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Review Article

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PATHOGENESIS OF DIABETIC NEUROPATHY

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Abstract

Diabetic neuropathy is the most common heterogeneous and debilitating microvascular complication of diabetes mellitus, which affects more than 50% of diabetic patients and is one of themajor cause of pain and mortality in patients. Diabeticneuropathic pain is that whicharises as a direct consequence of a lesion or disease affecting the somatosensory nervous system. Neuropathy is a common complication of both type 1 as well as type 2 diabetes. Diabetic peripheral neuropathy is the most prevalent peripheral neuropathy because Peripheral nerves involvement is highly frequent in diabetes mellitus and it has been documented that about one third of diabetic patients have peripheral neuropathy. Diabetic neuropathy represents a dynamic flux between neuronal degeneration and regeneration.Hyperglycemia showed the strongest evidence for diabetic neuropathy because it activate the various pathway such as- polyol pathaway, advanced glycation end products, protein kinase C, and hexosamine pathway which causes mitochondrial dysfunction and produced reactive oxygen species as well as reactive nitrogen species and decrease antioxidant enzymes such as glutathione, superoxide dismutase which ultimately generated oxidative stress and endothelial dysfunction in nerves.

Keywords: Diabetic neuropathy, Hyperglycemia, Oxidative stress, Polyol pathway, Cytokines.

INTRODUCTION

Diabetic neuropathy is the most common and debilitating complication of diabetes mellitus, leading to the greatest morbidity and mortality among diabetic patients worldwide (Vinik *et al.*,1995). Diabetes is chronic condition in which the body does not form sufficient insulin to metabolite the glucose therefore the level of glucose increases in the nerves and this elevated blood glucose may be toxic for nerves thus chronic hyperglycemia showed the strongest evidence for the development of diabetic neuropathy (Narayan *et al.*, 2003). There are two well known type of diabetes such as Type 1 and Type 2 and diabetic

neuropathy has been noted to occur both forms of diabetes i.e. type 1 (insulin dependent diabetes mellitus) and type 2 (non-insulin dependent diabetes mellitus) (Zimmet *et al*., 1996, Zimmet *et al*., 1997). Diabetic neuropathy represents a dynamic flux between neuronal degeneration and regeneration, so usually about more than 50% of diabetic people with duration of diabetes of 25 years or more affected, making it one of the most common disease of the nerve disorders. One of the largest published series documented a prevalence of diabetic neuropathy about 8% in newly diagnosed patients and greater than 50% in patients with long-standing disease (Pirat *et al* .,1947, Boulton *et al*., 2005). In India, studies have demonstrated that about 40 million people are suffering from diabetes out of which 10.4 million are suffering from DN. In addition, it has been frequently associated with devastating pain. Most of the neuropathy cases are assocaited with abnormal pain and sensations. Neuropathic pain, is defined as "pain arising as a direct consequence of a lesion or diseases affecting the somatosensory nervous system" (Treede *et al*., 2008,Winkler *etal*., 2010). It has been demonstrated that the chances of development of neuropathy increases with duration of diabetes (Tesfaye *et al*., 1996). Diabetic neuropathy is a descriptive term that encompasses spectrum of clinical and subclinical syndromes with various anatomical distribution, clinical courses, and possibly several underlying pathogenic somatic or autonomic nerve fibers resulting from diabetes mellitus. Diabetic neuropathy encompasses a variety of forms whose impact ranges from discomfort to death.

CLASSIFICATION OF DN:

Diabetic neuropathy is not a single entity but a number of different syndromes, ranging from subclinical to clinical manifestation depending on the classes of nerve fibers involved. It has been well documented that the signs and symptoms of DN vary depending upon the types of neuropathy and the nerves affected.

DN can be classified as:

- Peripheral neuropathy,
- Autonomic neuropathy,
- Proximal neuropathy and
- Focal neuropathy (Vinik et al., 2003; Chance et al., 2006; Kanji et al., 2010).

Peripheral neuropathy:

Peripheral neuropathy, also called distal symmetric neuropathy or sensorimotor neuropathy. It is the most common type of DN in which the distal parts of the extremities are affected resulting in sensory loss. It involves both small as well as large fibers and has insidious onset. Moreover, it involves the damage of nerves in legs, hands and arms (Boulton et al.,1983). The symptoms can be manifested by altered temperature perception, hyperaesthesia, par aesthesia, numbness, hyperalgesia, allodynia, lancinating pain tingling or burning feeling, muscle weakness, serious foot problems, bone and joint pain and deadness in the lower limbs (Sugimoto et al.,

2000).These symptoms are often worse at night. Foot deformities, such as hammertoes and the collapse of the midfoot, may occur.

Autonomic neuropathy

Autonomic neuropathy is a serious and often overlooked component of diabetic neuropathy. Any organ of the body which is supplied by autonomic nerves can affected ultimately leads to the altered functions of digestive system, heart, sweat glands, sexual organs, bowel and bladder function, perspiration and urinary system. Autonomic neuropathy can also cause hypoglycemia unawareness, a condition in which people no longer experience the warring symptoms of low blood glucose levels (Gibbons et al., 2010). It has been documented that about 65% of type 2 diabetic patients have autonomic neuropathy. Further, the severe form ofautonomic neuropathy affects the survival and leads to sudden death (Toyry *et al*., 1996).

Proximal neuropathy:

Proximal neuropathy, sometime called lumbosacral plexus neuropathy, femoral neuropathy, or diabetic amyotrophy, starts with pain in the thighs, hips, buttocks, or legs, usually on one side of the body. It mainly affects the elderly males (> 50 year) suffering from type 2 diabetes mellitus. They may be symmetrical or asymmetrical, with or without sensory loss (Barohn et al., 1990). It predominately affects anterior (quadriceps) and adductor compartments of thigh. Wasting and weakness of quadriceps is so severe that the knee often given way, and patient may fall. In addition, patients presented with this class of DN usually find difficulty in climbing the stairs due to pain, getting up from squatting position followed by marked weight loss.

Focal neuropathy:

Focal neuropathy appears suddenly and affect specific nerve which is mainly assocaited with head, torso or leg. Focal neuropathy may cause inability to focus the eye, double vision, aching behind one eye, paralysis on one side of the face which is well known Bell's palsy syndrome, severe pain in the lower back or pelvis, pain in the front of a thigh, pain in the chest, stomach, or side, pain on the outside of the shin or inside of the foot, chest or abdominal pain that is sometimes mistaken for heart disease, a heart attack, or appendicitis (Boultonet al., 1984). It is well known type of painful and unpredictable neuropathy and occurs most often in order adults with diabetes. However, it tends to improve by itself over weeks or months and does not cause long-term damage. The major subtype which are involved in focal neuropathy are: Cranial neuropathy, Truncal neuropathy, Entrapment neuropathy.

Pathogenesis of diabetic neuropathy:

Hyperglycemia clearly plays a key role in the development of diabetic neuropathy as well as other diabetic complications. Over the past 25 years animal experiments and in vitro studies have comprehensively reported that hyperglycemia-induced signaling mechanism activate the various pathway such as- polyol

pathway, advanced glycation end products, protein kinase C, and hexosamine pathway, Poly (ADP-ribose) polymerase pathways which causes mitochondrial dysfunction and produced reactive oxygen species as well as reactive nitrogen species and decrease antioxidant enzymes such as glutathione, superoxide dismutase which ultimately generated oxidative stress and endothelial dysfunction in nerves and contribute to the pathogenesis of DN (Winkler *et al*., 2001, Obrosova *et al* 2009., Fernyhough *et al*., 2010). In addition, other growth factors like insulin like growth factor (IGF), Pro inflammatory mediators such as nuclear factor κB, various cytokines and C-peptide also finds their role in development and progression of DN. While each pathway may be injurious alone, collectively they cause an imbalance in the mitochondrial redox states of the cell and lead to excess formation of reactive oxygen species (ROS) (Kong et al.,1999, Vinik et al., 2003).

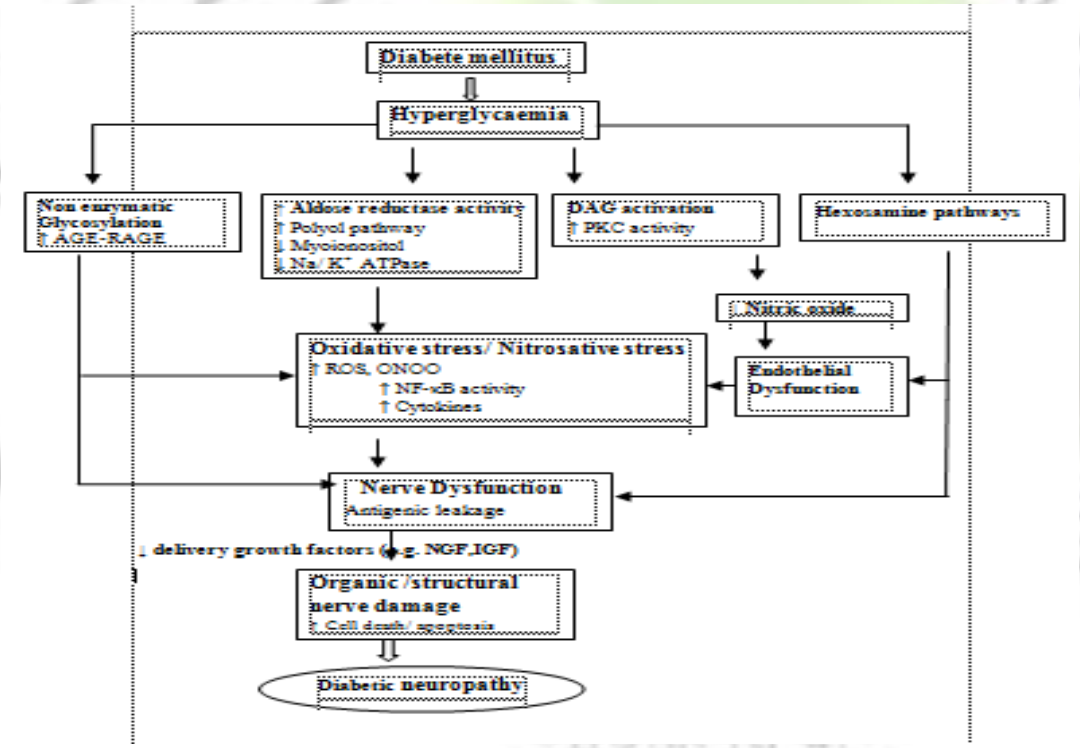

Fig1: Possible interaction of various pathogenic mechanisms for the development of DN.

Polyol pathways:

In chronic hyperglycemia, the increased intracellular glucose level has to be metabolized by the polyol pathway, also called as sorbitol/aldose reductase pathway. In the event of hyperglycemic intercellular glucose level rises and excess glucose is shunted into the polyol pathways through their enzyme such as aldose reductase and sorbitol dehydrogenase respectively (Oates *et al*., 2002). The first enzyme aldose reductase (AR) reduces glucose into sorbitol with the help of NADPH Co-factor, and the second enzyme, sorbitol dehydrogenase (SDH) with the aid of its CO-factor NAD^+, converts sorbitol to

fructose (Figure.1). However, the nerve cell membrane is relatively impermeable to sorbitol and fructose, which tend to accumulate within the nerve (Raccah *et al.*, 1989). Fructose and sorbitol both being osmotically active compounds lead to increase in the water content in the nerve. In addition free carnitine and myo-inositol in the caudal nerves of diabetic rats were significantly decreased with polyol pathways (Nakamura *et al*., 1998). The NADPH, used up when the pathway is activated, acts to promote nitric oxide and glutathione production, and its conversion during the pathway leads to reactive oxygen species. Glutathione deficiencies can lead to hemolysis caused by oxidative stress, and we already know that nitric oxide is one of the important vasodilators in blood vessels. NAD^+, which is also used up, is necessary to keep reactive oxygen species from forming and damaging cells. Furthermore, the high levels of sorbitol are believed to reduce the cellular uptake of another alcohol, myoinositol, decreasing the activity of the plasma membrane Na^+/K^+ ATPase pump required for nerve function, further contributing to the neuropathy. In summary, excessive activation of the polyol pathway leads to a) excess production of sorbitol b) deficiency or depletion of glutathione (GSH), c) excess production of ROS and d) excess production of AGEs. Thus, intracellular accumulation of sorbitol is harmful because firstly, it causes cell damage, and second, it potently activates stress-sensitive signaling pathways including P3 MAPK and JNK and these both are highly responsible for diabetic neuropathy. Moreover, both AR deficiency and AR inhibition reduced oxidative stress in the peripheral nerves and markedly protected mice from diabetes-induced functional deficits (Ho *et al*., 2006). All the finding suggest that AR contributes to the pathogenesis of diabetic neuropathy via oxidative stress. Although a number of AR inhibitors have been tested or are currently undergoing testing in clinical trails (Giannoukakis *et al*., 2008), the clinical efficacy is uncertain and there are concerns with assocaited adverse effects such as hepatic damage. Sorbinil was the prototype ARI to be developed solely for diabetic neuropathy treatment.

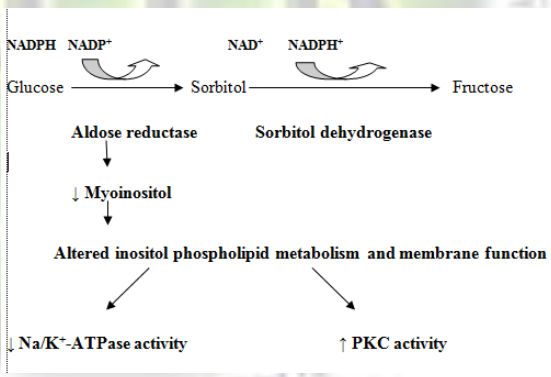

Fig.2 Hyperglycemia induced sorbitol pathway/ Polyol pathway

AGEs PATHWAY:

In hyperglycemia states, glucose is combined with protein and sugar unit in plasma . The process is called protein glycation end products formation and the products obtained by these process is called Advanced glycation end products (AGEs) (Ahmed *et al*., 2005,

Schleicher *et al*, 2007.,). AGEs are a heterogeneous group of compounds that are produced by nonenzymatic, sequential glycation and oxidation of sugars with free amino groups on proteins, peptides, or amino acids. This sequence of events is known as the Maillard reactionwhich firstly identified in 1912 (Vlassara *et al*., 2002, Peppa *et al*., 2004, Fu *et al*.,1996, Finot*et al.*, 2005).

There are three main pathways involved in the formation of AGEs precursors:

1) Oxidation of glucose to form glyoxal
2) Degradation of Amdori products (Fructose lysine adducts)
3) Aberrant metabolism of glucolytic inetmediates to methyglyoxal

Methylglyoxyl, a highly reactive dicarbonyl, is shown to induce sensitivity to vascular damage in endothelial cells (Yao *et al*., 2007).

Mechanism to induce diabetic neuropathy through AGEs and RAGEs formation

Hyperglycemia induced AGEs on peripheral nerve myelin contributes to segmental demyelinationby increasing its susceptibility tophagocytosisby macrophages; it also modifies axonal cytoskeletal proteins (tubulin, neurofilament,actin), resulting in axonal atrophy and degeneration withreduced regenerationdue to glycation of laminin (Boulton *et al*., 2010). A vicious cycle gradually supervenes; AGE – RAGE interaction producing ROS and these ROS accelerate AGE generation, and AGE quenching NO (Bucala *et al*.,1991). The quenching action of AGE binding on NO is relevant to nerve ischemia. The reduction of NO is one of the most important mechanisms of ischaemic nerve injury. AGEs results in axonal atrophy/degeneration and impaired axonal transport; and glycation of extracellular matrix protein laminin leads to impaired regenerative activity in diabetic neuropathy. Therefore AGEs playing the role of an amplifier of the surmounting inflammatory response in the diabetic hyperglycemic state, brings about a plethora of changes through activation of NF-κB, expression of adhesion molecules, activation of cytokines, inhibiting NO and generation of superoxide anions which finally leads to diabetic neuropathy. Glycation occurs in virtually all proteins expose to hyperglycemia. Although initial glycation is reversible, chronic exposure to hyperglycaemia leads to irreversible formation of advanced glycation end products (AGEs) (Cameron *et al*., 1992, Rosen et al., 2001).

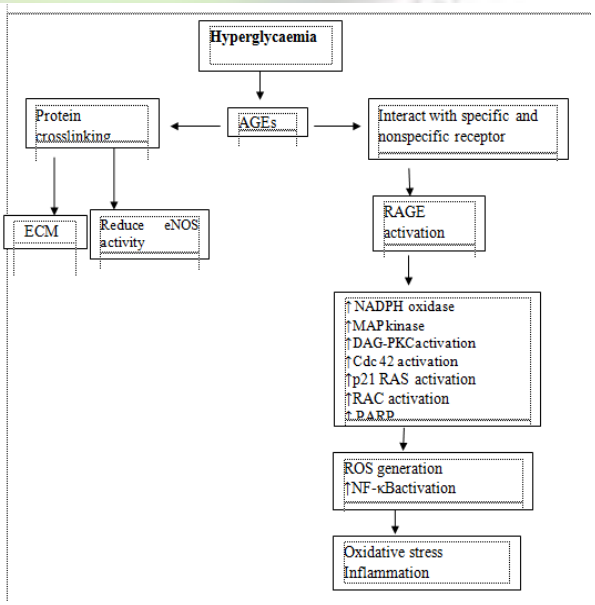

Fig 3 The AGE cascade inducing oxidative stress as well as inflammation in diabetic neuropathy

Cdc42, Cell division cycle 42 protein; DAG, diacyl glycerol; eNOS, endothelial nitric oxide synthase; LDL, low density lipoprotein; MAP, mitogen-activated protein; NAD(P)H nicotinamide dinucleotide phosphate; NO, nitric oxide; PKC, protein kinase C; ROS, reactive oxygen species.

Protein kinase C:

The protein kinase C (PKC) pathway is an additional mechanism by which hyperglycemia causes injury in complications-prone tissues. Long term hyperglycemia modulates diacylglycerol (glyceraaldehyde-3-phosphate dehydogenase), which in turn activate protein kinase C (PKC)

(Cameron *et al*.,1999). PKC belongs to the family of serine-threonine kinases which are multifunctional isoenzymes acting as an intracellular signal transduction system for many hormones and cytokines (Nishizuka *et al*., 1992). In DN, the PKCs have been noted to be activated by increased DAG levels either by the inhibition of DAG kinase or by the denovo synthesis. Moreover, it has been observed that the PKC activation causes abnormalities in the blood flow and promotes the activation of nuclear factor kappa-B (NF-κB). The complications in blood flow result in the interrupted blood supply to nerves ultimately causing neuronal damage (Cameron *et al*., 2002).

Hexosamine pathway:

Hyperglycemia stimulates hexosamine pathway through production of ROS in endothelial cells. During hyperglycemia fructose 6-phosphate is converted to glucosamine 6-phosphate through glutamine fructose 6-phosphate aminotransferase (GFA1) enzyme (Thornalley *et al*., 2005). Fructose-6-phosphate is a metabolic intermediate of glycolysis. Future processing Glucosamine-6 phosphate is then converted to uridine diphosphate-N-acetyl glucosamine (UDPG1cNAc), a molecule that attaches to the serine and threonine residues of transcription factor (Brownlee *etal*., 2001). This pathway leads to increased transcription of transforming growth factor (TGF-α and TGF-β) and plasminogen activator inhibitor-1 and has been implicated in insulin resistances. Inhibition of GFAT blocks the transcription of TGF-α, TGF-β and PAI-1. Glucosamine has been shown to elevate H_2O_2 levels and antioxidants tend to inhibit this effects (Evans *et al*., 2005). Over expression of both TGF-β and PAI-1 has been reported to contribute to contribute to pathogenesis of diabetic neuropathy. Both of these factors are affected by increased shunt as well as by PKC activation. Hexosamine pathway also functions as a cellular sensor of energy availability and mediates the effect of glucose on the genes, inflammatory cytokines and plasminogen activator-I of several gene products. Obviously the over activation of hexosamine pathway in hyperglycemic

condition promotes several complications (Brownlee *et al*., 2005).

Benfotiamine is a fat-soluble analogues of thiamine/vitamin B1 that activated transketolase, an enzyme converting fructose-6-phosphate into pentose-5-phosphates. The reduced fructose-6 phosphate input decreases flux through the hexosamine pathway (as well as flux through the advanced glycation end product (AGE) and the diacylglycerol (DAG)-protein kinase C (PKC) pathways (Hammes *et al*., 2003).

Oxidative stress:

The AGEs, polyol pathway, hexosamine, PKC and PARP pathways all contributes to system neuronal damage due to formation reactive oxygen species. AGE and polyol pathways directly alter the redox capacity of the cell either through direct of ROS or by deplection of necessary components of glutathione recycling. The hexosamine, PKC, and PARP pathways exhibit damage through expression of inflammation proteins. ROS have been noted to play crucial role in the pathogenesis of DN.

ROS are the small molecules which are highly reactive molecules that include free radicals, peroxides and oxygen ions, formed by cellular energy metabolism as their natural by products (Erol *et al*., 2007). Moreover, studies have shown that ROS can directly damage neuronal cells, i.e., Schwann cells. ROS have been noted to produce perfusion of peripheral nerve which produces the earliest defects in nerve function and further increases in nerve damage by causing ROS dependent effects (Lelkes *et al*., 2001). Furthermore, it has been shown that ROS inhibition helps in restoration of both vascular and metabolic imbalances which may lead to the blockage of initiation and progression of complications in DN (Feldman *etal*., 2003).

"Oxidative stress mainly occurs when there is an imbalance between free radicals and the scavenging capacity of antioxidants defense mechanism of the organism" (Sies *etal*., 1991).

The progression of diabetic neuropathy in a distal-proximal axon length-dependent manner suggests that damage is initiated in the axon (Leinninger *et al*., 2006). Axons are susceptible to hyperglycemic damage both due to their access to nerve blood supply and their large population of mitochondria. Hyperglycemia environment coupled with a comprised blood supply overloads the metabolic capacity of mitochondria producing oxidative stress (Brownlee *et al*., 2001). This oxidative stress leads to mitochondria damage followed by axonal degeneration and death.

Inflammation:

Inflammatory agents includingC-reactive protein and TNF-α are present in the blood of both type1 and type 2(Gomes *et al*., 2003; Gonzalezclemente *et al*., 2005). Higher levels of these proteins correlate with the incidence of neuropathy (Gonzalez-Clemente *et al*., 2005). Recent data demonstrates a correlation between diabetic neuropathy and plasma levels of HSP 27 (Gruden *et al*., 2008). HSP

27 is a required intermediate in the pathway of TNF-α induction of the inflammatory mediators cyclooxygenase-2 (COX-2), IL-6 and IL-8. The production of the initiating inflammatory mediators TNF-α and TNF-β results from several of the glucose induced pathways already outlined (Vincent and Feldman *et al*., 2004; Brownlee *et al*., 2005). When excess glucose is shunted through alternative metabolic pathway such as the fructose 6 phosphate or diacyl glycerol the signaling intermediates and modified transcription factors lead to increases in TGF-β and NF-Kb (Brownlee *et al*., 2001). COX-2 is an important enzyme that is upregulated by NF-κB (Lee *et al*., 2004). This upregulation is observed in peripheral nerves an vascular tissues in experimental diabetes (Kellogg and Pop-Busui *et al*., 2005). COX-2 activity appears to drive a fed-forward loop since COX-2 is upregulated by NF-κB and in turn it generates prostaglandin E2 and ROS that activate NF-κB. Pharmacological blockade or gene ablation of COX-2 prevents diabetes-induced changes in peripheral nerves including deplection of GSH, increases in TNF-α, and bloodflow and nerve conduction deficits (Kellogg et al., 2007; Matsunage *et al*., 2007). All of the inflammatory mechanisms in diabetic neuropathy appear to converge upon the activation of NF-κB. Because of chronic NF-κB activation, blood vessels and nerve cells are more susceptible to injury in ischemia reperfusion (Wang *et al*., 2006). Subsequent to ischemia reperfusion there is extensive infiltration of monocyte macrophages and modest infiltration of granulocytes in diabetic peripheral neuropathy (Wang *et al*., 2006). The cytokines induced by NF-Kβ in endothelial cells, Schwann cells and neurons also lead to macrophage recruitment in diabetic nerves (Yamagishi *et al*., 2008). Two classes of TNF antagonists are currently commercially available: soluble TNF receptor-Fc fusion proteins (etanercept) and anti-TNF monoclonal antibodies (infliximab and adalimumab). Any benefit of treatment with etanercept was probadly mediated by inhibition of the pro-inflammatory role of TNF in the pathogenesis of inflammatory demyelination neuropathies (Hartung *et al*., 1992; Hartung *et al*., 1993). By modulating cytokine activity, TNF-antagonists have potential as an antigen-nonspecific treatment approach to inflammatory demyelination of the central and peripheral nervous systems.

Growth factors:

Growth factors promote the growth and survival of neurons and direct neurite outgrowth (Leinninger *et al*., 2004). Given that diabetic neuropathy is characterized by neuronal degeneration and damage to supporting Schwann cells, perturbations in growth factors such as nerve growth factor (NGF), insulin like growth factor (IGF) and neurotrophins 3 (NT-3) have been suggested to be involved in the pathogenesis of diabetic neuropathy. These factors bind to heterodimeric tyrosine kinase receptors. Expression levels of multiple growth factors

are altered in animals models of DPN. NGF is the most studies growth factor in diabetic neuropathy. NGF is produced by muscle and keratinocytes, and its trkA receptor is expressed on sensory and sympathetic neurons (McMahon *et al*., 1994,1995; Averill *et al*., 1995; Fang *et al*., 2005). Insulin like growth factors have been reported to be reduced in some animal models of diabetes, although this varies and may be dependent upon the model, type of diabetes, and tissue examined (Ekstrom *et al*., 1989; Wuarin *et al*., 1994; Zhuang *et al*., 1997; Craner *et al*., 2002; Schmidt *et al*., 2003; Kamiya *et al*., 2006). A number of preclinical studies in diabetic rats suggest systemic or intra thecal IGF therapy can improve neuropathy (Ishii& Lupien *et al*., 1995; Zhuang *etal*., 1997; Schmidt *et al*., 1999,2000: Lupienet *et al*., 2003; Brussee *et al*., 2004; Toth *et al*., 2006). IGFs have been noted to act on specific receptors which are present 100 times more as compared to insulin in the circulation. The IGF receptors are present in sensory neurons and Schwann cells (Ranke *et al*., 2005). Consequently, the insufficiency of IGFs may lead to the pathogenesis of regenerative capacity, neurodegeneration and irreversible stages of DN (Brussee *et al*., 2004). In addition, some other factors like C-peptide have also been found to possess crucial role in the pathogenesis of DN. Futuremore, C-peptide is a segment of proinsulin molecule which is used to form insulin. The C-peptides produces multiple insulin and IGF-like effects by acting on its own receptors and by modulating the activity of insulin receptors (Sima *et al*., 2004). It has been demonstrated that the autophosphorylation of insulin receptors and the effects of insulin are increased by C-peptide (Kamiya *et al*., 2004). Moreover, the insufficiency of C-peptide has an important role in the pathogenesis of DN. The C-peptide treatment regulates skin microcirculation in the diabetic patients, thermal hyperalgesia, atrophy and endoneurial blood flow confirming the role of C-peptide in the progression and development of DN (Stevens *et al*., 2004; Pittenger *et al*., 2005).

TREATMENT AND MANAGEMENT OF DN:

Antidepressants:

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) have represented the first line treatment for painful diabetic peripheral neuropathy (Collins *et al*., 2000). Studies have been shown that these agents promote successful analgesia to thermal, mechanical and electrical stimuli in diabetic patients (Nash *et al*., 1999, Mc Quay *et al*., 1996). They may have, however, intolerable side-effects related mainly to their anti-cholinergic action (Backonja *et al*., 1998). These include sedation, blurred vision, dry mouth, orthostatic hypotension and cardiac arrhythmias. The major drugs which are involved in TCAs are- Amitriptyline, nortriptyline, imipramine, Desipramine (Norpramin, Pertofrane). TCAs inhibit re-

uptake of noradrenaline and serotonin (Rang *et al*.,1998). They also seem to alter the mode of action of α1 adrenergic receptors, reducing sympathetic activity and blocking hyperalgesia induced by NMDA receptors (Courteix *et al*., 1994).

Selective serotonin re-uptake inhibitors

Selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) have been more recently developed, based on the significant role of norepinephrine in endogenous pain modulation through the descending norepinephrine inhibitory pathway. Well-conducted studies have shown efficacy with duloxetine (Cymbalta) in PDN (Raskin *et al*., 2005; Wernicke *et al*., 2006). The use of higher dosage does not improve efficacy, but is instead assocaited with more frequent side effects (Goldstein *et al*., 2005, Raskin *et al*., 2005). The effects of SSRIs are limited in DPN. Fuloxetine, 40 mg/kg is not different from placebo. In crossover study with paroxetine and imipramine, significant benefits from paroxetine (Paxil) 40 mg/day are obsereved (Sindrup *et al*., 1990b). The improvement is less than imipramine 50 mg/day but butter than placebo. Citalopram (Celexa) 40 mg/day has also been shown to be better than placebo for treating DPN (Sindrup *et al*., 1992). The other types of SSNRIs are Venlafaxine, Bupropion (Welbutrin).

Opioids and opioid like drugs such as controlled-release oxycodone, an opioid; and tramadol (Ultram), an opioid that act as antidepressant. Tramadol is a weak opioid agonist and a relatively effective serotonin and norepinephrine reuptake inhibitor.

Anti-convulsants:

Gabapentin:

Gabapentin is widely used for neuropathic pain due to its effectiveness and relatively fewer side effects than TCA and other anticonvulsants. Gabapentin produces analgesia via binding to the α2-δ site of L-type voltage gated calcium channels and decreasing calcium influx. Randomized clinical trails using 165 patients demonstrated that gabapentin < 2400 mg/day is effective in treating DPN compared to amitryptyline <90 mg/day (Backonja et al., 1998; Dallocchio et al., 1998; Dallocchio et al., 2000). However, another clinical study found no difference between gabapentin (900-1800 mg/day) and amitriptyline (25-75 mg/day) (Morello et al., 1999).

Anticovulsants control neuronal excitability by blocking sodium and/or calcium channels (Wiffen et al., 2005). Sodium valproate enhanced GABA levels in the central nervous system, inhibits T-type calcium channels, and increases potassium inward currents. Again side effects, including hair loss, weight gain, hepatotoxicity, and cognitive dysfunction are not insignificant and increase with log term use, although a dose of 500 mg/day decreases DPN (Kochar et al., 2004).

Pregabalin:

Pregabalin are approved by U.S. Food and Drug Administration specifically for treating painful diabetic peripheral neuropathy and

postherpetic neuralgia. It is a GABA analogue with apparently no effect on GABA receptor (Bennett et al., 1998). Current evidence also suggests no direct interaction with sodium or calcium channels, and its mechanism is known (Tremont-Lukats et al., 2000). Pregabalin, like gabapentin, is excreted unchanged in the urine. However, Pregabalin requires divided doses similar to gabapentin.

Carbamazepine:

It is commonly used drug in neuropathic pain. When initating carbamazepine, it is advisable to begin with a low dose of 100 mg and then increase granually until there is significant relief of symptoms or side effects are encounted. Carbamazepine has been shown in animal models to reduce pain induced by inflammatory mediators (Killian et al., 1964).

Others drugs: Lamotrigine, Topiramate, Zonisamide and Oxcarbazepine, phenytoin, are some other anticonvulsants drugs that are used for the treatment of DPN (Vinik et al., 2007; Raskin et al., 2004; Atli and Dogra et al., 2005).

Anti-arrhythmic agents

Mexiletine:

Mexilitine is an anti-arrythmia medication and has been for treating a variety of painful neuropathic conditions including DPN (Jarvis and coukell et al., 1998). Several randomized placebo control control trails have been performed, but none of the studies revealed greater than 50% reduction in pain scores. Slow release oxycodon 20 mg/day relieves DPN over a 6-week period (Gimbel et al., 2003). In a crossover design treatment strategy, slow release oxycodon was effective against DPN at a maximum dose of 80 mg/kg (Watson et al., 2003). Although opioids are effective against DPN, long-term use of opioids will result in side effects.

Lignocaine:

The potential beneficial use of lidocaine in diabetic painful neuropathy was first reported by Kastrup (Petersen et al., 1986). Lignocaine is often reserved for patients exhibiting excruciating neuropathic pain and is not appropriate for long-term treatment because oral dosing is unavailable and electrocardiogram (ECG) monitoring is required during intravenous administration (Coe et al., 1991).

Analgesics

Paracetamol, salicylate and non-steroidal anti-inflammatory drugs (NSAIIDs) are demonstrate to be ineffective or poorly effective against neuropathic pain (Argoff et al., 2006; Attal et al., 2010).

On one end they have poor efficacy and the other end they have adverse effects. Long term NSAIDs ingestion causes heptotoxicity, while narcotic analgesia causes addiction and worsening of autonomic neuropathic symptoms.

Tropical treatments:

The major drugs which are involved in the treatment of painful neuropathy are: Capsaicin, Op-site, ARC-4558(0.1% Clonidine gel).

NMDA antagonists:

Dextromethorphan

The role of excitatory amino acids in neuropathic pain has lead to the use of dextromethorphan, a low affinity NMDA receptor blocker, which shows promising results in relieving diabetic neuropathic pain (Sindrup et al., 1999). It was reported significant pain improving with dextromethorphan over placebo using a crossover design (Nelson et al., 1997). However, the sample size in this study was small (*n*=13).

Neurokinin receptor antagonists:

Lanepitant

Substance P is throught to mediate pain and inflammation through binding to the neurokinin 1 receptor (NK-1) (Watson et al., 1837). Lenepitant is a potent selective NK-1 antagonist, the effects of which have been found to be successful in animal models of persistent pain (Tjolsen et al.,1992). However, there is little evidence for its role in human painful diabetic neuropathy. Althought lanepitant is an ineffective monotherapy, it may have a role as an adjunct therapy with NMDA antagonists (Goldstein et al., 2001).

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