

Diabetic Neuropathic Pain

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Diabetes associated complications are major reason for morbidity and mortality associated with this disease and is major factor causing ramifications in the life of diabetic patients. Diabetic Neuropathy is one of diabetic complication having the most common occurrence. This disorder of peripheral nerves ends up in conduction deficits, deficit in nerve perfusion, and development of altered sensory perceptions. The quality and distribution of neuropathic pain is variable, although descriptions of burning pain in limbs are commonly reported. Neuropathic pain is one of the clinical manifestations of diabetic neuropathy and still persists as unmet clinical need. None of available treatments ensure complete reversal of sensorimotor changes that happen in patients with diabetic neuropathy. In this review we have tried to discuss newer therapeutic interventions that can be targeted in amelioration and reversal of developed sensorimotor changes.

Diabetic Neuropathy and Diabetic Neuropathic Pain

Almost 50-60% of the patients having history of diabetes are bound to suffer from diabetic neuropathy. Diabetic complications and especially diabetic neuropathy is adding economical burden to the patients in developing as well as in developed countries. The quality of life also suffers severe ramifications due to this complication of diabetes.

Diabetic neuropathy encompasses a spectrum of clinical and subclinical conditions that results in structural and functional alterations in peripheral as well as autonomic nerves¹. In Distal Peripheral Neuropathy (DPN), sensory deficits usually overshadow motor nerve dysfunction and appear first in the distal portions of the extremities and progress with increasing duration or severity of diabetes. The signs and symptoms of DPN vary depending on fibre type involved, with large fibre disease impairing proprioception and light touch. Small fibre disease impairs pain and temperature perception, leading to paresthesias, dysesthesias, and/or neuropathic pain². Distal weakness occurs only in the most severe cases. Diminished or absent deep-tendon reflexes, particularly the Achilles tendon reflex, often indicates mild and otherwise asymptomatic DPN. More advanced asymptomatic neuropathy may first present with late complications such as ulceration or neuroarthropathy¹.

Diabetic autonomic neuropathy (DAN) is the other form of

diffuse diabetic neuropathy. DAN often accompanies DPN and, as detailed in Table 2, can impair any sympathetic or parasympathetic autonomic function³.

Pain Pathology

The presentation of pain in diabetic neuropathy is very diverse. Patient may describe neuropathic pain as lancinating; burning; pins and needles; shooting; aching; jabbing; sharp; cramping; tingling; cold or allodynia in nature⁴. Pain can be of acute type or chronic based on the duration for which it persists. The pain can be ongoing, spontaneous; or hyperalgesic and its intensity may range from moderate to severe and some times intractable. When a patient having neuropathic pain visits a clinic, physicians are puzzled about the therapies for treating or giving symptomatic relief to the patient².

The need of understanding the neuropharmacology of pain is very crucial in setting out newer therapies and agents. Recent research suggests that, GABA, glutamate receptor, opioid receptors have been involved in pathophysiology of neuropathic pain. The increasing knowledge of neural and pharmacologic basis of pathophysiology of neuropathic pain is likely to affect the treatment implications and may lead to development and refinement of symptom-mechanism based approach to neuropathic pain.

Genesis of DPN

The major consequences of hyperglycemia assisted nerve damage are, sensitization of nerves, sprouting of nerve fibres, central sensitization, tissue injury due to inflammatory processes⁵.

The lesions in diabetic nerves are the primary structural dysfunction correlated with neuropathic pain. It results in

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increased excitability of the damaged and surrounding neurons. The neuronal hyperexcitability arises in the primary afferent fibres and spreads centrally. Accumulation of abnormal Na^+ channels in the periphery, as well as generation of new Na^+ channels results in excessive signalling to CNS⁶.

Uncontrolled neuronal firing leading to hyperexcitability of nerve is largely attributed to increased expression of Na^+ channels. The voltage gated Ca^{2+} channels are also increased after nerve insult and damage. Ca^{2+} entry is instrumental in the release of substance P and glutamate from the diseased nerves. The two mediators have profound effect in pathogenesis of diabetic neuropathic pain. The effectiveness of Ca^{2+} channel blockers (pregabalin and gabapentin) in treating the hyperalgesic and allodynic conditions associated with neuropathic pain⁶⁻⁸.

Nociceptors that are located in thinly myelinated A delta fibres and unmyelinated C fibre/neurons transduces multiple stimuli that include noxious, chemical and mechanical stimuli. The structural changes in these nociceptive fibres are well documented to be participating in pathophysiology of diabetic neuropathic pain^{4, 9-11}.

Sprouting of axons, sensitization and regeneration of frustrated and insulted nerve fibres are the outcome of persistent hyperglycemia in diabetic condition. Sprouting axons are also the major effectors of nerve fibre sensitization which further lead to complex pain pathways (Fig. 1). Whenever there is damage to C afferent fibres, A- δ fibres sprout into the space vacated by C fibres. These sprouted fibres make new contacts with the free central nociceptive neurons. This anatomic restructuring leads to the input from mechanoreceptors A- δ fibres (light touch) to be perceived as exaggerated pain^{2, 7, 9, 12}.

Peripheral sensitization also mediates major role in generation of diabetic pain (Fig. 2). It causes spontaneous pain sensation, mechanical hyperalgesia and thermal hyperalgesia. The spontaneous activation of nociceptors induces secondary changes in central processing of various stimuli. In the case of sensitization the condition of and their modulation in pain pathways. Both ionotropic (AMPA, NMDA and Kainate) and metabotropic receptors are reported in persistent pain states as well as in diabetic neuropathic

pain. The pharmacological modulation of these receptors has yielded and in future may yield fruitful results for treating diabetic pain^{11, 13, 14}.

AMPA receptors are expressed on dorsal root ganglion (DRG), and in both myelinated and unmyelinated sensory neurons. It is also widely expressed in spinal cord and many regions of brain. AMPA receptors have been implicated in synaptic plasticity associated with nociceptive signalling. They have profound effect on 2nd phase of formalin induced paw licking in rodents. It is also known to be involved in development of mechanical and thermal hyperalgesia along with mechanical allodynia. So targeting these receptors may turn instrumental in designing newer intervention for diabetic neuropathic pain¹⁴.

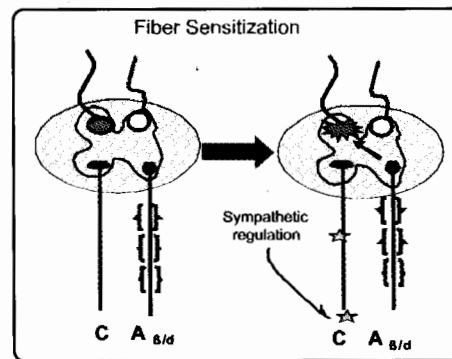


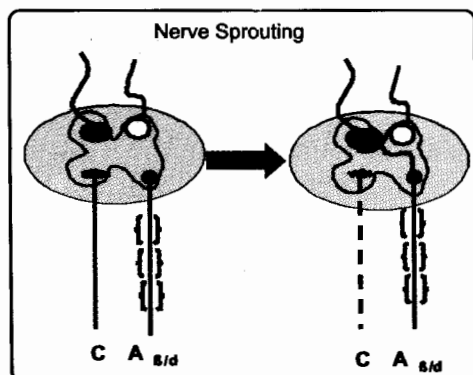
Fig. 2 : Schematic representation of the generation of diabetic neuropathic pain (Fiber Sensitization). Spinal cord is illustrated as an oval.

NMDA receptors are also expressed in DRG as well as on primary afferent neurons. They have also been traced over spinal cord neurons. The distribution of NMDA receptors in nociceptive pathways in the brain also proves its role in neuropathic as well as inflammatory pain. The development of NMDA receptor antagonist has been the subject of intense research for decades and has potential for pharmacological interventions¹⁵⁻¹⁷.

Kainate receptors are believed to have structural similarity with AMPA and NMDA receptors. Kainate receptors are widely distributed in peripheral as well as central nervous system. They are also located on neuronal dendrites and postsynaptic terminals. They have also been associated with pain physiology and pathophysiology. Targeting these can be attractive avenue for drug designing against neuropathic pain¹³.

Metabotropic glutamate receptors are known to be present on both pre and post synaptic neurons. The role of these receptors in nociceptive transmission is well known. They are present in periphery on DRG and peripheral terminal ends. These receptors have critical role in central sensitization in spino-thalamic tract neurons and have also known to play role in inflammation led sensitization of nerve fibres. Interventions targeting the metabotropic glutamate receptors may be useful in looking for some newer and efficient therapies for diabetic neuropathic pain^{14, 18}.

Fig. 1 : Schematic representation of the generation of diabetic neuropathic pain (Nerve Sprouting). Spinal cord is illustrated as an oval.



Role of inflammatory pathway has also been studied. There are many agents which check inflammatory pathway of diabetic neuropathic pain. The cytokines and cyclooxygenase (COX) has been well correlated with pathophysiology of pain under pathophysiological parameters. Many COX inhibitors have been found to affect diabetic neuropathic pain pathways ^{4, 19, 20}.

Available Treatments

The clinical management of diabetic neuropathic pain is often inadequate because of many reasons like inadequate diagnosis, inappropriate drug therapy, obscurity in the pathophysiological pathways leading to diabetic neuropathy. The existing strategies for treatment of diabetic neuropathic pain can be broadly classified either as treatment based on pathogenetic concepts or based on the symptoms.

Many agents that target the multifactorial pathogenesis of diabetic neuropathy are at various stages of clinical trials. Agents like α -lipoic acid (an antioxidant), ruboxistaurin (PKC- α inhibitor), ranirestat (Aldose reductase inhibitor), C-peptide and various other agents are in clinical stages of drug development. The advantage of these agents or agents like them is that they can even act in persistent hyperglycemia too. In the future, combination of agents at low doses might produce beneficial effect via synergistic mechanisms ^{4, 7, 11, 19, 21, 22}.

The other strategy for designing neuropathic pain is based on symptoms developed during diabetic neuropathic pain. As we all know that the symptoms in diabetic neuropathic pain may constitute a considerable problem. The use of single agents has not been sufficient and they have been adequate to control pain. Effective pain treatment should be designed after evaluating the ability to produce pain relief and the side effects that may develop with the therapy. Also the step wise management of diabetic neuropathic pain is also advisable.

There are many agents belonging to different categories have been studied and used for the treatment of diabetic neuropathy. The major categories are antidepressants, anticonvulsants, NMDA antagonists, SSRI, Na^+ channels blockers, Ca^{2+} channel modulators, opioids, NSAIDs etc.

Antidepressants

These are the agents that have been studied for last 3-4 decades for the treatment of diabetic neuropathic pain. Tricyclic antidepressants, Benzodiazepines, selective serotonin reuptake inhibitors, Na^+ and Ca^{2+} channel blockers fall under this category. In some countries drugs from this category has been licensed for treatment of neuropathic pain. Almost the conventional antidepressants have benefited one third patients which were treated for neuropathic pain. There are various adverse events that are associated with their usage. Thus we require evaluating their benefit Vs adverse effect profile. Activation of descending

norepinephrergic and serotonergic pathways to the spinal cord limit pain signals ascending to the brain. Antidepressants will relieve neuropathic pain in non-depressed persons ^{23, 24}.

Antiepileptics

Antiepileptic drugs have a long history of effectiveness in the treatment of diabetic neuropathic pain. Principal mechanisms of action of the drugs from this category include sodium channel blockade (felbamate, lamotrigine, oxcarbazepine, topiramate, and zonisamide), potentiation of γ -aminobutyric acid activity (tiagabine and topiramate), calcium channel blockade (felbamate, lamotrigine, topiramate, and zonisamide), antagonism of glutamate at N-methyl-d-aspartate receptors (felbamate), or -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (felbamate, topiramate). Very few drugs from this category (Carbamazepine and Gabapentin) have been approved by FDA for treating neuropathic pain. Others are in different stages of clinical trials ^{25, 26}.

Opioids

Opioids (narcotics), are increasingly recognized as second line treatment options for chronic pain. They are not considered as first line treatments in neuropathic pain but remain the most consistently effective class of drugs for this condition. Many agents from this category are used for treating the neuropathic pain. Adverse effect with opioid treatment are frequent as expected. The agents from this category can be also being tried in combination with the agents from other category ^{27, 28}.

NMDA antagonist

The NMDA receptor seems to play very important role in the pain pathophysiology. Various agents which are NMDA antagonist are being studied in neuropathic pain. Only few agents from this category are available commercially. These agents also can be attractive target for treatment of neuropathic pain ^{15, 17}.

NSAIDS

The agents from this category have been used to provide symptomatic relief from neuropathic pain. Agents like Ibuprofen and sulindac has been found effective in ameliorating neuropathic pain to some extent. These agents are not effective enough to provide complete relief in complex neuropathic pain conditions ^{29, 30}.

Topical agents

In this category mainly the local anesthetics (lidocaine, lignocaine, and procaine) and counterirritant (capsaicin) has been clinically tried for relieving the neuropathic pain symptoms and to alleviate the disease. These agents stabilization of membranes by inhibiting ionic fluxes necessary for the conduction of action potentials. Repeated topical applications of capsaicin, are followed by a

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prolonged period of reduced skin sensibility referred to as desensitization, or nociceptor inactivation. Capsaicin not only depletes substance P but also results in a reversible degeneration of epidermal nerve fibers⁸.

Cannabinoids

Marijuana and its active ingredients are called cannabinoids have been studied for efficacy in neuropathic pain. Various agents like dronabilone, nabilone, dihydrocodeine has been studied in neuropathic pain. The potent side effect like CNS and respiratory depression are major hurdle apart from its dependence causing potential in treated patients^{31, 32}.

Future Prospects of Newer Therapies

Even after decades of dedicated research on interventions targeted at diabetic neuropathic pain we don't have a single agent that can cure neuropathic pain fully or promise to reverse the developed sensory abnormalities in diabetic neuropathic pain. We still have to rely upon the handful of agents which belongs to category of opioids, NSAIDS, anti depressants, anti convulsants for pain treatment. There have been many reports on different agents being used to treat diabetic neuropathic pain. Recent literature shows that many agents are at different stages of clinical trial for diabetic neuropathic pain treatment⁴.

Their still persist some sort of lacuna in either diagnosing the disease or in developing a good therapeutic agent for treatment of diabetic neuropathic pain. Therefore the quest for a better agent with full credits of efficacy and safety is still on.

Now with the aid of newer techniques and advanced instrumentation we can elucidate deeper knowledge about neurobiology of this disease. The perception of increasing importance of drugs for pain treatment has lead to enormous increase in research of these agents. There are many agents who are either in clinical trials or knocking the doors of clinical trials for the treatment of neuropathic pain. These agents mainly belong to glutamate antagonist, cytokine inhibitors, vanilloid receptor antagonists, ion-channel blockers, anticonvulsants, opioids, cannabinoids and adenosine agonists etc.

The newer mechanism based therapies and multiple drug or combination therapies should be explored for efficacy in diabetic neuropathic pain. The combination of different agents targeting multiple pathways may be explored.

Conclusion

Although we are still some way from developing effective treatment of diabetic neuropathic pain, we do have now reasonably clear picture of major pathophysiological

pathways. The accessed knowledge should form a strong base for drug treatment and development. The research that is being currently pursued using advanced molecular techniques and highly equipped instruments and the frequency with which pathogenetic pathways are uncovered, very soon diabetic neuropathic pain will not be considered as mysterious condition.

Acknowledgement

Dr. SS Sharma would like to thank CSIR for financial support. Prof. Anil Gulati would like to thank for support of Fulbright and USIES.

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