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Recent developments in neuropathic pain mechanisms : implications for treatment

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SUMMARY POINTS

- Neuropathic pain is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system".
- Characteristic symptoms include an increased evoked pain response to noxious (hyperalgesia) and innocuous (allodynia) stimuli, spontaneous pain, shooting electric shock like pain. Sensory deficits can also exist.
- Available treatments are not adequate in many patients due to many factors including the complexity of the pain state, disease progression, intolerable side effects and low analgesic efficacy.
- A number of peripheral, spinal and supraspinal mechanisms of hyperexcitability underlie neuropathic pain, these include changes in the activity and expression of voltage gated sodium, calcium and potassium channels, as well as TRPV1 channels and alterations in the activity of neuroimmue pathways.
- NeP patients often experience depression, anxiety, sleep disturbances etc. alongside their pain. These co-morbidites significantly reduce quality of life and as such are key treatment considerations..
- Improved understanding of NeP mechanisms is encouraging targeting of treatment to the mechanisms that produce painful symptoms as opposed to the etiology of disease.

Introduction

Neuropathic pain (NeP) can arise as a direct consequence of a lesion or disease affecting the somatosensory system. Initiating factors are varied and include cancer, metabolic disorders and viral infections[1]. Clinically, symptoms include an increased evoked pain response to noxious (hyperalgesia) and innocuous (allodynia) stimuli and spontaneous shooting electric shock like pain. Additionally, pain has an affective component, and so co-morbidities such as fatigue, anxiety and depression can occur, which interact with the sensory aspects of the pain to substantially reduce quality of life in NeP patients and are part of the medical problem[2].

NeP treatment remains a large unmet clinical need and this has served as a powerful research stimulus into the pathophysiological mechanisms that underlie NeP, thus forming the basis for targeted drug therapy[1,3]. This review highlights some of the key mechanisms.

Mechanisms of Neuropathic Pain

Mechanisms of NeP include ectopic (spontaneous) nerve activity, peripheral and central sensitisation, phenotypic switching of peripheral nerve fibres and structural plasticity within the central nervous system. At the molecular level these changes can be driven by changes in function and expression of multiple channels, receptors and induction of new genes, some of which are detailed below.

Peripheral mechanisms

Following nerve lesion, damaged and uninjured primary afferent neurones display ectopic (spontaneous) activity that drives NeP[4]. Ectopic activity, which serves as a raw pain signal and an inducer of central sensitisation, has been related to nerve injury-induced changes in the distribution, accumulation, clustering and functional activities of voltage-gated sodium channels (Na_v) 1.7 and 1.8, and the a re-emergence of the embryonic Na_v 1.3 channel[5].

There is considerable evidence linking the reduced inactivation kinetics of Na_v channels to NeP[5]. Compelling evidence for the Na_v 1.7 subtype in pain signalling comes from human genetic studies where a gain or loss of function mutation in the encoding gene,

SCN9A, causes pain in erythromelalgia patients or a congenital absence of pain perception respectively[6]. Surprisingly, NeP behaviors develop as normal in Na_v 1.3, 1.7 and 1.8 knockout mice[7]. Despite these contradictions, rodent studies have improved understanding of Na_v channels and their contribution to NeP. These have led to the development of a potent and selective small molecule Nav 1.8 blocker (A-803467)[8], the discovery of a novel class of benzazepinone Na_v 1.7 blockers[9] and a newly synthesized tocainide congener, NeP1, that blocks Nav 1.7 channels, producing significant reversal of allodynia and anti-hyperalgesia in neuropathic rats[10], reinforcing the case for Na_v 1.8 and 1.7 as analgesic targets for NeP.

Voltage gated potassium channels (K_v) channels set resting membrane potentials and repolarize action potentials, thus limiting neuronal excitability. Pathological changes in channel activity have been demonstrated[11] and a recent genetic study found that the potassium channel alpha subunit, KCNS1, involved in neuronal excitability, is markedly down-regulated in sensory neurons in neuropathic rats. Importantly the KCNS1 allele, rs734784, was strongly associated with NeP in humans[12]. Targeting K_v channels for NeP treatment has yet to prove successful, however further research is warranted given the human genetic evidence[12].

Hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels also generate spontaneous rhythmic activity and play an important role in modulating neuronal excitability and plasticity. Neuropathy results in increased HCN1 expression in dorsal root ganglia (DRG) and spontaneous activity in damaged nerves, and antagonism decreased ectopic activity and allodynia[13].

Peripheral sensitization of primary afferent neurons, which may result in reduced thresholds, spontaneous activity and increased response to suprathreshold stimuli, occurs by multiple possible mechanisms. These include activation of immune pathways, recruitment of silent nociceptors and expression of new receptors and ion channels. The increased expression of transient receptor potential vanilloid 1 receptors (TRPV1R) on primary afferents is an important mechanism of NeP. A recent advance comes in the form of a single high concentration (8%) capsaicin (agonist at TRPV1Rs) patch that produces long-term analgesic effects with few systemic side effects in patients. The mechanism of action relies on decreasing the density of epidermal sensory fibres from the injured area and hence loss of receptors[14]. Interestingly a recent human genetic study found that TRP channel polymorphisms contributed to the somatosensory abnormalities experienced by NeP patients. This may have treatment implications if genetic variation has a bearing on response, non-response or symptom-specific efficacy, and would suggest sub-grouping of patients for clinical trials[15].

Another important molecular change that causes peripheral sensitization and hence drives NeP and one that has also been validated from human genetic profiling studies is the tetrahydrobiopterin (BH4) synthesis and metabolism pathway. Peripheral nerve injury causes a marked increase in BH4 levels in sensory neurons linked to an increase in pain hypersensitivity[16].

Central mechanisms

Voltage gated calcium channels (Cav) are important for primary afferent neurotransmitter release and neuronal excitability. Pregabalin and gabapentin, agents that inhibit Cav are considered by many as "gold-standard" analgesics for NeP treatment in patients[17]. These drugs uniquely reverse conditions of neural sensitization such as after nerve injury without affecting normal physiological pain[18]. This state-dependent effect may contribute to their favourable side-effect profile. Their analgesic mechanism, however, remains unclear. An upregulation of the binding site, the α_2-δ-1 subunit, (an accessory protein involved in trafficking the receptor to the cell membrane) occurs in the DRG and spinal cord after neuropathy, which has been linked to the onset of allodynia and analgesic efficacy[19]. A unique mode of action of pregabalin was recently described – by binding to the α_2-δ-1 subunit, upregulation is unaltered in DRG but reduced in the spinal cord, implicating an action on the trafficking of the protein so it no longer locates to the cell membrane[20].

Central sensitisation (CS) occurs as a result of increased peripheral neuronal barrage after peripheral sensitization. Activation of the NMDA receptor (NMDA-R) plays a key role by increasing calcium influx and initiating a cascade of intracellular events to further promote neuronal hyperexcitability, but adverse psychotomimetic effects has meant antagonists, such as ketamine, have limited use. However, selective targeting of NR2B subunit-containing NMDA-Rs, which have a restricted distribution within sensory pathways and are specifically upregulated after nerve injury, has renewed efforts into their therapeutic utility[21,22]. Another valuable target would be uncoupling of the protein tyrosine kinase Src, a key enhancer of NMDA receptor function, as this attenuated NeP without the side effects associated with direct receptor blockade[23].

Alterations in neuroimmune interactions, such as microglial activation, due to the release of pro-inflammatory cytokines also promotes CS, consequently glial and chemokine inhibitors are in development. Downregulation of inhibitions such as a decrease in GABAergic and opioidergic mechanisms also occur and this disinhibition promotes central neuronal hyperexcitability. CS is largely contingent on an increased peripheral neuronal barrage but could become independent, although many would argue against this. However thalamic dysfunction occurs in patients with diabetes and recent evidence suggests that thalamic neurons can act as central generators or amplifiers of NeP in diabetes[24]. If CS does become independent, then this has important treatment implications, as drugs targeting peripheral initiating processes won't be effective.

Descending pathways

Nociceptive traffic within higher centers converge upon descending pathways, with the final output stations originating in the periaqueductal gray and raphe nuclei systems, to exert excitatory and inhibitory effects on spinal neuronal activity. The major transmitter systems implicated are noradrenaline (NA) and 5-hydroxytryptamine (5-HT), and so the comorbidities of anxiety and depression could result from the dual roles of NA and 5-HT in these functions and in pain (25). Human imaging studies have demonstrated a link between high pain ratings, descending facilitation and a pivotal role of the

brainstem (26); and an enhanced role for descending facilitation mediated by 5-HT acting at pronociceptive spinal 5-HT2 and 3 receptors, coupled with a decrease in noradrenergic descending inhibition was shown in nerve-injured rats (27, 28). Descending controls do not just modulate pain but are permissive for the actions of tricyclic antidepressants (TCAs) and serotonin noarderaline reuptake inhibitors (SNRIs), which rely on altering activity at monoamine synapses and are therefore dependent on activity in descending circuits. Further, evidence exists linking gabapentin's analgesic efficacy to activity within descending facilitatory pathways (29, 30), thus individual variations in pain comorbidities may underlie the NNT (the number of patients needed to be treated before one patient achieves 50% pain relief) for these drugs, and so clinical investigations relating the analgesic efficacy of TCAs, SNRIs, and gabapentinoids with affective measures could predict treatment responsiveness in patients.

Neurotrophic factors and reversing pathology

Current NeP therapy is limited to symptom management without necessarily reversing the pathological adaptations that maintain NeP. Modulating the activity of neurotrophic factors could alter neuronal pathophysiology and produce a disease-modifying effect since these factors affect nerve development and maintenance. It has been shown that enhancing artemin action, which promotes neuronal survival, and blocking nerve growth factor activity reverses NeP in rats, together with normalization of neuronal activity. This represents an important step forward towards achieving both pain relief and reversal of the pathophysoiological mechanisms maintaining NeP (31).

Therapeutic opportunities

Bearing in mind these peripheral and central changes, opportunities for NeP treatment include reducing neuronal hyperexcitability, increasing inhibitions, neuroimmune modulation and restoration of the neuronal phenotype. Recent guidelines support using hyperexcitability blockers such as gabapentin and pregabalin, which act to modulate Cav activity, and agents that increase descending monoaminergic inhibition such as TCAs and SNRIs as first line medication for NeP. Other licensed excitability blockers include the lidocaine patch and carbamezepine. Tramadol (a single molecule with both mu opioid and SNRI activity) and opioids alone, restore normal neuronal excitability by activating inhibitory mechanisms, are second line treatments. The high concentration (8%) capsaicin patch has had success in recent clinical trials (32). Increasing neuronal inhibitions via activation of cannabinoid receptors holds therapeutic promise, and they are currently proposed for refractory cases (33).

Multiple pathological mechanisms at multiple sensory sites may underlie NeP, forming the basis for combination therapy. Accordingly gabapentin combined with TCA or opioids appears useful for patients who show partial response to these drugs alone (33). This avenue is being exploited through the development of single molecules that combine different mechanisms of analgesic action. For instance a novel slow-inactivation-specific ion channel modulator that stabilizes voltage gated sodium and calcium channels, and attenuates NeP in a rat model of peripheral nerve injury, was recently described (34). Tapentadol, which stimulates mu-opioid receptors (MOR) and acts as a noradrenaline reuptake inhibitor (NRI), appears to be an advance on its predecessor tramadol (a licensed drug with weak opioid activity and inhibits NA and 5-HT reuptake inhibitor), due to removal of the 5HT reuptake component, so that any pronociceptive effects of augmented 5HT after neuropathy are lost (35, 36).

Finally, current therapeutic treatment of NeP centres around pharmacological agents, delivered via oral, transdermal and intravenous methods, however, newer more invasive approaches hold promise, these include gene and cell therapies. Furthermore non-pharmacological treatment options are gaining ground, such as spinal cord stimulation and radiofrequency ablation techniques (37-39)}.

Conclusion

Neuropathic pain is a highly complex and multidimensional disorder. The ability of preclinical studies to explain the mechanisms of action of drugs and provide a multitude of putative NeP mechanisms suggests that a key step forward in NeP treatment could be based upon understanding that drugs have differential effects on patients based on their sensory characteristics. If so, the action of the drug would be able to shed light on mechanisms operating in these patients. This would also allow improvements in NNT values by selecting patients for particular treatments.

Earlier recognition of NeP requires better diagnosis. Here gauging the temporal changes in patients will be important in knowing when and what agent to give. Genetic bases for pain syndromes and polymorphisms in proteins implicated in pain are becoming frequent and these will provide further insights into potential targets and, in time, the development of better treatment strategies.

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