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EMERGING INTERVENTIONS IN THE MANAGEMENT OF NEUROPATHIC PAIN

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Review Article

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ABSTRACT

Neuropathic pain (NP) may arise as a consequence of a lesion or disease affecting the somatosensory system. It is one of the most incapacitating reasons for pain disorder in large number of population worldwide. The hallmark signs of NP are chronic allodynia and hyperalgesia. Various analgesics like opoids and NSAIDS lack antinociceptive effect in the management of NP but they are associated with various adverse effects and resistance. Hence the present review delineated with the recent targets for the management of NP along with their signalling pathways.

KEYWORDS: neuropathic pain, trauma, inflammation.

Introduction

Neuropathic pain (NP) is referred as "most terrible of all nerve tortures" [1], initiated by a primary lesion to somatosensory nervous system that involves an element of sensory dysfunction.[2] It was estimated that about 37.6 million individuals suffered from NP across the seven major markets in 2005 and it is forecasted that its prevalence will increase to 39.1 million individuals by 2011.[3] Various studies indicate that 95% of patients with spinal cord injuries have NP.[4] The symptoms of NP includes burning, cramping, electric shock, numbness, shooting and stabbing.[5] NP is characterized by disproportionate hypersensitivity to stimuli (hyperalgesia), abnormal pins and-needles or electric-shock-like sensations (hyperpathia) and finally nociceptive responses to non-noxious stimuli (allodynia).[6] Various factors are implicated in the pathogenesis and progression of NP like vascular lesions, avulsion injuries, traumatic injury, tumors[7] and diabetes.[8] Among all of them allodynia (pain perception in response to normally non painful stimuli) and hyperalgesia (exaggerated pain sensation to normally painful stimuli) are regarded as the major symptoms of NP.[1] It has been well documented that during nerve injury numerous mediators are found to be up regulated.[9] Mast cells are found to play key role in the release of various inflammatory mediators[10] like are cytokines such as [interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNFα)], prostaglandin E2 (PGE2) and nitric oxide (NO).[9] During nerve injury, microglial cells causes up regulation of adenosine triphosphate (ATP) receptors (P2X4and P2X7)[11] , chemokine receptor (CX3CR1)[12] , TNFα[13] , IL-1β and IL-6[14] which mediate their effect via activation of mitogen-activated protein kinase (p38MAPK)[15] and contributes to NP.[16] Moreover, it has been reported that NO which is a potent vasodilator too is responsible for the progression of NP[17,18] via causing increase in the expression of inducible nitric oxide synthase (iNOS).[19,20] Further, during NP there is increased generation of reactive oxygen species (ROS) via activation of

NADPH oxidase-2 (Nox2), which further plays a critical role in NP.[21]

Biology of NP

As discussed earlier that NP may arise as a consequence of a lesions or disease affecting the somatosensory system.[22] Various factors are responsible in the progression of NP like trauma, metabolic abnormalities, chemotherapy, surgery, irradiation, neurotoxins, inherited neurodegeneration, nerve compression and inflammation.[23] NP is characterised by hyperalgesia (Provoked by heat stimulation) and chronic allodynia (Pain due to stimulus that does not normally provoke pain, it can be provoked by touch stimulation or cooling).[19,5] NP is a complex entity, it can be classified into various types such as trigeminal neuralgia, diabetic neuropathy (DPN) and postherpetic neuralgia (PHN).[23] Nerve injury in NP initiates either by central or peripheral mechanisms.[24] Around the site of injury, inflammation occurs, due to mast cell degranulation[25,26] and by proliferation of neutrophils[27] and macrophages[28] which has been reported to trigger the release of various proinflammatory mediators such as histamine, cytokines and proteases.[29,30] In peripheral mechanisms, the pain arises due to noxious stimuli at nociceptive C-fibers and non nociceptive Aδ-fibers neurons.[31] These neurons become abnormally sensitive due to development of pathological spontaneous activity by proinflammatory mediators.[32] Furthermore, there is increased expression of messenger RNA (mRNA) for sodium channel (Na^+) present at these neurons[33,34] and contribute to action potential threshold and hyperactivity.[35] Moreover, in peripheral nerve injury the non-neural glial cells too play a pivotal role and they have been reported to release various cytokines and excitatory amino acids (EAA)[36] EAA by acting on N-methyl-D-aspartate (NMDA) receptors and neuropeptide substance P produces symptoms associated with NP.[37]

In central mechanism, microglial cells causes upregulation of ATP receptors and chemokine receptor[38,39,40,12], which are elicited in progression of NP. TNF-α activates tumour necrosis factor receptor 1 (TNFR1) and TNFR2 receptors, which are upregulated during inflammation[6] which further activates Na^+, thus increases membrane potassium (K^+) ion conductance which lead to overall neuronal hyperexcitability and causes NP.[13] IL-1β and IL-6 are too implicated in progression of NP by activating tyrosine kinases (TKs) and protein kinase C (PKC).[41,14] Further, various evidences indicates that during NP there is increased expression of Inos[42] that causes the activation of cyclooxygenase (COX) and results in the marked increase in the level of prostaglandin E_2 (PGE_2), which plays critical role in NP[43] Moreover, peripheral nerve injury results in increase generation of ROS production via activation of Nox2, which further causes activation of spinal glial cells and proinflammatory cytokines.[21,19] Various evidences indicates that there is upregulation in activity of p38 MAPK which in return is responsible for activating various transcription factor like NF-κB, which lead to pain hypersensitivity[44] **Figure 1** indicates the pathogenesis of NP initiated by nerve injury.

Thus, by knowing various signalling mechanisms responsible in the progression of NP, various new safer, efficacious therapeutic interventions can be designed. Hence, the review deals with emerging drugs used in the management of neuropathic pain.

Emerging drugs management in NP

Capsaicin patches

Capsaicin is an agonist of the TRPV1 receptor and activates TRPV1 ligand-gated channels on nociceptive fibers results in depolariation and

thus initiate action potential (AP).[45] The increase AP causes transmission of pain signals to the spinal cord.[46] Capsaicin at high doses deactivates the mechanism of vanilloid receptor.[47] Capsaicin containing creams are effective in PHN. Recently, the efficacy of a one-off application of high concentration (8%) capsaicin patch (30, 60 or 120 min) applied to the painful area compared to low concentration (0.04%) has been demonstrated from weeks 2 to12 in PHN neuropathy.[48] Adverse effects include local capsaicin-related reactions at the application site pain, erythema, sometimes edema, and itching.[49,50]

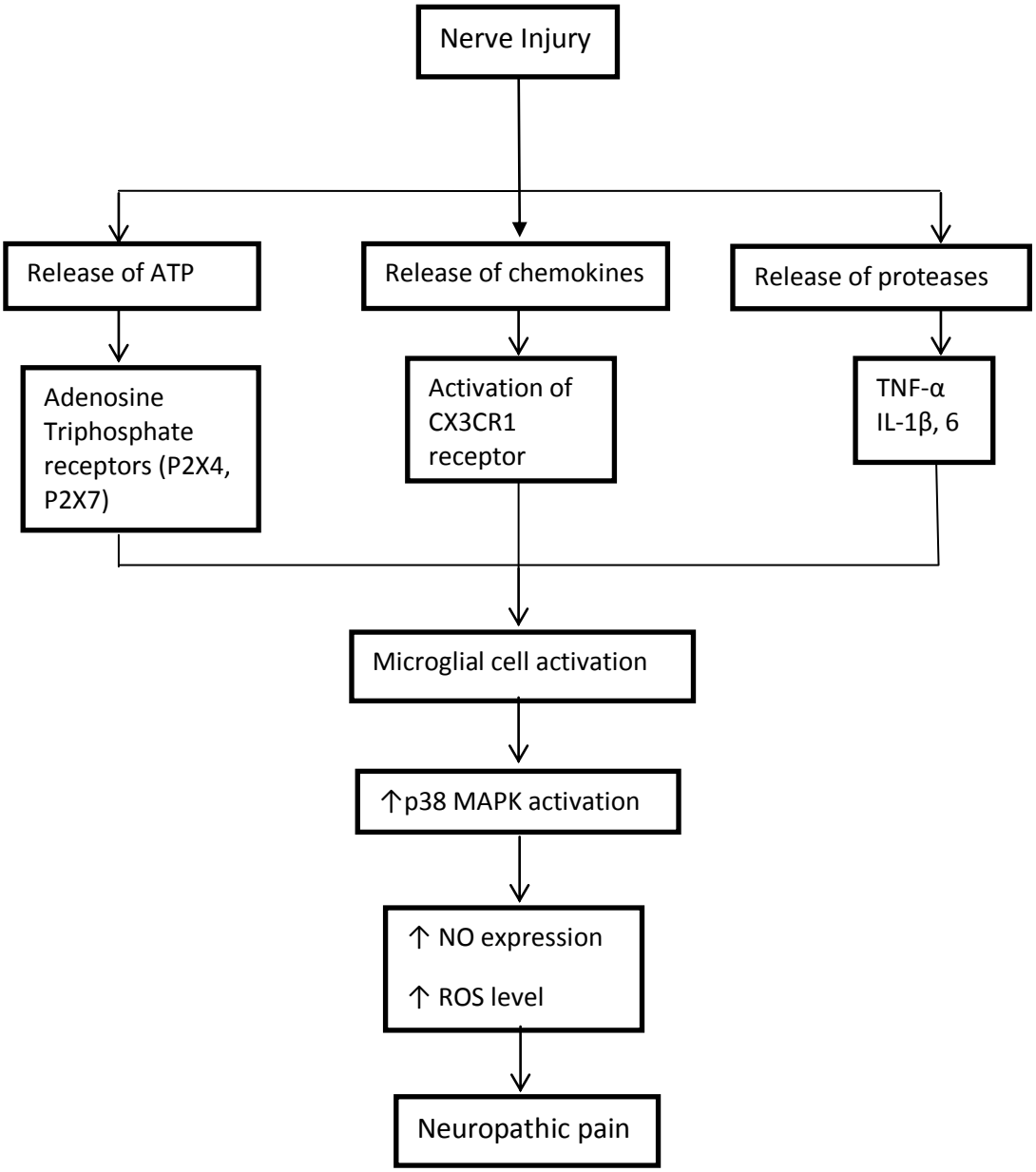

Figure 1: Pathophysiology of neuropathic pain occurs as a result of nerve injury.

Botulinum toxin A (BTX-A)

BTX-A, a potent neurotoxin used for the treatment of focal muscle hyperactivity, by acting on neurogenic inflammation.[51] Clinically subcutaneous injection of BTX-A is used in management of allodynia and diabetic polyneuropathy.[51,52] The drug has an excellent safety profile with no systemic side effects and only pain during injection.

Cannabinoids

Cannabinoids have therapeutic potential in chronic pain following the discovery of cannabinoid receptors and their endogenous ligands.[45] Cannabinoids acts as agonist TRPV1 receptor, leads to desensitization and consequent behavioral analgesia.[53] Cannabinoids via acting on TRPV1 receptor channel help in increasing pain threshold.[54,55] Clinically, cannabinoids (2.7 mg delta-9-tetrahydrocannabinol/ 2.5 mg cannabidiol) administered by oromucosal route are effective in pain associated with multiple sclerosis[56] and in refractory peripheral NP associated with allodynia[57] .Adverse reactions include dizziness, dry mouth, sedation, fatigue, gastrointestinal effects, and oral discomfort.[56,57] In long-term studies of oromucosal cannabinoids, no tolerance was observed, but 90% of the patients experienced adverse reactions.[56]

NMDA antagonists

NMDA is a receptor for the excitatory neurotransmitter glutamate, which is released with noxious peripheral stimuli.[58] The activation of NMDA receptors has been associated with hyperalgesia, neuropathic pain, thus results in increased spinal neuron sensitization, leading to neuropathic pain.[59] Therefore, NMDA antagonist may have a role in these areas of pain management.[60]

Ketamine is a strong NMDA antagonist and is effective at doses of 2-4 mg/kg, *i.m.* and 0.2-0.75 mg/kg, *i.v.*[61] Other antagonists include memantine, amantadine (200 mg, infused over 3 hr, *i.v.*), dextromethorphan (400mg/d) and methadone (2.5-10 mg, oral dose).[62,61]

TNF-α antagonists

TNF-α have a pivotal role in the genesis of mechanical allodynia and thermal hyperalgesia during inflammatory and neuropathic pain.[63] Etanercept is a potent antagonist of TNF-α.[64] It reduces tissue injury and improves motor recovery by enhanced axonal regeneration.[65] It is effective when i.p. injection 1 hr before and 6 hr after injury is given.[66] Preclinical studies demonstrated that aqueous extract of *Mangifera indica* L. act as antagonist of TNF-α.[3]

Conclusion

As NP is regarded as one of the major disorder associated with Hyperalgesia and Allodynia. But no evident management is available for this deadly disorder. Hence the present review opens the vista for the management of neuropathic pain via newer emerging drugs.

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