REVIEWS IN PAIN

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NEUROPATHIC PAIN

EDITORIAL

Neuropathic pain (NeP) is currently defined by the International Association for the Study of Pain (IASP), as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." The large majority of NeP cases (approx. 90%) arise from injury to peripheral sensory nerves fibres as opposed to central neuronal damage, with initiating factors as varied as the human pain experience itself; arising from e.g. cancer, metabolic disorders and viral infections as well as from medical interventions themselves e.g. surgery and chemotherapy. Clinically, characteristic symptoms include an increased evoked pain response to noxious (hyperalgesia) and innocuous (allodynia) stimuli, and spontaneous shooting electric shock like pain. Pain has an affective component, and so co-morbidities such as fatigue, anxiety and depression can complicate pain symptomatology. These co-morbidities interact with the sensory aspects of the pain to substantially reduce quality of life in NeP patients and must also be considered as part of the medical problem.

NeP, and its treatment, represents a highly complex medical problem but current treatments are unsatisfactory in many patients. This is due to many factors, which include disease progression, low efficacy and intolerable side effects of available drugs. This large unmet clinical need has served as a powerful research stimulus into the pathophysiological mechanisms that underlie NeP, thus forming the basis for targeted drug therapy.

Mechanisms of NeP include ectopic (spontaneous) nerve activity, peripheral and central sensitisation, phenotypic switching of peripheral nerve fibres and structural plasticity. To this end, therapeutic opportunities include reducing aberrant neuronal hyperexcitability, increasing inhibitions, neuroimmune modulation and restoration of the neuronal phenotype (reversing pathology). Accordingly, recent guidelines support the use of hyperexcitability blockers such as gabapentin and pregabalin, which act to modulate voltage gated calcium channel activity, and agents that increase descending inhibition via modulation of activity at monoaminergic synapses such as tricyclic antidepressants (TCAs) and serotonergic - norepinephrine re-uptake inhibitors (SNRIs) as first line medication for NeP. Other licensed excitability blockers include the lidocaine patch, a first line treatment for painful diabetic neuropathy, and carbamazepine, although this is only recommended for patients who are intolerant to first or second line treatments. Tramadol (a single molecule with both mu opioid and SNRI activity) and opioids alone, activate neuronal inhibitions to restore normal neuronal excitability, and are second line treatments. Capsaicin patches are promising for painful HIV neuropathies or post herpetic neuralgia, in particular the recently developed, 8% patch (Qutenza) has had

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significant success in recent clinical trials. The role of capsaicin, an agonist at TRPV1 receptors, which are located on peripheral nerve endings as well as centrally, and its role in NeP is discussed in detail in the review by Bhaskar and Mittal. The analgesic effects of cannabinoids remain unclear but targeting of this inhibitory receptor holds therapeutic promise, and they are currently proposed for refractory cases. Future studies and clinical trials will reveal the outcome of neuroimmune modulators and disease modifying agents for NeP relief.

Multiple pathological mechanisms at multiple sensory sites may underlie NeP and this forms the basis for combination therapy. Accordingly gabapentin combined with TCA or opioids appears useful for patients who show partial response to drugs administered alone. This avenue is being exploited through the development of single compounds that combine different mechanisms of analgesic action in a single molecule and are gaining momentum. For instance a novel slow-inactivation-specific ion channel modulator that stabilizes voltage gated sodium and calcium channels in their inactivated state attenuates neuropathic pain in a rat model of peripheral nerve injury, has recently been described. Tapentadol, which stimulates mu-opioid receptors (MOR) and acts as a noradrenaline reuptake inhibitor (NRI) in the CNS, appears to be an advance on its predecessor tramadol, a licensed drug, which has weak opioid activity and inhibits noradrenaline and 5-HT reuptake.

Despite the major advances made in unravelling the cellular and molecular mechanisms that underlie NeP, translation to the pain clinic has been much less successful with about 1/3 of NeP patients responding to active drugs and often no advancement seen over placebo in many trials. There are many reasons for these findings, e.g. large placebo effect or current drugs not acting on relevant pathophysiological targets. An intriguing possibility gathering recognition is that many trials have failed because they did not take into account the heterogeneity of NeP symptoms and signs that are presumably linked to distinct mechanisms. An important step forward to improve NNTs (number of patients needed to be treated before one patient achieves 50% pain relief), therefore, would be to identify those potential patients who might respond to a drug. An advance is the division of patients into groups based on symptoms assessed by quantitative sensory testing (QST). The next stage would be to determine which groups respond to which agents, since if different drugs have differential effects, analysis of sensory responses in patients would aid effective treatments. In this regard, it may also be possible to use questionnaires.

Finally, current therapeutic treatment of NeP centres largely around pharmacological agents, delivered orally, transdermally and intravenously and in rare cases via intrathecal methods, however, newer more invasive approaches hold promise. These include gene therapy using vector delivery systems and cell therapy utilising stem and chromaffin cells. Furthermore non-pharmacological treatment options are gaining ground, such as spinal cord stimulation and radiofrequency ablation techniques. This latter neuromodulatory approach is discussed in the review by Bhaskar and Mittal.

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