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Novel mechanisms in peripheral neuropathic pain

Recent advances in our understanding

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Neuropathic pain is a chronic disease with an incidence of about 8% of the population and thus constitutes a major medical and socioeconomic problem [1]. It is defined as pain caused by a lesion or disease of the somatosensory system and the mechanisms underlying neuropathic pain are distinct from those associated with other chronic pain syndromes, such as inflammatory pain [2]. The aetiology of neuropathic pain is complex and includes nerve trauma (accidental or surgical), viral infections, autoimmune disease (e.g., Guillain-Barré syndrome), inherited channelopathies, anticancer drug treatments and consequences of uncontrolled diabetes. Depending on the type of fibre affected, a variety of painful sensations, including burning pain, paroxysmal pain, and mechanical, heat and cold allodynia to mention a few, are reported by patients [3]. However, not all patients with peripheral nerve lesions develop neuropathic pain. This is the case for postoperative surgical pain, an important medical problem that has a variable incidence depending on the type of surgery, age of patient, type of anaesthesia and postoperative analgesia used (table 1) [4].

Current pharmacological treatments for neuropathic pain include the use of repurposed antiepileptics (pregabalin, gabapentin) and tricyclic antidepressants (amitriptyline) and, as a last resort, opiates. However, these treatments have considerable side-effects in long-term use and are relatively inefficient; hence, there exists a pressing need for novel approaches.

In this short review I will consider some recent advances, gleaned from preclinical studies in animal models, in our understanding of peripheral neuropathic pain.

Intense research efforts currently underway aim at deciphering the molecular and cellular mechanisms underlying the transition from normal nociceptive responses to noxious stimuli to the initiation of a neuropathic pain state [5]. Important conceptual advances are emerging from recent research; primary somatosensory neurones respond to peripheral insults by modulation of ion channel expression and activity, changes in signalling pathways and changes of gene expression, resulting in hyperexcitability and spontaneous activity in primary sensory neurones that drive plastic changes in the dorsal horn and alter neuronal circuitry. Primary afferents also release peptides and cytokines that alter dorsal horn neuronal excitability and modify the function of dorsal horn glial cells, which in turn promotes excitatory and diminishes inhibitory mechanisms. Thus, the emerging consensus is that the neuropathic pain state is the result of an altered balance between excitatory and inhibitory processes in the pain circuits of the dorsal horn, with the excitatory influences tipping the balance in favour of reduced pain thresholds and persistent pain signals being sent to the brain (figure 1).

Key ongoing questions in this research area include: What accounts for the different susceptibilities of individuals to develop persistent pain in response to similar lesions, such as surgical operations or diabetes-induced lesions? How do the changes in the somatosensory pathways during the initiation of persistent pain interact with endogenous opioid systems? In the light of the enormous functional diversity of somatosensory neurone subtypes, how do these different subtypes, both nociceptive and non-nociceptive, respond in pathological conditions and what are the contributions of specific subtypes to the pathological process? How does persistent pain affect higher processing centres and how does the psychological state of the patient affect his or her susceptibility to develop chronic pain? Are there multiple pathological mechanisms that converge to a common pathway or do different neuropathic pain conditions have distinct underlying mechanisms? To what extent are the changes induced in neuropathic pain conditions reversible? What are the roles of neuroimmune interactions in neuropathic pain?

In recent studies, our team has have uncovered two novel signalling systems that play roles in the maintenance of neuropathic pain in animal models. We found that the a modulatory subunit of the Na/K-ATPase called Fxyd2 is expressed in specific subtypes of mechanoceptive and nociceptive neurones and is necessary for the maintenance of pain behaviour in rodent models of neuropathic pain [6].

Table 1: Incidence of chronic post-surgical pain (based on Correll 2017 [4]).

Intervention	Incidence at 12 months
Abdominal surgery	17–31%
Breast surgery	30–60%
Sternotomy	4–43%
Hysterectomy	26%
Inguinal hernia	29–43%
Thoracic surgery	50%
Thyroidectomy	37%

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Mice lacking the Fxyd2 gene or rats treated with an antisense small interfering (siRNA) directed against Fxyd2 failed to maintain the characteristic pain behaviour induced by peripheral nerve lesions. This was accompanied by reduced excitability of somatosensory neurones as measured in electrophysiological analyses. We also showed that Fxyd2 is present in human dorsal root ganglion neurones and the finding that Fxyd2 is relatively poorly expressed in the central nervous system renders this molecule an interesting potential target for therapeutic intervention.

In a separate study, we analysed the role of the tyrosine kinase receptor Flt3, expressed in sensory neurones, in neuropathic pain [7]. In mice lacking the Flt3 receptor gene, acute nociceptive behaviours are normal, but neuropathic pain induced by peripheral nerve lesions is not maintained over time, suggesting that Flt3 activity is necessary to maintain the functional changes that cause the pain behaviour. By expression of an anti-Flt3 small hairpin RNA (shRNA) from an adeno-associated virus vector directed specifically to dorsal root ganglion neurones, we could show that Flt3 activity in these neurons is necessary for induction and maintenance of nerve-injury induced neuropathic pain behaviour in mice. Interestingly, loss or diminution of Flt3 expression in somatosensory neurones attenuated many of the molecular changes that normally occur in these neurones during the initiation and maintenance phases, including the increased expression of the cytokine colony-stimulating factor-1 (CSF1) that has been shown to be transported to and released in the dorsal horn, where it activates microglia as part of the process underlying pain pathology [8]. Interestingly, our study demonstrated that immune cells at the lesion site express the Flt3 ligand, suggesting that neuroimmune crosstalk could play a role in the disease process.

Altogether, these examples reveal novel pathways to persistent pain involving sensory neurone hyperexcitability and peripheral neuroimmune interactions. These findings, with many others in this rapidly moving research field, are providing novel targets for the development of new treatments for peripheral neuropathic pain.

Key points

- A modulatory subunit of the Na/K-ATPase called Fxyd2 is expressed in specific subtypes of mechanoceptive and nociceptive neurones and is necessary for the maintenance of pain behaviour in rodent models of neuropathic pain.
- Tyrosine kinase receptor Flt3 activity seems to be necessary for induction and maintenance of nerve-injury induced neuropathic pain behaviour in mice.
- Neuroimmune crosstalk could play a role in the disease process

Disclosures

The author holds a patent on the role of FXYD2 as a therapeutic target in neuropathic pain condition.

References

1 Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primers. 2017;3:17002. doi: http://dx.doi.org/10.1038/nrdp.2017.2. PubMed.

2 Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci. 2009;32(1):1–32. doi: http://dx.doi.org/10.1146/annurev.neuro.051508.135531. PubMed.

3 Truini A, Garcia-Larrea L, Cruccu G. Reappraising neuropathic pain in humans--how symptoms help disclose mechanisms. Nat Rev Neurol. 2013;9(10):572–82. doi: http://dx.doi.org/10.1038/nrneurol.2013.180. PubMed.

4 Correll D. Chronic postoperative pain: recent findings in understanding and management. F1000 Res. 2017;6:1054. doi: http://dx.doi.org/10.12688/f1000research.11101.1. PubMed.

5 von Hehn CA, Baron R, Woolf CJ. Deconstructing the neuropathic pain phenotype to reveal neural mechanisms. Neuron. 2012;73(4):638–52. doi: http://dx.doi.org/10.1016/j.neuron.2012.02.008. PubMed.

6 Ventéo S, Laffray S, Wetzel C, Rivat C, Scamps F, Méchaly I, et al. Fxyd2 regulates Aδ- and C-fiber mechanosensitivity and is required for the maintenance of neuropathic pain. Sci Rep. 2016;6(1):36407. doi: http://dx.doi.org/10.1038/srep36407. PubMed.

7 Rivat C, Sar C, Mechaly I, Leyris JP, Diouloufet L, Sonrier C, et al. Inhibition of neuronal FLT3 receptor tyrosine kinase alleviates peripheral neuropathic pain in mice. Nat Commun. 2018;9(1):1042. doi: http://dx.doi.org/10.1038/s41467-018-03496-2. PubMed.

8 Guan Z, Kuhn JA, Wang X, Colquitt B, Solorzano C, Vaman S, et al. Injured sensory neuron-derived CSF1 induces microglial proliferation and DAP12-dependent pain. Nat Neurosci. 2016;19(1):94–101. doi: http://dx.doi.org/10.1038/nn.4189. PubMed.

Figure 1: The major pathways conveying somatosensory information to the brain. Proprioceptive and mechanosensory primary afferents enter the spinal cord and send ipsilateral processes to the cuneate and gracile nuclei in the brainstem. Second relay neurones cross the midline and synapse in the thalamus. Thalamic neurones project to the somatosensory cortex. Thermo- and nociceptive primary afferents synapse on second order neurones in the dorsal horn. Dorsal horn projection neurones project across the midline and ascend contralaterally to the thalamus from which the information is carried to the somatosensory cortex. Peripheral lesions release signals that cause changes in excitability and gene expression of dorsal root ganglion (DRG) neurones (peripheral sensitisation). Increased primary afferent drive promotes changes in the excitatory/inhibitory balance in the dorsal horn (central sensitisation), resulting in long-lasting alterations in neuronal plasticity in the dorsal horn and higher processing centres.