemically induced ischaemia model.<sup>51</sup> The translation of these models from rat to mouse is important as novel transgenic tools, useful for the study of neuropathic pain, are developed further. However, mice are not merely small rats and often respond in a quantitatively and qualitatively different manner to an insult, and the translation of pain models from rats to mice is more than simply an adaptation of surgical techniques. Other developments in genetics could be exploited to enhance understanding of painful neuropathy. For example, one such approach described the induction of mutants identified in inherited peripheral neuropathies into mice.<sup>89</sup>

## Mechanisms of neuropathic pain

A variety of pain-related phenomena, both central and peripheral, have been associated with peripheral nerve injury (Fig. 3). These are generally not mutually exclusive and it is entirely possible that any one of these (or more likely a combination) contribute to symptomatology in individual patients suffering from neuropathic pain. It is, therefore, inappropriate to attempt to generate a unifying hypothesis of pathophysiology for all neuropathic pain states. The next challenge is to diagnose which of these phenomena may be operative in an individual patient and to interpret each symptom within the mechanistic framework arising from work with neuropathic pain models. In this regard, neuropathic pain is ideally suited to the mechanistic based treatment of chronic pain recently proposed.<sup>145</sup>

## Peripheral mechanisms

### Ectopic discharges and ephaptic conduction

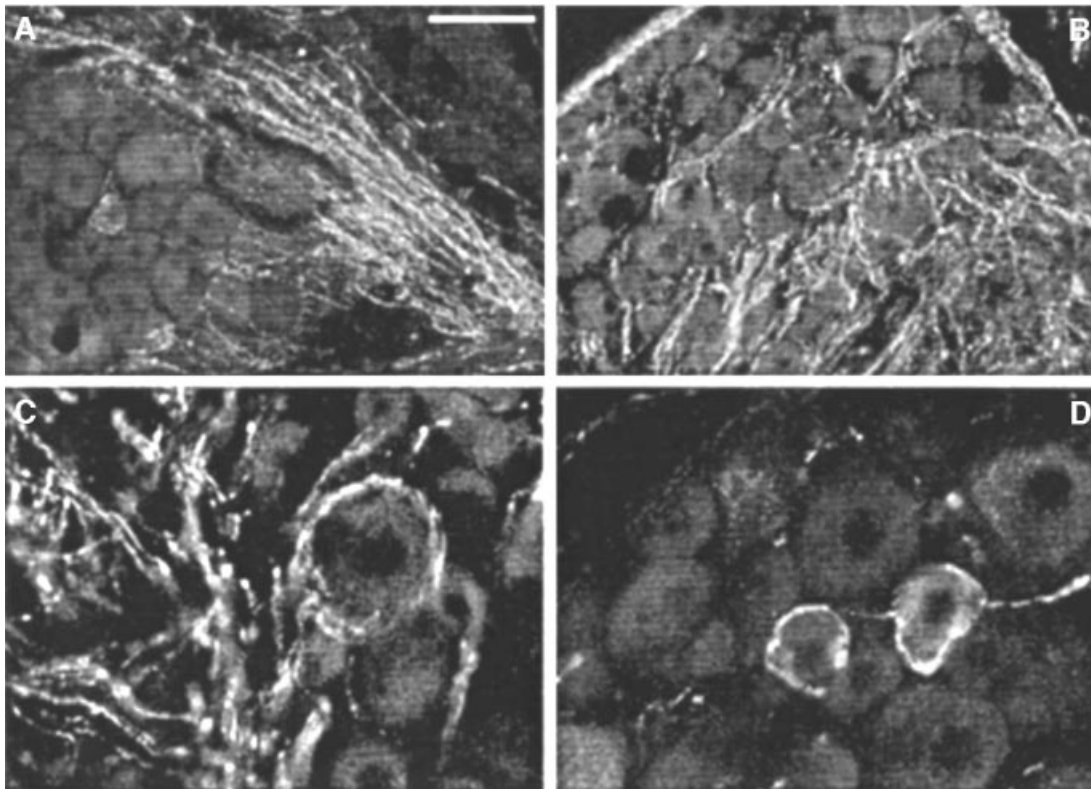
In normal primary afferent neurones, it is rare for firing threshold to be reached without the input of a stimulus. However, following a nerve injury, it has been demonstrated that there is a large increase in the level of spontaneous firing in the afferent neurones linked to the injury site (Fig. 4).<sup>139</sup> This has been termed ectopic discharge and has also been demonstrated in humans, suffering from neuropathic pain. A microneurographic investigation of phantom limb pain patients examined the site of origin of the ectopic

discharge and demonstrated that whilst the pain and discharge evoked by tapping the neuroma were locally initiated, the spontaneous pain and discharge were not.<sup>99</sup> However, there has been criticism of the techniques used to glean this information.<sup>110</sup> Because of the practical problems of recording from humans, most of the studies have been carried out in animal models. Ectopic discharges were originally described as arising in the neuroma itself.<sup>139</sup> However, further studies revealed that some ectopic discharges could also originate from the DRG and other points along the nerves.<sup>137</sup> Having demonstrated the presence of ectopic firing in peripheral nerve injury animal models, as well as in human patients, it is important to investigate the cause of these discharges.

A small number of A-fibres (10%) exhibit sub-threshold membrane oscillations in their resting state or under depolarization conditions.<sup>81</sup> Following SNL, this was seen to increase to 23% at 9 days post-operation. A similar increase in membrane oscillations of both A- and C-fibres was also seen by Amir and colleagues.<sup>5</sup> This increased oscillatory behaviour leads to an increase in ectopic firing as the oscillations more frequently reach threshold and subsequent 'cross-excitation' of other neurones serves to amplify this effect. As the DRG neurones are all effectively isolated from each other, cross-talk or ephapsis is unlikely to normally occur within the DRG and does not do so after

| Peripheral effect  | Central effects   |
|--|---|
| <ul style="list-style-type: none"> <li>• Ectopic and spontaneous discharge</li> <li>• Ephaptic conduction</li> <li>• Alterations in ion channel expression</li> <li>• Collateral sprouting of primary afferent neurones</li> <li>• Sprouting of sympathetic neurones into the DRG</li> <li>• Nociceptor sensitization</li> </ul> | <ul style="list-style-type: none"> <li>• Central sensitization</li> <li>• Spinal reorganization</li> <li>• Cortical reorganization</li> <li>• Changes in inhibitory pathways</li> </ul> |

**Fig 3** Summary of the phenomena which have been observed in the central and peripheral nervous system after experimental peripheral nerve injury, which may contribute to neuropathic pain.



**Fig 4** Tyrosine hydroxylase immunoreactivity within the DRG showing post-ganglionic sympathetic fibre invasion after sciatic nerve axotomy (A) and intrathecal administration of NGF (B). Higher power magnification shows the distinct 'basket' structures surrounding sensory cell bodies (C), (D). Adapted from Jones and colleagues.<sup>62</sup>

**Table 2** Summary of the properties of those sodium channels preferentially expressed by primary sensory neurones and how these properties alter after inflammation or peripheral nerve injury. \*NB redistribution from DRG

|           | TTX sensitivity | Normal DRG expression | Growth factor dependence | Inflammation | Neuropathy |
|-----------|-----------------|-----------------------|--------------------------|--------------|------------|
| SNS2/ NaN | Resistant       | Yes                   | GDNF                     | ↑            | ↓          |
| III       | Sensitive       | No                    | ?                        | X            | ↑          |
| SNS/ PN3  | Resistant       | Yes                   | NGF                      | ↑            | ↓*         |

nerve injury.<sup>34</sup> However, chemically mediated cross-excitation has been shown to occur in the DRG.<sup>3</sup> Cross-depolarization has been demonstrated to occur following tetanic stimulation in most (90%) neurones within the DRG.<sup>134</sup> This depolarization is transient following neighbouring cell stimulation and is sub-threshold for eliciting an action potential.<sup>3</sup> However, as has been discussed, following peripheral nerve injury, many DRG neurones exhibit alterations in their membrane potential to bring them closer to the firing threshold. It is, therefore, possible that the cross-excitation will then be sufficient to evoke ectopic firing. It is important to note that there is no increase in the level of cross-excitation itself in response to nerve injury, just in the excitability of the DRG.<sup>82</sup> A more recent study has demonstrated evidence of cross-excitation between A- and C-fibres.<sup>4</sup>

These observations suggest that the development of ectopic activity may be particularly important for the development of hyperalgesia, allodynia and ongoing pain associated with nerve injury. Clinical observations suggest that ectopic activity is responsible for ongoing neuropathic pain.<sup>49</sup> It is now recognized that two populations of afferent fibres develop ectopic activity following nerve injury, the injured sensory neurones themselves and their uninjured neighbours.<sup>48</sup> To what degree each population is responsible for the maintenance or initiation of neuropathic pain is currently under debate. Support for a major role of injured afferents comes from the work of Sheen and Chung<sup>117</sup> who used the SNL model of neuropathic pain, ligation of the L5 and L6 spinal nerves. They reported that cutting the dorsal roots of injured segments eliminated pain behaviours. Three other recent studies have demonstrated a direct correlation in the time course of behavioural changes following spinal nerve injury with that of ectopic activity in A-fibres that gives support to the 'injured afferent' hypothesis.<sup>67 82 83</sup> Note that changes in ectopic C-fibre activity only occur 3–4 weeks following axotomy and may persist for many weeks following injury.<sup>31</sup>

Evidence has also been obtained that signals in uninjured neighbouring afferents have a role in the development of neuropathic pain behaviours. Using a modified spinal SNL model, Yoon and colleagues<sup>154</sup> and Li and co-workers<sup>80</sup> showed that an L4 rhizotomy would abolish pain behaviours evoked by L5 SNL. This suggests that the signals involved in pathological nociception arise from the intact neurones. It

is important to bear in mind, therefore, that pain arising as a result of peripheral nerve damage may reflect activity in both damaged as well as intact sensory neurones.

Sodium channels are critical to the physiology of excitable membranes, including neuronal membranes. One important finding of potential significance to the generation of ectopic firing is alterations in the expression of sodium channels in the cell bodies and the terminal neuroma of peripheral nerves following nerve injury (summarized in Table 2). In 1989, Devor and colleagues demonstrated the accumulation of Na<sup>+</sup> channels in the neuroma of cut sensory axons<sup>32</sup> and then demonstrated that the Na<sup>+</sup> channels were the cause of ectopic discharge.<sup>90</sup> However, molecular biology has since revealed that there are many different and distinct voltage-gated Na<sup>+</sup> channels, of which at least six are expressed on the cell bodies of primary afferent neurones within the DRG.<sup>141</sup> These can be further split into tetrodotoxin (TTX)-sensitive and TTX-resistant sub-types. TTX-sensitive channels are expressed throughout the central nervous system, and predominantly in A-fibres within the DRG. TTX-resistant channels are found only within a subset of primary afferent neurones of the DRG, specifically in the smaller C-fibres associated with nociception.<sup>2</sup> Following peripheral nerve injury, it has been demonstrated that there is a re-organization of the nature and levels of expression of the various channels.<sup>142</sup> The expression of some sodium channels sub-types in DRG cell bodies is diminished following nerve injury, whilst others appear *de novo* and others translocate to different parts of the neurone. More specifically, there is an up-regulation of type III TTX-sensitive channel gene expression (these are not normally expressed by DRG cells),<sup>142</sup> and a down-regulation of SNS (aka PN3) and NaN (aka SNS2) TTX-resistant channels gene expression.<sup>36</sup> This has been demonstrated to occur both after axotomy<sup>36 142</sup> and after CCI with a 40% decrease in SNS and NaN mRNA after CCI.<sup>37</sup> The SNS channel expression appears to translocate from the cell body to the neuroma, which may explain the hypersensitivity of the neuroma. These findings were corroborated in an immunohistochemical study (for NaN and SNS) of tissue taken from patients suffering from chronic neuropathic pain after traumatic brachial plexus avulsion.<sup>24</sup> Another study investigated the changes in SNS/PN3 and SNS2/NaN TTX-resistant Na<sup>+</sup> channels in injured human sensory nerves.<sup>153</sup> This demonstrated degradation products of the

SNS2/NaN and an increase in SNS/PN3 expression in injured nerves localized close to the injury site and within the neuroma.

There is also supportive evidence for these findings from electrophysiological studies. Cummins and Waxman demonstrated that, after axotomy of the sciatic nerve, there was a reduction in the density of TTX-resistant currents within the DRG.<sup>26</sup> This study also demonstrated no increase in TTX-sensitive current density after axotomy, but an increase in the repriming speed of these currents, up to four times faster. Similar experiments in the CCI model of neuropathy demonstrated the same reduced density of TTX-resistant currents, and also demonstrated a shift in the voltage dependence of activation to a more negative potential.<sup>37 72</sup>

The mechanism contributing to the changes in Na<sup>+</sup> channel expression in peripheral nerve injury is unclear, but neurotrophin supply appears to be a crucial factor. It has been shown that DRG neurones in culture will increase expression of type III channel expression and decrease SNS channel expression in the absence of NGF.<sup>13</sup> NaN channel expression is similarly reliant on another growth factor, for example, glial-derived neurotrophic factor (GDNF). It seems clear that the decrease in SNS2/NaN expression, the relocation of SNS/PN3 channel expression and the *de novo* synthesis of type III channels are central in the spontaneous generation of action potentials. These changes in DRG following peripheral nerve injury suggest a contribution to neuronal hyperexcitability from sodium channels and this Na<sup>+</sup> channel-induced hyperexcitability is likely to manifest itself as an increase in ectopic firing, because of the rapid repriming and lower resting thresholds. It is likely that the rapidly repriming, normally silent, type III TTX-sensitive channel has a significant role to play in this, and this is supported by low dose TTX studies. Omana-Zapata and colleagues demonstrated in axotomized rats that i.v. TTX produced dose-dependent inhibition of ectopic activity.<sup>100</sup> Similarly, Lyu and colleagues demonstrated that topically applied, at the DRG level, sub-action potential blocking levels of TTX reduced mechanical allodynia in the SNL model.<sup>84</sup> The sodium channel blocker lidocaine has also been demonstrated to be of some benefit in neuropathic pain treatment,<sup>8</sup> but currently available sodium channel blockers do not, by and large, discriminate between the different types of channel and are, therefore, associated with potentially lethal side-effects. Tailoring novel compounds to specifically act at the sodium channels implicated in neuropathic pain may represent a significant therapeutic advance.

Sodium channels are not the only voltage-gated channels, which are altered following peripheral nerve injury. Calcium channels have also been shown to influence the generation of hyperalgesia and allodynia. Specific antagonists for neuronal N-type Ca<sup>2+</sup> channels have been shown to reduce heat hyperalgesia and mechanical allodynia in the CCI model when administered directly to the site of nerve

injury.<sup>149</sup> Further studies then demonstrated that subcutaneous administration of an N-type, but not P- or Q-type, Ca<sup>2+</sup> channel antagonist attenuated mechanical hyperalgesia in the PNL model of neuropathic pain, suggesting a local effect of N-type Ca<sup>2+</sup> channels in the generation of hyperalgesia.<sup>143</sup> This alteration of Ca<sup>2+</sup> currents after peripheral nerve injury has also been demonstrated electrophysiologically.<sup>7</sup> More specifically, N-type current measured in the DRG was seen to decrease after axotomy, with no significant change in P- or Q-type currents. Cannabinoids CB<sub>1</sub> receptor agonist attenuate Ca<sup>2+</sup> flux at N-type channels<sup>103</sup> and we have recently demonstrated that the synthetic cannabinoid Win 55,212-2 attenuates thermal hyperalgesia and mechanical and cold allodynia in the SNL model of painful neuropathy via the CB<sub>1</sub> receptor.<sup>15</sup> Furthermore, the anti-convulsant gabapentin binds to the  $\alpha_2\delta$  sub-unit of calcium channels<sup>46 130</sup> and is effective in relieving allodynia and hyperalgesia in animal models and neuropathic pain in man.<sup>1 101 113</sup>

The changes in both Na<sup>+</sup> and Ca<sup>2+</sup> channels detailed above are important in neuropathic pain. The *de novo* synthesis of rapidly repriming III channels, down-regulation of TTX-resistant Na<sup>+</sup> channels and loss of high-voltage activated N-type Ca<sup>2+</sup> channels seen in response to peripheral nerve injury, increases the excitability of the neurones. This in turn will lead to an increase in firing susceptibility and frequency, possibly resulting in not only spontaneous pain, but also central sensitization as discussed later.

#### *Collateral sprouting*

Sprouting of collateral fibres from sensory axons in the skin into denervated areas has been described following nerve crush injuries.<sup>33</sup> Sprouting was also observed from the saphenous nerve in the CCI model.<sup>111</sup> This sprouting occurred at around 10 days post-operation, but the degree of sprouting was not proportional to the degree of hyperalgesia after chronic sciatic section.<sup>68</sup> These results indicate that collateral sprouting is unlikely to contribute significantly to the pain behaviour seen in this model. The sprouting was effectively blocked by the administration of anti-NGF<sup>35</sup> and it is, therefore, likely that a local release of NGF from sources within the skin (keratinocyte, immune cells) is responsible for axon sprouting under these circumstances.

#### *Coupling between the sympathetic nervous system and the sensory nervous system*

Clinicians have observed for many years that in a small subset of patients suffering from neuropathic pain, the pain is somewhat dependent on activity in the sympathetic nervous system. This is often referred to as 'sympathetically maintained pain' and, for example, some patients suffering from complex regional pain syndrome type 1 (CRPS1) can be classified as having sympathetically maintained pain. It has recently been demonstrated that an abnormal contact develops between the sympathetic nervous system and the

sensory nervous system following peripheral nerve injury, which may underlie the enhanced sensitivity to catecholamines which some patients with neuropathic pain develop.<sup>61</sup> The key question is how and where does the sympathetic nervous system become coupled to the sensory nervous system to produce the pain observed in the clinical situation? The basic observation must be that activity in the sympathetic nervous system initiates abnormal impulse traffic in sensory neurones that leads to pain perception. Several sites of coupling between sensory and sympathetic nervous systems have been proposed and tested in animal models. The following have received experimental support.

1. Direct chemical coupling within peripheral effector sites between the noradrenergic and sensory neurone terminals.<sup>102</sup>

2. Ephaptic nerve coupling. Observed between sensory fibres in a damaged nerve but not so far between sympathetic and sensory fibres.<sup>14</sup>

3. Indirect coupling via peripheral sensitizing mechanisms involving the release of inflammatory mediators from sympathetic terminals and the sensitization of primary sensory neurone axons.<sup>78</sup>

4. Direct coupling between the sympathetic nervous system and the sensory nervous system in the dorsal root ganglion.

This latter possibility has received much attention recently with numerous studies demonstrating that peripheral nerve injury leads to sympathetic sprouting in the DRG (Fig. 4). McLachlan and colleagues described sprouting of noradrenergic perivascular sympathetic axons into the DRG following ligation of the sciatic nerve.<sup>91</sup> These axons were observed to form baskets around the large diameter neurones, leading to the possibility of sympathetic input being able to activate the neurones. Sympathetic sprouting has also been demonstrated following SNL<sup>19</sup> and CCI<sup>108</sup> models. In the McLachlan study, onset of sprouting occurred around 21 days after nerve injury, whereas Chung and others described visualization of sympathetic sprouts after 3 days which was maintained for up to 20 days before declining gradually.<sup>20</sup> It should be noted that onset of behavioural signs of neuropathy in SNL are developed by 3 days post-surgery. This study also demonstrated elimination of the majority of sprouting following sympathectomy, confirming that the sprouts were sympathetic post-ganglionic fibres. A direct comparison of the sympathetic sprouting in CCI, PNL, and SNL was performed<sup>76</sup> and demonstrated a similar pattern of sprouting in CCI and PNL, with an onset after 2 weeks, but a more rapid onset of within 1 week of SNL.

The mechanism for onset of the sympathetic sprouting is unclear. It is likely, however, that neurotrophic factors and cytokines linked to Wallerian degeneration are crucial to the process. Wallerian degeneration results in an increase of a large variety of cytokines and growth factors in the local milieu. Thompson and Majithia demonstrated the ability of the cytokine leukaemia inhibitory factor (LIF) to stimulate

sympathetic sprouting, akin to that seen in peripheral nerve injury, in non-nerve injured animals.<sup>132</sup> In previous studies, the neurotrophin nerve growth factor (NGF) has been demonstrated as being able to induce sympathetic sprouting in the CNS<sup>59</sup> and this led to the investigation of the role of NGF, and GDNF, in sympathetic sprouting in DRG.<sup>62</sup> This study demonstrated that exogenously applied NGF, but not GDNF, to uninjured rats resulted in sympathetic sprouting reminiscent of that in CCI rats. Also demonstrated, was that sequestration of endogenous NGF at the injury site did not reduce sprouting. This suggests a mechanism of sprouting involving the direct action of NGF at the level of the DRG, a theory supported by raised NGF mRNA levels in the DRG following sciatic nerve injury.<sup>115</sup> These studies have proposed some potential mechanisms for sympathetic sprouting in the DRG (see<sup>109</sup> for review).

Sprouting has been described in many animal models of peripheral nerve injury, but what are the consequences of such sprouting? The terminals of the sprouted neurones have been shown to form functional synapse-like structures with the cell bodies.<sup>91</sup> These structures could be involved in the formation and maintenance of abnormal excitation arising from the DRG, a hypothesis supported by electrophysiological studies in which sympathetic stimulation increased sensory ectopic discharge from the DRG.<sup>31</sup> As both sympathectomy<sup>118</sup> and guanethidine,<sup>98</sup> a noradrenergic depleting agent, have been demonstrated to relieve hyperalgesia in peripheral neuropathy models, it is fair to assume that these functional interactions have some importance in the sympathetically maintained pain subgroups of neuropathic pain patients. Sympathetic blocks have been used in treatment of neuropathic pain,<sup>148</sup> although adequately controlled data are not available to help fully determine the efficacy of this approach. With the time-scale of sprouting corresponding with the onset of behavioural signs of both hyperalgesia and allodynia, block of the input from these fibres, or more difficultly, prevention of sprouting has potential to reduce sympathetically maintained pain in neuropathic patients.

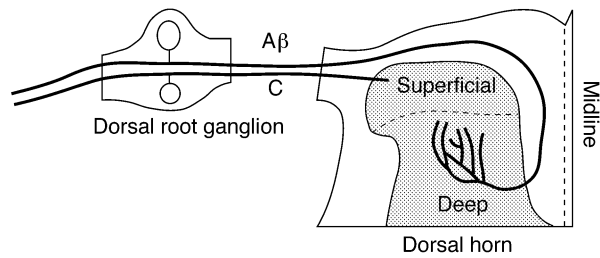
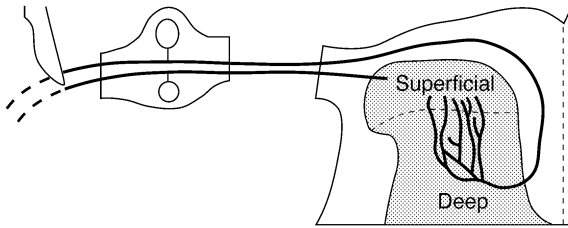
#### *Bradykinin*

There is an alteration in expression of bradykinin binding sites within dorsal root ganglion neurones after axotomy.<sup>104</sup> Bradykinin has been shown to play an important role in the hyperalgesia associated with inflammatory pain states.<sup>39</sup> Petersen and colleagues showed an increase in bradykinin binding sites at 2 days post-axotomy, suggesting a potential role for bradykinin antagonists in the treatment of neuropathic pain, specifically to combat hyperalgesia.<sup>104</sup>

### *Central mechanisms*

#### *Spinal cord—anatomical re-organization*

There is a considerable degree of re-organization of spinal cord in response to peripheral nerve injury (Fig. 5). Under normal physiological conditions, different classes of

**Normal terminations of primary afferents in the dorsal horn****After nerve injury, C-fibre terminals atrophy and A-fibre terminals sprout into the superficial dorsal horn**

**Fig 5** Schematic representation of reorganization of the spinal dorsal horn which is observed after peripheral nerve injury. After the peripheral nerve injury the unmyelinated primary afferent neurones which normally sub-serve nociception and terminate in the superficial dorsal horn degenerate. This allows the larger myelinated primary afferent neurones, which normally sub-serve innocuous sensory modalities, to sprout into the superficial dorsal horn from the laminae deeper in the dorsal horn which normally receive their central terminations. This observation allows some insight into the mechanisms of allodynia. (Adapted with permission from Woolf and Mannion.<sup>145</sup>)

primary afferent neurone fibres terminate in specific laminae of the dorsal horn. As a generalization, the nociceptive small diameter cells with myelinated  $A\delta$ -fibres and unmyelinated C-fibres terminate in the superficial laminae (I and II) of the dorsal horn whilst the large diameter neurones with myelinated  $A\beta$ -fibres terminate in laminae III and IV. Lamina V is a region of convergence of inputs. Woolf and colleagues demonstrated that after sciatic nerve axotomy, the central terminals of the large myelinated primary afferent neurones sprouted into lamina II of the superficial horn.<sup>146</sup> Koerber and colleagues also showed a sprouting of  $A\beta$ -fibres into lamina II of the superficial dorsal horn after peripheral axotomy.<sup>69</sup> Woolf and co-workers then demonstrated that this sprouting occurred within 1 week post-axotomy, was at its highest 2 weeks post-axotomy and persisted over 6 months post-axotomy.<sup>147</sup> The authors also demonstrated that this sprouting persisted beyond periods of peripheral nerve regeneration. One consequence of this synaptic rearrangement is that second-order neurones within the spinal cord, that normally receive predominantly high-threshold sensory input, begin to receive inputs from low-threshold mechanoreceptors. This misinterpretation of information within the spinal cord may result in low-threshold sensory information being interpreted as nociceptive, thus, providing another explanation for the emergence of allodynia after peripheral nerve injury.

The mechanisms responsible for this sprouting have been investigated. Bennett and colleagues investigated whether the intrathecal administration of either NGF, NT-3, or BDNF after sciatic nerve axotomy prevented such sprouting.<sup>9</sup> It was observed that NGF, but not NT-3 or BDNF was able to prevent the sprouting of the  $A\beta$ -fibres into lamina II.<sup>9</sup> Coupled with a study demonstrating that C-fibre degeneration after treatment with capsaicin was associated with a pattern of staining of  $A\beta$  sprouting indistinguishable from that of axotomy,<sup>87</sup> the authors concluded that the rescue of C-fibres by NGF was responsible for the prevention of  $A\beta$  sprouting. By inference, the normal retrograde supply of NGF to the cell body was necessary to maintain the normal laminar distribution of terminals within the spinal cord. Complete sciatic nerve axotomy does not result in the same pattern of hyperalgesia or allodynia observed in other animal models of neuropathic pain. As a result, Lekan and colleagues investigated the  $A\beta$ -fibre sprouting in the SNL model of neuropathic pain and established a robust sprouting of  $A\beta$ -fibres at 2 and 4 weeks post-surgery,<sup>77</sup> suggesting a similar mechanism to the axotomy studies. However, one note of caution needs to be considered when interpreting these sprouting studies. Hökfelt and colleagues demonstrated that the marker (cholera toxin  $\beta$  sub-unit) used to selectively image  $A\beta$ -fibres may also be taken up by C-fibres after peripheral nerve injury, but the full significance of this finding remains to be elucidated.<sup>133</sup>

The functional significance of this sprouting needs to be considered. C-fibres normally innervate lamina II and are responsible for nociceptive signalling, whilst  $A\beta$ -fibres are large fast conducting neurones that sub-serve low-threshold non-noxious inputs. Therefore, if the  $A\beta$ -fibres sprout into lamina II, and establish functional synaptic contact with second-order neurones, then low-threshold non-noxious inputs from the  $A\beta$ -fibres can be interpreted as nociceptive in origin. This would be a plausible explanation for allodynia, a hypothesis supported by electrophysiological data: recordings from dorsal horn neurones in a rat transverse spinal cord slice were examined. In normal rats, lamina II cells exhibited long-latency responses to high-threshold nerve stimulation. However, after sciatic nerve section, and subsequent sprouting of  $A\beta$ -fibres into lamina II, 54% of the activity in lamina II were initiated by low-threshold stimulation and the majority exhibited short-latency responses reminiscent of those in lamina III of normal rats.<sup>70</sup> However, it should be noted that optimal sprouting does not occur until 2 weeks post-injury and so cannot be solely responsible for the allodynia observed in neuropathic models.

*Spinal cord—hyperexcitability*

In a similar fashion to persistent inflammation, the afferent barrage associated with peripheral nerve injury is associated with the development of a sustained state of hyperexcitability of dorsal horn neurones, a process dubbed 'central



sensitization'.<sup>21 136</sup> In addition to events such as lowering of activation thresholds of spinal neurones, central sensitization is characterized by the appearance of 'wind-up'.<sup>93 140</sup> (For review see<sup>38</sup>.) Wind-up is characterized by an increasing response to repeated C-fibre volleys, and may contribute to hyperalgesia. However, the exact relationship of the relatively short lived phenomenon of wind-up and the persistent state of central sensitization remains to be fully elucidated.<sup>79 144</sup> Electrophysiological data demonstrated that about 90% of dorsal horn neurones studied in the lumbar enlargement of the spinal cord exhibited abnormal characteristics after CCI.<sup>74</sup>

Study of the pharmacology of central sensitization may open the door for novel analgesics effective in neuropathic pain. The excitatory amino acid glutamate is the major excitatory neurotransmitter released at the central terminals of primary afferent nociceptive neurones after noxious stimulation. Whilst glutamate acts at a number of post-synaptic receptors, a large body of evidence suggests that the ionotropic NMDA sub-type is the most intimately involved in both inflammation and nerve injury-induced central sensitization (see<sup>38</sup>). Removal of an Mg<sup>2+</sup> dependent ion channel block and receptor phosphorylation are critical events in 'activating' the NMDA receptor so that glutamate is able to exert its effects. NK1 (substance P), AMPA (glutamate), and trkB (BDNF) receptors are all involved in this permissive process.<sup>131</sup>

A number of lines of evidence suggest that NMDA receptor antagonists may have a role in attenuating features of neuropathic pain. First, glutamate concentration increases in the ipsilateral dorsal horn after CCI.<sup>64</sup> Davar and colleagues described the prevention of hyperalgesia development in the CCI model by continual pre- and post-injury i.p. administration of the NMDA receptor antagonist MK-801.<sup>27</sup> Mao and others described a reduction in hyperalgesia in the same model at a lower dose of MK-801 and also demonstrated the dose-dependent anti-hyperalgesic effect of intrathecally administered MK-801 3 days post-injury.<sup>88</sup> Electrophysiological data also demonstrates that MK-801 significantly reduces the hyper-responsiveness to noxious stimulation after peripheral nerve injury.<sup>123</sup> Interestingly, the authors found that MK-801 had no effect on the frequency of ectopic baseline firing (spontaneous pain), suggesting that this is not mediated through central NMDA receptors.

Glycine is recognized as a modulator of the agonist action of glutamate at the NMDA receptor.<sup>23</sup> This has led to investigation of the anti-nociceptive effects of antagonists to the glycine modulatory site of the NMDA receptor. Quartaroli and colleagues described the efficacy of a glycine site antagonist in preventing the development of hyperalgesia in the CCI model and attenuating wind-up in isolated spinal cord neurones.<sup>106</sup> Co-administration of a glycine/NMDA receptor antagonist and morphine has also been demonstrated to attenuate pain behaviour in an animal model of trigeminal neuralgia.<sup>18</sup> In human neuropathic pain,

ketamine, an NMDA receptor antagonist has been used to successfully treat neuropathic pain in some patients,<sup>107</sup> suggesting a place in therapy for NMDA antagonists and an area in which more investigation should be performed.

The mechanism by which NMDA receptors contribute to maintenance of central sensitization should also be discussed. After peripheral neuropathy, both an increase in excitatory amino acids and [Ca<sup>2+</sup>]<sub>i</sub> were observed to occur in an NMDA receptor dependent manner.<sup>64</sup> This suggests that initial NMDA receptor activation contributes to the increased levels of glutamate and aspartate, representing a continual positive feedback loop which maintains sensitization. The increased [Ca<sup>2+</sup>]<sub>i</sub> could also form a positive feedback loop, potentially through indirect activation of protein kinase C (PKC), a hypothesis supported by the anti-allodynic effect of a PKC inhibitor in the SNL model of neuropathic pain.<sup>56</sup>

The  $\gamma$ -aminobutyric acid (GABA) pathway forms a major inhibitory neurotransmitter system in the CNS. Suppression of this pathway by the GABA<sub>A</sub> receptor antagonist bicuculline is associated with a dose-dependent allodynia<sup>152</sup> and GABA receptor levels in the spinal cord are decreased within 2 weeks of sciatic nerve axotomy,<sup>17</sup> probably as a result of degeneration of the primary afferent neurone terminals on which the receptor is localized.<sup>16</sup> This suggests a role for GABA in modulating the response to peripheral nerve injury, and Sivilotti and Woolf hypothesized that central sensitization might be contributed to by a decrease in the efficacy of GABA pathways.<sup>120</sup> The GABA<sub>B</sub> agonist baclofen is anti-nociceptive in naïve animals, but its potency increases 3-fold in the CCI model of neuropathic pain.<sup>121</sup> More recently, Hwang and Yaksh demonstrated a dose-dependent attenuation of SNL associated allodynia, mediated via both GABA<sub>A</sub> and GABA<sub>B</sub> receptors, after intrathecal administration of GABA receptor agonists.<sup>57</sup> Stiller and colleagues were able to measure the concentration of extracellular GABA concentrations in normal and nerve injured rats and established a significant decrease in extracellular GABA concentrations in the nerve injured rats exhibiting allodynia, but a much smaller decrease in non-allodynic rats.<sup>126</sup> They then demonstrated that spinal cord stimulation, a potential therapy in humans, increased the levels of GABA in allodynic rats and that this in turn attenuated the release of EAA's in the dorsal horn.<sup>25</sup> These studies again indicate a role for decreased efficacy of GABA pathways in neuropathic allodynia.

A separate inhibitory pathway in the CNS is that of the purinergic system, including specifically adenosine. Adenosine exhibits both pre-<sup>114</sup> and post-synaptic actions and could produce anti-nociception by indirect interaction with EAA release.<sup>22</sup> Levels of circulating adenosine within the blood and CSF of neuropathic, non-neuropathic nerve lesioned and control humans were compared.<sup>50</sup> This study reported a significant decrease in circulating blood and CSF adenosine concentrations in neuropathic patients. From these data, coupled with the effective attenuation of

| Inflammation   | Nerve injury  |
|--|---|
| <ul style="list-style-type: none"> <li>• Increased potency</li> <li>• Additional peripheral site of action</li> <li>• No increase in CCK expression</li> </ul> | <ul style="list-style-type: none"> <li>• Decreased potency</li> <li>• No peripheral effects</li> <li>• Loss of spinal receptors</li> <li>• Increased expression of CCK mRNA and CCK<sub>B</sub> receptor</li> </ul> |

**Fig 6** Mechanisms of opioid resistance in neuropathic pain: comparison of the effects of inflammation and nerve injury on features of the opioid system.

neuropathic pain seen after low-dose infusion of adenosine in a preliminary study,<sup>122</sup> a role of adenosine in modulating the development of neuropathic pain is a possibility.

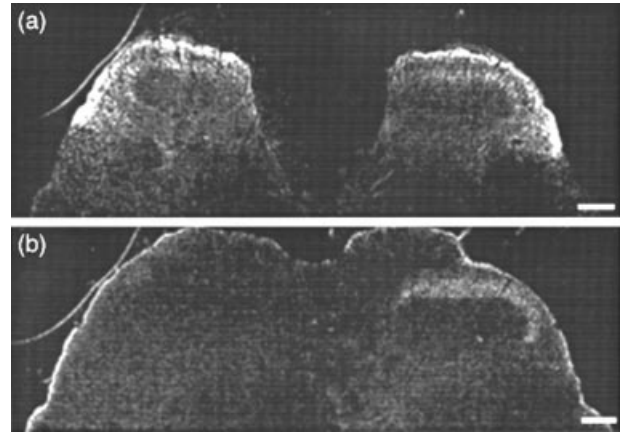
Thus, there is evidence that a combination of increased activity in the excitatory and a concomitant decrease of activity in inhibitory systems within the spinal cord contributes to the phenomenon of central sensitization after peripheral nerve injury.

#### *Endogenous opioid and cannabinoid systems*

It is generally accepted that opioids are less effective in relieving neuropathic pain than inflammatory pain.<sup>30 112</sup> Although, the exact extent of this is controversial, the balance of evidence supports the view of an unfavourable (right) shift in the dose response function for opioids in neuropathy. There are a number of plausible explanations for this observation, including a loss of peripheral opioid effects, loss of spinal opioid receptors and increased activity in physiological opioid antagonist systems (Fig. 6).

It is well established that a tertiary, peripheral site of opioid analgesia becomes operative during acute inflammation.<sup>125</sup> Not only are the immune components of this phenomenon unlikely to be operating during painful neuropathy to the extent that they are during inflammation, but peripheral nerve injury is associated with Wallerian degeneration and, therefore, a loss of axonally expressed opioid receptors. Zhang and colleagues demonstrated that peripheral axotomy was associated with a loss of  $\mu$ -opioid receptors in both rat and monkey DRG.<sup>155</sup> Simultaneous to this down-regulation in  $\mu$ -opioid receptors is an up-regulation in cholecystokinin (CCK) mRNA synthesized by neurones within the DRG.<sup>151</sup> CCK has opioid antagonistic properties<sup>124</sup> and so up-regulation will potentially further decrease the anti-nociceptive effects of opioids.

In the spinal cord, opioid-receptors are localized predominantly on the pre-synaptic terminals of primary afferents in the superficial dorsal horn.<sup>11</sup> However, after peripheral axotomy, a decrease in immunocytochemical receptor staining has been reported<sup>29 155</sup> and also after dorsal rhizotomy,<sup>53</sup> neonatal C-fibre degradation<sup>54</sup> and CCI<sup>12</sup> a decrease in  $\mu$ -opioid receptor binding is observed, presumably reflecting the degeneration of primary afferent neurones as discussed above. However, in the SNL model, intrathecal administration of morphine produced greater inhibition of noxious stimuli generated electrophysiological



**Fig 7** Preservation of cannabinoid CB<sub>1</sub> receptors in the dorsal horn after dorsal rhizotomy: sections A and B are transverse sections of rat lumbar spinal cord taken from animals which had undergone dorsal rhizotomy. Section A was immunostained for cannabinoid CB<sub>1</sub> receptors and there is no significant effect of dorsal rhizotomy. Section B was immunostained for the lectin IB4 (a marker of the GDNF dependent class of primary afferent nociceptor), the loss of IB4 staining ipsilateral to the dorsal rhizotomy indicates adequate degeneration of primary afferent nociceptors. After similar nerve injury, there is a considerable loss of  $\mu$ -opioid receptor binding (scale bar 100  $\mu$ m). Adapted from Farquhar-Smith and colleagues.<sup>40</sup>

responses than systemically administered morphine.<sup>127</sup> This suggests a potential role of spinally administered morphine where systemic morphine and other approaches have failed. Conversely, separate studies have demonstrated, immunocytochemically, an increase in  $\mu$ -opioid receptors in the ipsilateral dorsal horn after CCI injury and a decrease after tight ligation of the sciatic nerve<sup>47</sup> whilst SNL injury caused little change in  $\mu$ -opioid receptor binding or expression.<sup>105</sup>

As mentioned above, there is an increased expression of the endogenous opioid antagonist CCK mRNA after peripheral nerve injury. A corresponding increase in CCK<sub>B</sub> receptor staining in the superficial dorsal horn has also been observed after peripheral axotomy. This appears to be related to increased synthesis of the receptor in the DRG which is then transported to the primary afferent central terminals the spinal cord.<sup>6</sup> It is possible that this increased level of inhibition on the opioid system contributes to decreased potency of opioids in neuropathic pain. This hypothesis was supported by a recent study in which morphine potency was enhanced in the SNL model by co-administration with a CCK<sub>B</sub> receptor antagonist.<sup>71</sup>

Finally, recent advances in the understanding of cannabinoid analgesia<sup>55 103</sup> appear to indicate a therapeutic advantage of cannabinoids over opioids in the management of painful neuropathy (Fig. 7). Cannabinoid CB<sub>1</sub> are located in areas of the spinal dorsal intimately associated with nociception.<sup>40</sup> In contrast, to the situation for spinal opioid receptors described above, no biologically relevant decrease in CB<sub>1</sub> receptor immunostaining was evident after dorsal rhizotomy suggesting a relative sparing of CB<sub>1</sub> receptors, compared with opioid receptors, after peripheral nerve

injury<sup>40</sup> (Fig. 6). Similarly, using an alternative experimental approach, in which neonatal capsaicin treatment was used to deplete primary afferent C-fibres, Hohmann and Herkenham demonstrated only a modest decrease (~16%) of cannabinoid receptor binding in the superficial dorsal horn.<sup>54</sup> Meanwhile,  $\mu$ -opioid receptor binding was considerably decreased (~60%) in the same region. In behavioural studies, cannabinoids have been shown to attenuate the sensory changes associated with CCI and SNL.<sup>15 52</sup>

## Conclusion

This brief overview of the known mechanisms of neuropathic pain outlines the complex nature of the responses to a peripheral nerve injury. A unifying hypothesis of a single mechanism of all neuropathic pain is most unlikely to be proven and it is probable that an inter-related portfolio of mechanisms contribute to the generation of neuropathic pain in any given patient, with peripheral, spinal and brain events possibly all playing a role. Further elucidation of mechanisms underlying neuropathy will assist in developing novel targets for drug therapy.

Eventually, it may be possible to improve the ethos of clinical management protocols so that there will be a move away from the current disease based treatment towards symptom or, ultimately, mechanism based therapies, as suggested by Woolf and Mannion.<sup>145</sup> It is a clinical challenge to determine which mechanisms may be operating and hence responsible for individual symptomology in each patient. However, whilst a symptom-based approach is feasible it remains largely unevaluated in the clinic. Mechanism based therapy will require a better understanding of mechanisms involved in neuropathic pain and reliable convenient tools for their assessment in the clinic. Advances in our understanding of genetics may uncover genetic variation in the susceptibility of individuals to develop neuropathic pain after a nerve injury<sup>96 97</sup> and ‘genetically tailor’ analgesics based on an individual’s pharmacogenetic profile.<sup>95</sup>

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## Note added in proof

Since the original submission of this article, an important study has appeared.<sup>1</sup> This demonstrates that, following peripheral nerve injury, an increased expression of the noxious heat gated VR-1 receptor, which in the physiological state is generally restricted to C-fibre cell bodies, is observed on the DRG cell bodies of uninjured A-fibres. This supports the hypothesis that uninjured neurones contribute to the development and maintenance of neuropathic pain states and that the phenotype of primary afferent neurones which express VR-1 is altered.

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