ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD

Volume - 01 Issue - 03 MAY-JUN 2013

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Research Article

MOLECULAR MECHANISMS AND NEUROPATHIC PAIN OCUURING DUE TO DIABETIC CONDITION

Gursimranpreet Singh, Ankit Dhir, Manveen Bhardwaj, Neha machhan, R.D.Budhiraja, Saurabh Sharma.

Department of Pharmacology, ISF College of pharmacy, Moga, India

Received: 22 May 2013, *Revised and Accepted: 28 May 2013*

ABSTRACT

This review is focussed on the various pathways which are involved in the neuropathic pain which mainly arises due to diabetic condition, like Polyol pathway, AGE pathway, hexosamine pathway etc. also the various mediators of pain are discussed understanding of which is useful in detailed study of neuropathic pain, like interleukins, cytokines, macrophages etc. All these processes involved lead to the painful neuropathic condition.

INTRODUCTION

Neuropathic pain is defined as ‘‘pain arising as a direct consequence of a lesion or disease affecting the somatosensory nervous system” [1]. Diabetic neuropathy is a descriptive term that encompasses spectrum of clinical and subclinical syndromes with various anatomical distributions, clinical courses, and possibly several underlying pathogenic mechanisms. It has been estimated that by the year 2030 the total number of effected patients by diabetes mellitus will stand at 350 million. [2]. Micro and macrofunctional abnormalities are associated with both type 1 and type 2 diabetes, and these complication include retinopathy, nephropathy, painful neuropathy and cardiomyopathy. [3].

*For Correspondence:
Gursimranpreet Singh
Department of pharmacology
I.S.F. College of Pharmacy, Moga, Punjab

Painful diabetic neuropathy in mainly due to presence of chronic state of diabetes.In diabetic peripheral neuropathy, both myelinated and unmyelinated nerves are damaged; the most affected being the longest axon, these damaged nerves often results into abnormal pain perception and produce the sensory symptoms [4]

Various mechanisms has been thought to be involved in the development of painful diabetic neuropathy, these include oxidative stress [5], formation of advanced Glycation end-product (AGE) [6], increased flux through the Polyol pathway [7], myoinositol depletion and reduction in Na^+/K^+-ATPase activity, deficits in neurotrophism neurotrophin-3 And insulin-like growth factor as well as alterations in Axonal transport (kuwabara and misawa, 2008) and PARP over-activation [8]. In addition to this, altered Sensory processing in the spinal cord may contribute to the development of diabetic Neuropathic pain [9].

Advanced Glycation End-products (AGEs) Pathway and PDN

Long standing hyperglycaemia has been reported to be involved in the formation of advanced glycation end- products [10-11]. AGEs are heterogeneous modified intracellular and extracellular bio-molecules formed via a non-enzymatic reaction between reducing sugars and amine residues on proteins, lipids, or nucleic acids [12]. Extracellular protein AGEs include Plasma and matrix proteins that disrupt cellular adhesion and activate the receptor for AGEs (RAGE) [13]. Activation of RAGE or AGE-RAGE interaction induces oxidative stress (Yamagishi. 2009), PKC [14] and the transcription of nuclear factor kappa B (NF-κB) [15]. The promoter region of RAGE contains functional binding elements for NF-κB, and one consequence of NF-κB translocation is the up-regulation of RAGE itself . NF-κB is a pleiotrophic gene regulator that regulates genes involved in promoting inflammatory reactions and neuronal dysfunction. Diabetic mice lacking RAGE showed significant improvement in PDN and diminished expression of NF-κB and PKC as compared to wild type diabetic [10]. Collectively, the biochemical damage induced by AGEs results in increase ROS, impaired nerve blood flow and diminished neurotrophic support contributes to neuronal injury [13-16]. A growing body of data demonstrate that AGEs are intimately involved in the pathophysiology of cardiovascular disease by stimulating inflammation, contributing to atheroma formation, and modulating vascular stiffness [17].

Polyol Pathway and PDN

Increased flux, through the polyol-pathway leading to multiple biochemical abnormalities in the diabetic nerve, is thought to play a significant role in the pathogenesis of diabetic neuropathy [18]. In polyol pathway, glucose is converted into sorbitol by aldose reductase (AR) and sorbitol dehydrogenase oxidises sorbitol to fructose. Nicotinamideadenosine dihydrogen phosphate (NADPH) is consumed by aldose reductase- mediated reduction of glucose to sorbitol [19] and NADPH is required for regeneration of antioxidant enzyme glutathione (GSH), thus deficient amount of glutathione contributes to oxidative stress. Moreover conversion Of glucose to sorbitol induces osmatic stress, and to restore osmotic equilibrium to cell, other osmolytes particularly taurine and myo-inositol are effluxes from cells, depletion of taurine and myo-inositol in nerve cells are implicated in PDN. [20] and supplementation of taurine and myoinositol prevented neuropathic deficits [20]. On the other hand. Excess formation of fructose in polyol pathway promotes advanced glycation end-product as well as depletes NADPH, further augmenting reactive Reactive oxygen species (ROS) mediated damage of cellular protein, lipid and neuron [21].

Aldose-reduetase inhibitors (ARI), block the increased activity of aldose reductase, the rate-limiting enzyme that converts glucose to sorbitol [22], reduces sorbitol level implicated in PDN [18]. Transgenic mice over-expressing aldose reductase in Schwann cells shown severe nerve conduction velocity deficit and oxidative stress under hyperglycaemic stress. On the contrary, aldose reductase deficiency or inhibitors improves nerve conduction velocity deficits, wallerian degeneration and nerve regeneration in diabetic animals [7]. The first trials of ARIs in diabetic neuropathy were carried out 20 years ago and offer attractive therapeutic option to treat PDN [22]. Later on, various compounds have been evaluated such as alrestatin. Sorbinil, ponalrestat, tolrestat, epalrestat, zopolrestat and zenarestat for the treatment of PDN [23, 24]. However, clinical trials with ARIs discomfited and shown lack of efficacy and potential toxicity.

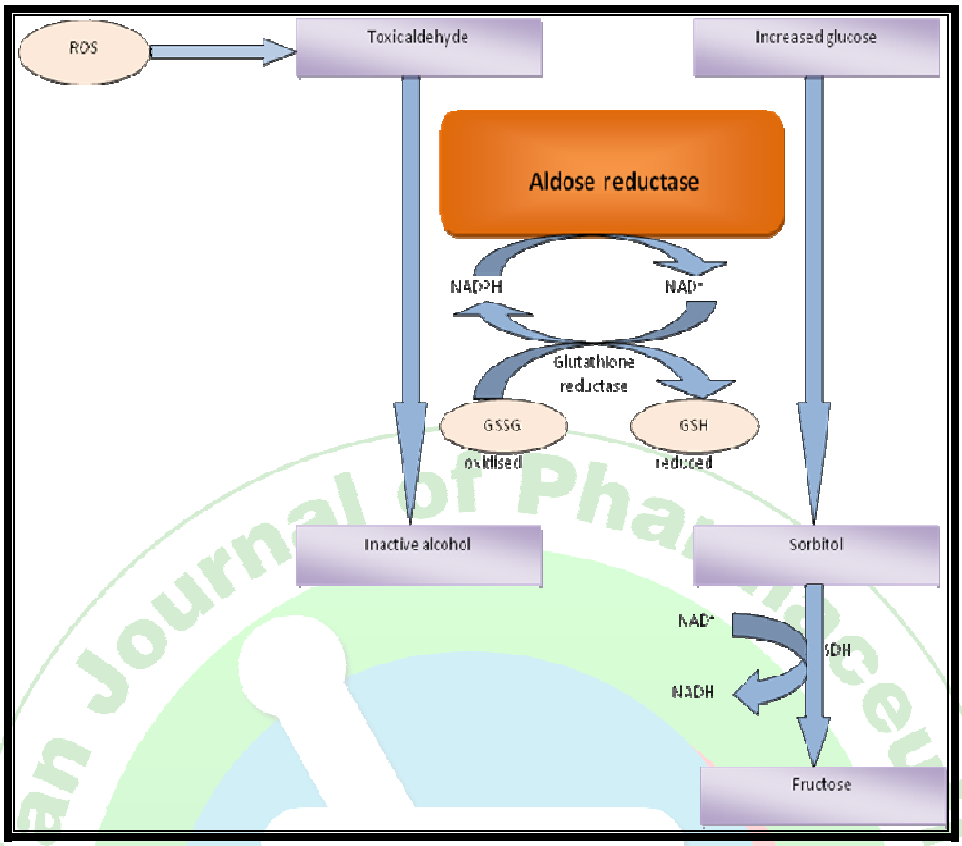


Fig 1: Hyperglycaemia Increases Flux through Polyol Pathway

Hexosamine-Pathway and PDN

Hexosamine pathway is activated when excess metabolite of glycolysis acumulated and was implicated in diabetes- induced oxidative stress and complications. Fructose-6 phosphate is a metabolic intermediate of glycolysis. However, during glucose metabolism some fructose-6 phosphate is shunted from the glycolytic pathway to the hexosamine pathway and is converted to glucosamine-6 phosphate by glutamine fructose-6 phosphate amidotransferase (GFAT) [19]. The end-product of this pathway, UDP-N acetylglucosamine (UDP-G1cNAc), is a substrate for the glycation of important intracellular factors including transcription factor, thereby affecting the expression of many genes including plasminogen activator inhibitor (PA-1) and transforming growth factors (TGF) and leads to diabetic micro -vascular complications, Inhibition of GFAT block the transcription of TGF and PA-I and are beneficial in PDN [19]. In addition, the hexosamine biosynthesis inhibitor azaserine prevents endothelial inflammation and dysfunction under hyperglycemic condition through antioxidant effects [25].

Mitogen-activated protein kinase (MAPK) and PDN

MAPKs play an instrumental role in the transmission of signals from cell surface receptors and of environmental cues to the transcriptional machinery. MAPKs are activated in response to extracellular stimuli through dual phosphorylation at conserved threonine and tyrosine residues (serine/threonine specific kinases). In vertebrae, at least three such pathways have been identified; these activate different MAP kinase classes known as extracellular signal-related kinase (ERK), c-Jun N-terminal kinase (JNK) and p38. MAPKs have key roles in cellular proliferation, differentiation, and apoptosis. Previous studies indicated that ERKI/2 had an opposite role to JNK and p38 in neuronal survival; ERKI/2 promotes neuronal survival, whereas JNK/p38 brings the neuronal cell to apoptosis. However, it is

controversial whether even JNK/p38 induces neuronal cells to apoptosis or to survival. Three major hypothetic pathways in the pathogenesis of diabetic complications including enhanced sorbitol pathway, non-enzymatic glycation of increased oxidative stress may contribute to activation of MAPK, leading to tissue dysfunction through the phosphorylation of transcription factors. In addition, PKC, which has been shown to be a potent candidate for diabetic complications is able to activate MAPK. thus, MAPK may act as a single transducer and trigger all the cellular events in the development of diabetic complications, including neuropathy, possibly in part by affecting nerve regenerative capacity

Poly (ADP-ribose) polymerase pathway

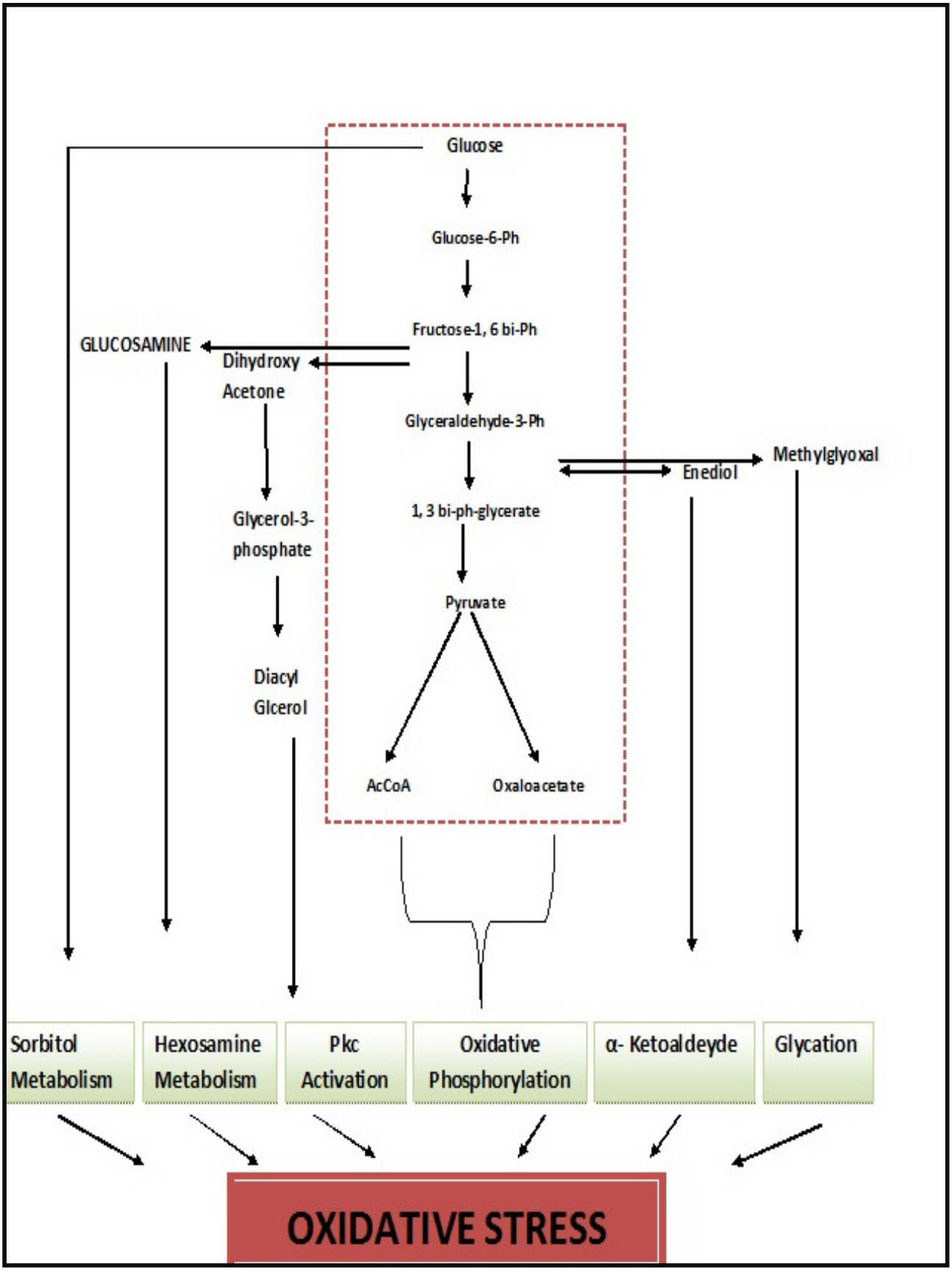
PARP found in Schwann, endothelial cells, and sensory neurons is also implicated in glucotoxicity. PARP is a nuclear enzyme closely associated with oxidative–nitrosative stress: free radicals and oxidants stimulate PARP activation. Recent evidence also suggests that the two act in concert: PARP both causes and is activated by oxidative stress . PARP acts by cleaving nicotinamide adenine dinucleotide (NAD+) to nicotinamide and ADP-ribose residues attached to nuclear proteins. The results of this process include NAD+ depletion, changes in gene trafnscription and expression, increased free radical and oxidant concentration, and diversion of glycolytic intermediates to other pathogenic pathways such as PKC and AGE formation [26]. PARP inhibitors such as 1,5-isoquinolinediol and 3-aminobenzamide have successfully improved these PARP-mediated dysfunctions in STZ-induced diabetic rats .Additionally, Nicotinamide (vitamin B3) has been shown to act as both a PARP inhibitor and antioxidant in rodents, improving the complications of early diabetic peripheral neuropathy.

Protein kinase - C pathway

The protein kinase C (PKC) pathway is an additional mechanism by which hyperglycemia causes injury in complications-prone tissues. Elevated glucose levels stimulate diacylglycerol (DAG), which in turn activates PKC. Increased production of the PKC PKC-β-isoform in particular has been implicated in overexpression of the angiogenic protein vascular endothelial growth factor (VEGF), PAI-1, NF-κB, TGF-β and the development of diabetic complications such as retinopathy, nephropathy, and cardiovascular disease. Ruboxistaurin is a PKC-β competitive inhibitor that has effectively managed many complications of diabetes in clinical trials. It has been particularly successful in reducing the progression of diabetic retinopathy, endothelial vasodilation, and (to a lesser extent) nephropathy

OXIDATIVE STRESS AND DNP

Oxygen free radicals (ROS) at the site of injury result from several sources including activated neutrophils and mitochondria. Free radicals then proceed to damage many cellular components including phospholipids A containing cellular membranes, which are converted to malanodialdehyde (MDA) by lipid peroxidation. ROS include free radicals such as superoxide ($\bullet O_2$-), hydroxyl (•OH), peroxyl ($\bullet RO_2$), hydroperoxyl (HRO_2 -) as well is nonradical species such as perchloric acid (HOC1). RNS include free radicals like nitric oxide (•NO) and peroxynitrite (RONOO-), nitrous oxide (HNO_2) and alkyl peroxynitrates (RONOO•). Of these reactive molecules, $\bullet O_2$ -, •NO and ONOO- are the most widely studied species and play important roles [27] in the development and maintenance of NP. Chronic hyperglycaemia causes oxidative stress in tissues prone to complications in patients with diabetes. ROS cause metabolic changes [26], impaired neurotrophic support abnormal sensation, and pain [28], as well as morphological abnormalities characteristic for peripheral DN. Under normal conditions, ROS is cleared from cells by the action of superoxide dismutase (SOD), catalase or glutathione, as well as antioxidant vitamin C and E.


Glucose
Glucose-6-Ph
Fructose-1, 6 bi-Ph
GLUCOSAMINE
Dihydroxy Acetone
Glyceraldehyde-3-Ph
Methylglyoxal
Enediol
1, 3 bi-ph-glycerate
Glycerol-3-phosphate
Pyruvate
Diacyl Glcerol
AcCoA
Oxaloacetate
Sorbitol Metabolism
Hexosamine Metabolism
Pkc Activation
Oxidative Phosphorylation
α- Ketoaldeyde
Glycation
OXIDATIVE STRESS

Others mediators affecting diabetic neuropathic pain

Cytokines and Np

Mainly two kinds of cytokines are present: pro-inflammatory such as IL-1β, IL-6 and TNF, while others such as IL-4 and IL-10 are anti-inflammatory. These pro-inflammatory cytokines contribute to the genesis of neuropathic pain [29,30]. These cytokines are also induced in the CNS by activation of non-neuronal cells such as microglial cell following nerve injury. The algesic effects of pro-inflammatory cytokines are often indirect, so that they may not act directly on the nociceptor but they induce the expression of agents (such as PGE2 and NO) that themselves sensitize nociceptors [31].

Interleukin-1β and Np

IL-1 is implicated in neuropathic pain since both IL-1α and IL-1β are up regulated within hours following peripheral nerve injury. The immediate release of IL-1β at the injury site appears to be mediated via the calcium sensitive protein, calpain, which is activated by calcium influx following nerve injury. Different molecular pathways are responsible for IL-1β regulation at different time-points following peripheral nerve injury [32]. treatment with the non-selective glial inhibitor, propentofylline and minocycline completely reversed stimulation evoked IL-1β efflux, as well as normalising pain hypersensitivity, indicating the involvement of glial cell in pain hypersensitivity [32].

Tumour Necrosis Factor-A and Np

TNF is known as a major pro-inflammatory cytokine with the ability to induce a cascade of additional cytokine production and has been associated with both the immediate and ongoing stages of chronic neuropathic pain. , peripheral nerve injury is associated with a rapid immune response characterised by endogenous TNF release from Schwann cells, resident macrophages and mast cells [33]. Increased expression of TNF receptors has also been reported on primary afferent fibres in the dorsal horn, as well as spinal glia. Binding of TNF to its receptors in DRGs and in spinal dorsal horn activates nuclear factor-kappa B (NF-κB), which in turn induces transcription of genes encoding pro-inflammatory cytokines and therefore, plays a role in pain facilitation [34].

Growth Factors

Growth factors promote the growth and survival of neurons and direct neurite outgrowth . 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 neurotrophin 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 animal models of DPN. NGF is the most studied growth factor in diabetic neuropathy. NGF is produced by muscle and keratinocytes, and its trkA receptor is expressed on sensory and sympathetic neurons. 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. A number of preclinical studies in diabetic rats suggest systemic or intrathecal IGF therapy can improve neuropathy [15].

Nerve Growth Factor (Ngf) and Np

Neurotrophic factors regulate the long-term survival, growth or differentiated function of discrete populations of neurons. The prototypical neurotrophin is NGF. Critical evidence for a role of NGF in pain production was the identification of a mutation in the gene encoding trkA. This mutation in trkA leads to congenital insensitivity to pain by disrupting NGF signalling and demonstrates its importance for normal nociceptive functioning. The role of NGF in pain signalling is now well understood. Small doses of NGF produce pain and hyperalgesia in adult animals and humans. In rodents, thermal and mechanical hyperalgesia develop after systemic NGF administration . NGF produces sensitization of nociceptors both directly (after activation of trkA on

nociceptors) and indirectly, mediated via other peripheral cell types. The direct mechanisms involve both altered gene expression and posttranslational regulation of receptors and ion channels, including TRPV1 and tetrodotoxin-resistant Na^+ channels [35]. Indeed, NGF over expressing mice display a marked hypersensitivity to both mechanical and thermal stimuli after CCI, suggesting that excess NGF may enhance neuropathic pain behaviours. Several groups have therefore tested the use of anti-NGF treatment in models of neuropathic pain. Anti-NGF antibodies are able to delay the development of neuropathic pain behaviours after both CCI and SNL.

Tumour Necrosis Factor-A and Np

TNF is known as a major pro-inflammatory cytokine with the ability to induce a cascade of additional cytokine production and has been associated with both the immediate and ongoing stages of chronic neuropathic pain. In naive animals, topical application of TNF to the sciatic nerve and DRGs leads to changes in the properties of neurons, such as ectopic firing in Aδ-, Aβ-, and C-fibres [35], and lowering of mechanical thresholds required to activate C-fibres [36]. Moreover, electrophysiological changes resulting from TNF application are associated with induction of thermal hyperalgesia and mechanical allodynia [37, 38]. Moreover, peripheral nerve injury is associated with a rapid immune response characterised by endogenous TNF release from Schwann cells, resident macrophages and mast cells [33]. Increased expression of TNF receptors has also been reported on primary afferent fibres in the dorsal horn, as well as spinal glia Binding of TNF to its receptors in DRGs and in spinal dorsal horn activates nuclear factor-kappa B (NF-κB), which in turn induces transcription of genes encoding pro-inflammatory cytokines and therefore, plays a role in pain facilitation [39].

Nerve Growth Factor (Ngf) And Np

Neurotrophic factors regulate the long-term survival, growth or differentiated function of discrete populations of neurons. The prototypical neurotrophin is NGF. Critical evidence for a role of NGF in pain production was the identification of a mutation in the gene encoding trkA. This mutation in trkA leads to congenital insensitivity to pain by disrupting NGF signalling and demonstrates its importance for normal nociceptive functioning. The role of NGF in pain signalling is now well understood. Small doses of NGF produce pain and hyperalgesia in adult animals and humans. In rodents, thermal and mechanical hyperalgesia develop after systemic NGF administration . NGF produces sensitization of nociceptors both directly (after activation of trkA on nociceptors) and indirectly, mediated via other peripheral cell types. The direct mechanisms involve both altered gene expression and posttranslational regulation of receptors and ion channels, including TRPV1 and tetrodotoxin-resistant Na^+ channels [35]. Indeed, NGF over expressing mice display a marked hypersensitivity to both mechanical and thermal stimuli after CCI, suggesting that excess NGF may enhance neuropathic pain behaviours Several groups have therefore tested the use of anti-NGF treatment in models of neuropathic pain. Anti-NGF antibodies are able to delay the development of neuropathic pain behaviours after both CCI [40] and SNL.

Chemokines, Insulin Like Growth Factor And Np

Chemokines are small chemotactic cytokines that are important for leukocyte migration and recruitment to sites of nerve injury. In the CNS, different types of cells have been identified as sources of chemokines, including microglia, astrocytes, neurons and endothelial cells [41]. Except for CX3CL1 (fractalkine) and CXCL12, which are principally expressed by neurons and astrocytes, respectively. Most chemokines are not constitutively expressed but can be induced during diverse neurodegenerative disease conditions [41]. Chemokines have been shown to contribute directly to nociception by producing excitatory effects on DRG neurons, induce allodynia after intraplantar injection in rats as well as activating spinal glial cells leading to pain hypersensitivity.

NF-κB and NP

NF- kB is a pleiotropic activator that participates in the induction of a wide variety of cellular genes . Another inflammatory enzyme regulated by NF-κB is inducible nitric oxide synthase (iNOS) [42]. Like COX-2, iNOS both induces and is induced by NF-κB, leading to a vicious cycle of inflammation [43, 42]. The NO generated by iNOS directly modulates the blood supply to nerves and participates in micro vascular changes following injury. NO has direct role in axon and myelin breakdown following an injury and also contributes to the development of neuropathic pain . Excessive local levels of NO during inflammation may damage axons and growth cones. All of the inflammatory mechanisms in 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 [44]. Subsequent to ischemia– reperfusion there is extensive infiltration of monocyte macrophages and modest infiltration of granulocytes in peripheral nerves [44].

Mast Cells and Np

Mast cells are generally considered to be critical effectors cells in allergic disorders and are also important initiators and effectors of innate immunity, and are resident in many tissues, including nerves [45]. Mast cells are degranulated at the site of a nerve lesion releasing mediators such as histamine, serotonin, proteases, prostaglandins and cytokines [45]. Neuronal histamine receptors are up regulated after a crush injury to the sciatic nerve . Several mast cell mediators have the ability to sensitise nociceptors, including histamine and tumour necrosis factor-a (TNF) resulting in increased firing rates; whilst serotonin can elicit hyperalgesia by direct activation of nociceptors[29]. These studies suggest that activated mast cells contribute directly to neuropathic pain by releasing algogenic (bradykinin, prostaglandin) mediators after degranulation.

Neutrophils and Np

Neutrophils are found in high numbers close to the site of injury and participate in the very early stages following peripheral nerve injury, peaking at 24 h. Neutrophil recruitment is mediated by the release of chemoattractants, such as nerve growth factor-ß (NGF-ß), monocyte chemo-attractant protein-1 (MCP1) and leukotriene-B4 [46]. In addition, depletion of circulating neutrophils at the time of peripheral nerve injury significantly attenuated the induction of neuropathic hyperalgesia. Furthermore, blood-derived neutrophils obtained from injured nerve displaying hyperalgesia appear to be primed, having increased superoxide burst [47]. Activated neutrophils also release pro- inflammatory cytokines such as TNF, IL-1β, IL-2 and IL-6, capable of cellular toxicity and directly exciting neurons [38].

Macrophages and Np

Macrophages are large phagocytic leukocytes present in tissues act by phagocytosing the dead or dying remnants of injured schwann cells and axotomised axons. Besides a role in phagocytosis and regeneration of damaged nerves, macrophages are also implicated in pain-related behaviour. Macrophage depletion by pharmacological means led to reduced pain hypersensitivity in several models of neuropathy[48]. It reported that macrophage depletion did not relieve mechanical allodynia following neuropathy. chemokines, which selectively attract or activate macrophages, such as IL-6, colony stimulating factor-1 (CSF-1) and MCP-1 [49] Macrophages after engulfment also secrete various mediator implicated in pain are ROS and many cytokines which plays potential role in hyperalgesia [29].

REFERENCES

1. *Treede RD, Jensen TS, Campbell JN. Neuropathic Pain: Redefinition And A Grading System For*
2. *Clinical And Research Purposes- Neurology. 2008; 70 (18): 16-30*
3. *Sarah W, Giojka R, Anders G, Richards S, Hlilary K. Global Prevalence OF Diabetes; Estimates For The*

Year 2000 And Projections Lin 2030 Diabetes Care. 2004;27(5), 1047-1053
4. Ziegler D. Can diabetic polyneuropathy be successfully treated, "MMW Fortschr Med., 2010; 152(9), 64-68
5. Bastyr EJ, Prince KL, Bril V. Development And Validity Testing Of The Neuropathy Total Symptoms Score-6: Questionnaire For The Study Of Sensory Symptoms Of Diabetic Peripheral Neuropathy. Clin. Ther., 2005; 27, 1278-1294
6. Ozkul A, Ayhan M, Yenisey C, Akyol A, Guney E, Ergin FA. The Role Of Oxidative Stress And Endothelial Injury In Diabetic Neuropathy And Neuropathic Pain. Neuro Endocrinol Lett., 2010; 31(2), 261-264
7. Sugimoto K, Yasujima M, Yagihashi S. Role of Advanced Glycation End Product In Neuropathic Pain. Curr Pharm Des,. 2008; 14(10), 953-61
8. Chen YS, Chung SS, Chung SK. Aldose Reductase Deficiency Improves Wallerian Degeneration And Nerve Regeneration In Diabetic Thy1-YFP Mice. J Neuropathol Exp Neurol, 2010; 69(3), 294-305
9. Negi G, Kumar A, Sharma SS, "Current Targeting of Nitrosative Stress PARP Pathway Current Functioan, Behavioral And Biochemical Deficits In Experimental Diabetic Neuropathy." Biochem Biophys Res Commun., 2010; 391(1), 102-106
10. Morgado C, Terra Pp, Tavares I. Neuronal Hyperactivity At The Spinal Cord And Periaqueductal Grey During Painful Diabetic Neuropathy: Effects Of Gabapentin. Eur J Pain., 2010; 4(7), 693-699
11. Lukic IK, Humpert PM, Nawroth PP, Bierhaus A. The RAGE pathway: activation and perpetuation in the pathogenesis of diabetic neuropathy" Ann N Y Acad Sc., 2008; 1126, 76-80.
12. Yamagishi S. Advanced Glycation End Products And Receptor-Oxidative Stress System In Diabetic Vascular Complications, Ther Apher Dial., 2009;13(6). 534-539
13. Barbosa JH, Oliveira SL, Seara LT. "The Role Of Advanced Glycation End Products (Ages) In The Development Of Vascular Diabetic Complications" Arq Bras Endocrinol Metabol., 2008; 52(6), 940-950
14. Yan SF, Ramasamy R, Schmidt AM. The RAGE Axis: A Fundamental Mechanism Signaling Danger To The Vulnerable Vasculature" Circ Res., 2010; 106(5), 842-853
15. Xu y, Wang S, Feng L, Zhu Q, Xiang P, He B. "Blockade of PKC-beta protects HUVEC from advanced glycation end products induced inflammation. Int. Immunopharmacol., 2010; 10(12), 1552-1559
16. Toth C, Rong LL, Yang C, Martinez J, Song F, Ramji M, Brussee V, Liu W, Durand J, Nguyen MD, Schmidt AM, Zochodne DW. Receptor for advanced glycation end products (RAGEs) and experimental diabetic neuropathy. Diabetes., 2008; 57(4),1002-1017
17. Loseth S, Stalberg E, Jorde R, Mellgren SI. Early Diabetic Neuropathy: Thermal Thresholds And IntraepidermalNerve Fibre Density In Patients With Normal Nerve Conduction Studies. J Neurol ., 2008; 255(8), 1197-1202
18. Prasad Anand MD, Bekker, Peter MD. Tsimikas, Sotirios MD Cardiology in Review: 2012; 20(4), 177–183
19. Takafumi M, Yoshiyuki O, Akemi K, Kaoru T, Yoshinaka U, Vera B. Long-Term Treatment With Ranirestat (AS-3201), a Potent Aldose Reductase Inhibitor, Suppresses Diabetic Neuropathy and Cataract Formation in Rats", J Pharmacol Sci., 2008; 107, 340 -348
20. Srinivasan V, Sandhya N, Sampathkumar R, Farooq S, Mohan V, Balasubramanyam M. Glutamine fructose-6-phosphate amidotransferase (GFAT) gene expression and activity in patients with type 2 diabetes: inter-relationships with hyperglycaemia and oxidative stress. Clin Biochem., 2007; 40(13-14), 952-957
21. Trevor A, Wei Z, Margaret CE, Martin JS. Oxidative stress and dysregulation of the taurine transporter in high-glucose-exposed human Schwann cells: implications for pathogenesis of diabetic neuropathy. Am J Physiol Endocrinol Metab., 2009; 297, E620-E628
22. Sugimoto K, Yasujima M, Yagihashi S. Role of Advanced Glycation End Product In Neuropathic Pain. Curr Pharm Des,. 2008; 14(10), 953-961
23. Ramirez MA, Borja NL. Epalrestat: an aldose reductase inhibitor for the treatment of diabetic neuropathy. Pharmacotherapy., 2008; 28(5), 646-655
24. Bril V, Hirose T, Tomioka S, Buchanan R, "Ranirestat Study Group" -Ranirestat For The Management Of Diabetic Sensorimotor Polyneuropathy. Diabetes Care., 2009; 32(7), 1256-1260
25. Shimoshige Y, Minoura K, Matsuoka N, Takakura S, Mutoh S, Kamijo M. Thirteen-month inhibition of aldose reductase by zenarestat prevents morphological abnormalities in the dorsal root ganglia of streptozotocin- induced diabetic rats. Brain Res.,2009; 1247 182-187
26. Angana GR, Xi-Fen M, Joao MC, Zhihong Y, The Hexosamine Biosynthesis Inhibitor Azaserine Prevents Endothelial Inflammation And Dysfunction Under Hyperglycemic Condition Through Antioxidant Effects. Am J Physiol Heart CIRC Physiol., 2009; 296, 11815-11822
27. Obrosova IG, Mabley JG, Zsengeller Z, Charniauskaya T, Abatan OI, Groves JT. Szabo C. Role Of Nitrosative Stress In Diabetic Neuroapathy: Evidence From Studies With Peroxynitrite Decomposition Catalyst. FASEB J., 2005; 19, 401-403.
28. Drel VR, Pacher P, Vareniuk I, Pavlov I, Ilnytska O, Lyzogubov VV, Tibrewala J, Groves JT, Obrosova IG. A Peroxynitrite Decomposition Catalyst Counteracts Sensory Neuropathy In Streptozotocin Diabetic Mice. Eur. J. Pharmacol., 2007; 569, 48-58.
29. Obrosova IG, Drel VR., Oltman CL, Mashtalir N, Tibrewala J, Groves JT, Yorek MA. Role Of Nitrostative Stress In Early Neuropathy And Vascular Dysfunction In Streptozotocin Diabetic Rats. Am J Physiol Endocrinol. Metab., 2007; 293, 1645-1655.
30. Sommer C, Kress M. Recent Findings On How Proinflammatory Cytokines Cause Pain:Peripheral Mechanisms In Inflammatory And Neuropathic Hyperalgesia. Neurosci Lett., 2004; 361,184–187.
31. Valko M, Leibfritz D, Moncol J, Cronin M, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol., 2007; 39, 44–84.
32. Verri WA Jr, Cunha TM, Parada CA, Poole S, Cunha FQ, Ferreira SH. Hypernociceptive role of cytokines and chemokines: targets for analgesic drug development? Pharmacol. Ther., 2006; 112, 116-138.
33. Whitehead KJ, Smith CG, Delaney SA, Curnow SJ, Salmon M, Hughes JP, Chessell IP. Dynamic regulation of spinal pro-inflammatory cytokine release in the rat in vivo following peripheral nerve injury. Brain Behav. Immun., 2010; 24, 569–576.

34. Sacerdote P, Franchi S, Trovato AE, Valsecchi AE, Panerai AE, Colleoni M. Transient early expression of TNF-alpha in sciatic nerve and dorsal root ganglia in a mouse model of painful peripheral neuropathy. Neurosci. Lett., 2008; 436, 210–213
35. Wei F, Guo W, Zou S, Ren K, Dubner R. Supraspinal glial-neuronal interactions contribute to descending pain facilitation. J. Neurosci., 2008; 28, 10482–10495.
36. Zhang JM, Li H, Liu B, Brull S.J. Acute topical application of tumor necrosis factor alpha evokes protein kinase A-dependent responses in rat sensory neurons. J Neurophysiol., 2002; 88, 1387–1392.
37. Ozaktay AC, Kallakuri S, Takebayashi T, Cavanaugh JM, Asik I, DeLeo JA. and Weinstein JN. Effects of interleukin-1 beta, interleukin-6, and tumor necrosis factor on sensitivity of dorsal root ganglion and peripheral receptive fields in rats. Eur. Spine J., 2006; 15, 1529–1537.
38. Zelenka M, Schäfers M, Sommer C. Intraneural injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. Pain., 2005; 116, 257-263.
39. Murata Y, Onda A, Rydevik B, Takahashi I, Takahashi K, Olmarker K. Changes in pain behavior and histologic changes caused by application of tumor necrosis factor-alpha to the dorsal root ganglion in rats. Spine., 2006; 31, 530–535.
40. Wei F, Guo W, Zou S, Ren K, Dubner R. Supraspinal glial-neuronal interactions contribute to descending pain facilitation. J. Neurosci., 2008; 28, 10482–10495.
41. Gandhi R, Ryals JM, Wright DE. Neurotrophin-3 reverses chronic mechanical hyperalgesia induced by intramuscular acid injection. J. Neurosci., 2004; 24, 9405-9413.
42. Cartier L, Hartley O, Dubois-Dauphin M, Krause KH. Chemokine receptors in the central nervous system: role in brain inflammation and neurodegenerative diseases. Brain Res Brain Res Rev., 2005; 48, 16–42.
43. Kim DS, Figueroa KW, Li KW, Boroujerdi A, Yolo T, David- Luo Z. Profiling of dynamically changed gene expression in dorsal root ganglia post peripheral nerve injury and a critical role of injury-induced glial fibrillary acidic protein in maintenance of pain behaviors. Pain., 2009b; 143, 114–122.
44. Hasnis E, Bar-Shai M, Burbea Z. and Reznick A. Z. Mechanisms underlying cigarette smoke-induced NF-kappaB activation in human lymphocytes: the role of reactive nitrogen species. J Physiol Pharmacol., 2007; 58, 275–287
45. Wang Y, Schmeichel AM, Iida H. Enhanced inflammatory response via activation of NF-kappaB in acute experimental diabetic neuropathy subjected to ischemia reperfusion injury. J. Neurol. Sci., 2006; 247: 47–52.
46. Galli S, Nakae S, Tsai M. Mast cells in the development of adaptive immune responses. Nat. immunol., 2005; 6, 135-142.
47. Scholz J, Woolf CJ. The Neuropathic Pain Triad: Neurons, Immune Cells And Glia. Nat Neurosci., 2007; 10, 1361–1368.
48. Morin N, Owolabi SA, Harty MW, Papa EF, Tracy TF. Jr, Shaw SK, Kim M, Saab CY. Neutrophils invade lumbar dorsal root ganglia after chronic constriction injury of the sciatic nerve. J. Neuroimmunol., 2007; 184, 164-171.
49. Mert T, Gunay I, Ocal I, Guzel A, Inal T, Sencar L, Polat S. Macrophage depletion delays progression of neuropathic pain in diabetic animals. Naunyn Schmiedebergs Arch. Pharmacol. 2009; 379, 445–452.
50. Vega-Avelaira D, Geranton SM, Fitzgerald M. Differential regulation of immune responses and macrophage/neuron interactions in the dorsal root ganglion in young and adult rats following nerve injury. Mol. Pain., 2009; 5, 70.