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POTENTIAL INTERVENTIONS IN THE MANAGEMENT OF NEUROPATHIC PAIN

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Review Article

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ABSTRACT

Neuropathic pain (NP) is a wide term, associated with damage to peripheral nerves, spinal nerves and to the central nervous system (CNS). It is a leading cause of morbidity and mortality and its prevalence is continuously increasing in industrialised nations. It is characterised by allodynia, hyperalgesia and hyperpathia leading to sympathetic dysfunction and dystrophic changes. Number of synthetic drugs are used in the management of neuropathic pain but are of no use as they elicit several adverse effects. Hence the present review delineated with the management of neuropathic pain by the aid of herbal drugs and few newer synthetic drugs that are efficacious and potent.

KEYWORDS: neuropathic pain, allodynia, hyperalgesia, sympathetic dysfunction

Introduction

Neuropathic pain is defined as dysfunction of peripheral or central nervous system.[1] Nerve damage due to evoke pain results in allodynia (Pain due to stimulus that does not normally provoke pain, it can be provoked by touch stimulation or cooling) and Hyperalgesia (Provoked by heat stimulation).[2] Various mediators are implicated in the pathogenesis of NP such as neuropeptides,[3] neurokinins,[4] inflammatory mediators,[5] growth factors and adhesions molecules such as intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM).[6] Neuropeptides such as cholecystokinin (CCK), Vasointestinal polypeptide (VIP), galanin, and NO (Nitric oxide) and Neurokinins like substance P and calcitonin gene related protein (CGRP) increases during nerve injury.[7,8] It has been shown that inflammatory mediators such as prostaglandins (PGs) increases level of intracellular cyclic adenosine monophosphate (cAMP) which leads to hyperalgesia by activating protein kinase A (PKA) and calcium (Ca^{+2}) channels.[9] Further, Tumour Necrosis Factor (TNF-α), Interleukins (ILs) present in dorsal horn neurons are also implicated in neuropathic pain. TNF-α has been documented to activate the Tumour necrosis factor receptor 1 (TNFR1) and TNFR2 receptors, that are upregulated during inflammation,[5] Moreover activation of TNFR1 and TNFR2 are reported to activate tetrodotoxin- resistant (TTX-R) sodium channels via the p38 mitogen activated protein kinase (MAPK) system and increases membrane potassium (K^+) ion conductance in a non-voltage-gated fashion across the membrane leading to overall neuronal hyper-excitability and hence leading to NP.[10] IL-1α and IL-1β bind to the IL-1 receptor type I that in turn activates tyrosine kinases (TKs) and protein kinase C (PKC) that has been implicated in the progression of NP.[11,12] Moreover, in NP there is excessive formation of reactive oxygen species (ROS).[13] ROS has been show to enhance the effects of other inflammatory mediators including bradykinin and Prostaglandin E2 (PGE_2).[14]

Nerve injury induces pain sensitization either by central or peripheral mechanisms.[15] After nerve injury, there is expression of abnormal sodium channels in peripheral nerves. These changes are likely to be key factors in the pathogenesis of both spontaneous and evoked ectopic discharge in damaged and undamaged primary afferent neurons. Changes in sodium channel expression in CNS neurons leads to altered states of neuronal excitability and produce pathologic changes in the process that regulates

neurotransmitter release.[16] Various evidences too indicates that in NP there is activation of microglial and astrocytes that in return activates p[38] MAPK including extracellular regulating kinase (ERK).[17] Excitatory neurotransmitters like glutamate, aspartate also play a vital role in pathogenesis of NP. Glutamate has been found to stimulate N-methyl-D-aspartate (NMDA) receptors, which further elevates calcium levels and causes release of various neurotransmitters and neuromodulators like brain derived neurotrophic factor (BDNF), PGE2, IL-6.[18] Further PGE2 mediate the release of excitatory amino acids (EAA), Substance P (SP), Calcitonin gene related protein (CGRP), and NO that are responsible for generation of NP [19] Moreover, IL-6 by binding to IL-6 receptors (IL-6R) causes sensitisation in NP.[20]

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 management of NP via herbal drugs and few synthetic drugs.

Management of Neuropathic Pain

Pharmacological interventions

ANTIEPILEPTICS:

Antiepileptic drugs are the best option in the management of NP as both possess similar pathophysiologies.[21] Central sensitization and ectopic neuronal firing are common in epilepsy[22] and NP[23] as both the disorders are associated with central nervous system injury. Newer antiepileptics like Lamotrigine, Gabapentin, are widely used in the treatment of NP by causing blockade of sodium channels and calcium channels.[24] Further, Topiramate is reported to relieve NP by enhancing the GABAergic transmission and by inhibition of glutamatergic transmission.[25] Moreover, antiepileptic drugs such as zonisamide possess free radical scavenging property and reduces symptoms associated with NP.[26]

ANTIDEPRESSANTS

Antidepressants are commonly prescribed for NP.[27] Antidepressants have been reported to affect multiple neurotransmitter receptors and ion channels implicated in NP such as NMDA receptors and opioid receptors.[28] It has been well known that antidepressants have inhibitory effects on 5-hydroxytryptamine (5-HT) and noradrenaline (NA), which have been shown to modulate NP.[29] Tricyclic antidepressants (TCA) such as amitriptyline, nortriptyline, desipramine and certain novel antidepressants such as bupropion, venlafaxine, duloxetine are effective in the treatment of NP.[30] Tricyclic antidepressants in addition to blocking serotonin (5-HT) and norepinephrine (NE) reuptake are relatively potent sodium channel blockers.[31] Selective serotonin reuptake inhibitors such as Trazodone, Nefazodone, Venlafaxine act by blocking 5-HT reuptake pump, and by down regulation of 5-HT autoreceptors.[32]

OPIOIDS

Opioids have been reported to block A delta fiber and C fiber mediated NP.[33] Moreover, corticosteroids are widely accepted as analgesic in NP as they block the potassium-evoked release of SP. Strong opioids such as morphine, hydromorphone, fentanyl, levorphanol, oxycodone, and methadone are the common opoids used in treatment of NP.[34] Methadone binds to the NMDA receptor, a known modulator of NP and also inhibits the reuptake of norepinephrine and serotonin.[35] **Table 1** indicates synthetic analogues used in management of NP with mechanism of action.

Category	Drugs	Mechanism of action	Adverse effects
Antiepileptics	Lamotrigine/, Gabapentin Zonisamide	Blockade of sodium and calcium channels Free radical scavenging property	Blurred vision, ataxia, pruritis, somnolence, peripheral edema, anorexia, agitation &irritability
Antidepressants	Trazodone, Nefazodone, Venlafaxine	Blockade of serotonin (5-HT) reuptake pump, Down regulation of $5HT_{1A}$autoreceptors, Down regulation of postsynaptic5-HT_{2A} receptors	Constipation, ataxia, dry mouth, insomnia, seizures, dizziness, hot flashes, urinary retention, weight gain, arrhythmia.
Opioids	Morphine, Hydromorphone, Fentanyl, Levorphanol, Oxycodone, Methadone	NMDA receptor antagonist and inhibits the reuptake of norepinephrine and serotonin	Drowsiness, sedation, constipation, dizziness, nausea/vomiting

Table 1: Shows various synthetic drugs with their mechanism in the management of NP

Drug	Mechanism of action
Ginkgo biloba	Blocks induction of inducible nitric oxide synthase (iNOS) and release of nitric oxide (NO)
Panax ginseng	Inhibit the voltage-gated Na^+ channels
Ocimum sanctum	Decreases the oxidative stress and calcium levels
Acorus calamus	Decreases the oxidative stress and calcium levels
Emblica officinalis	Inhibits lipid peroxidation and restore antioxidant enzymes
Combination of Psidium guajava, Momordica charantia and Coccinia indica	Inhibits protein kinase C and act as antioxidant

Table 2 Shows Herbal drugs in the management of neuropathic pain

HERBAL DRUGS

Ginkgo biloba

Ginkgo is the dried leaves of Ginkgo biloba Linn., the only member of family Ginkgoaceae. It has been well reported that Ginkgo biloba extract shows anti-inflammatory and analgesic effects in formalin induced acute inflammatory pain model.[36] Ginkgo biloba has also been shown to decrease thermal hyperalgesia in a carrageenan induced inflammatory pain model.[37] The beneficial effect of Ginkgo biloba extract in NP is mainly due to a combination of an antioxidant, anti-inflammatory and a platelet activating factor antagonist effect and a protective effect against NMDA induced neurotoxicity.[38] Ginkgo biloba act by blocking induction of inducible nitric oxide synthase (iNOS) and release of nitric oxide(NO), which is known to play a significant role in nociceptive processing in the spinal cord.[39] Extracts of Ginkgo biloba contain two main groups of active constituents: ginkgo flavone glycosides (flavanoids) and terpene lactones.[38] Oral administration of the flavanoid, quercetin, was reported to reverse thermal hyperalgesia in a mouse model of diabetic neuropathy.[40]

Panax ginseng

Ginseng is the dried root of various species of Panax, like P.ginseng (Korean ginseng), P.japonica (Japanese ginseng), P. Notoginseng (Chinese ginseng) and P.quinquefolium (American ginseng), belonging to family Araliaceae. A polyacetylenic compound, (9R, 10S)-epoxyheptadecan-4,6-diyn-3-one (EHD), isolated from ginseng extract has been reported to inhibit the voltage-gated Na^+ channels in primary sensory neurons which has been implicated in the pathogenesis of NP perception, thus helpful in relieving neuropathic pain.[41]

Ocimum sanctum

Ocimum sanctum belonging to family Labiatae, also known as 'Holy Basil' is known for its therapeutic potentials. It has been demonstrated to block the NP by decreasing the oxidative stress and calcium levels, which play important role in pathogenesis of NP.[42] Saponins, important constituent in Ocimum sanctum is believed to be responsible for its beneficial effect in NP.[43] Ocimum sanctum is known to exert various other effects such as antidiabetic, antiulcer and antimicrobial.[44]

Acorus calamus

Acorus calamus belonging to family Araceae is an indigenous plant, used in the management of severe inflammatory disorders. Acorus calamus prevented chronic constriction injury (CCI) induced neuropathy which may be attributed to its multiple actions including anti-oxidative, anti-inflammatory, neuroprotective and calcium inhibitory actions.[45]

Emblica officinalis

Emblica officinalis (Amla) is a tropical, deciduous, small to medium sized tree with pale yellowish fleshy globose fruits. E. officinalis is famously known for its hepatoprotective and antioxidant activities.[46] the effective components in E.officinalis are flavanoids, tannins, Vitamin-C and are antioxidant in action.[47] Quercetin, a bioflavonoid is reported to attenuate neuropathic symptoms by inhibition of lipid peroxidation and restoration of antioxidant enzymes.[48]

Psidium guajava, Momordica charantia and Coccinia indica

P. guajava, commonly known as Guava is a native plant in tropical America and South East Asia. M. charantia, commonly referred to as bitterground or Korolla, is a climbing plant, cultivated throughout Southern Asia. C. indica, commonly known as Telakucha is a climbing plant, cultivated throughout Southern Asia. It has been reported that the combination of P. guajava, M. charantia and C. Indica attenuated neuropathic pain symptoms by inhibiting protein kinase C and oxidative stress.[49] **Table 2** indicates herbal drugs used in management of NP with mechanism of action.

Conclusion:

The present review opens vista for the management of neuropathic pain via herbal drugs and few synthetic drugs.

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