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Hemodynamic Considerations in the Pathophysiology of Peripheral Neuropathy

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<http://dx.doi.org/10.5772/intechopen.75872>

Abstract

Peripheral neuropathic pain presents one of the greatest on going challenges to both acute and chronic pain management yet our understanding of the origins and pathogenesis of this complex disease state are severely lacking. The purpose of this chapter is to review the current literature regarding neuropathic pain as impacted by hemodynamic alterations. Because of the varied origins of neuropathy, this cannot be discussed as a single entity but we can seek to identify a final common pathway. We will for this reason examine each known pathogenetic category of neuropathy separately then discuss the effect of hemodynamic alterations through changes in blood pressure to determine any correlations between these alterations and specific effects upon neural structure and function. We have divided this chapter into sections which describe the more commonly known and encountered neuropathies. These are diabetes mellitus, neurotoxic medications, alcohol-related neuropathy, Vitamin B₁₂ deficiency, end-stage renal disease, inflammatory bowel disease, and rheumatoid arthritis.

Keywords: peripheral neuropathy, pathophysiology, classifications, mechanisms, molecular basis, incidence, literature review

1. Introduction

Peripheral neuropathy is a relatively rare but well-known degenerative disorder of the peripheral nervous system with an estimated overall annual incidence of 1.6 per 100,000 and a prevalence of 2.4% in the United States [1, 2]. For persons forty years and older, the prevalence is about five-fold higher (11.5%) and 10 times higher in diabetic individuals (21.2%) [3]. Among the causes of peripheral neuropathies are caused by diabetes mellitus, toxins, alcohol abuse, or paraneoplastic syndromes. The most common cause of peripheral neuropathy worldwide is

diabetes mellitus. Both sensory and/or motor component (sensorimotor) of the peripheral nervous system can be affected. The symptoms, severity and duration of peripheral neuropathy depend on the type of nerve affected, sensory, motor or both, the inciting incidence or causative agent, and the length of exposure. Motor neuropathy is characterized by muscular weakness affecting mobility, coordination, and respiratory function. Sensory neuropathy is characterized by pain, numbness, burning sensation, absent or diminished reflexes and sensation to touch.

2. Background

2.1. Vascular supply to peripheral nerves

The vascular supply to peripheral nerves is often overlooked both in the natural history of common, well-understood diseases as well as in the management of acute and chronic pain syndromes. When chronic peripheral neuropathic pain develops the results can be devastating with significant impairment in quality of (QoL) functioning in the activities of daily living (ADL) and cause significant loss of income as well as lost productivity in the workplace. This chapter will focus primarily upon the vasa nervorum which are the vessels that supply the peripheral nerves. The chapter will review, first, the embryology of the vasa nervorum, then the resultant anatomy and the physiology of these vessels. This section will provide the groundwork for the discussion of molecular pathways that cause changes to both the integrity of these vessels as well as the diminution in the number of functional vessels.

2.2. Summary of neural lesions

Emphasis will be placed upon the second crush theory as a mechanism of vasculopathic contribution to decreases in axonal transport mechanisms (**Figure 1**), as well as specific diseases and drug interactions that result in perfusion dependent mechanisms of neural injury (**Table 1**). These syndromes will include diabetic neuropathy, rheumatoid arthritis-associated neuropathy; Vitamin B₁₂ deficiency- neuropathy; hypertensive and hypotensive neuropathy; chemotherapy and radiation neuropathies.

2.3. Neuropathies and double crush

It should be noted that peripheral neural blood flow has been thought to present as a double edged sword in the development of certain neuropathies. In a 1994 study, Jaap et al. examined the maximal microvascular hyperemic response to local heating in subjects with fasting hyperglycemia and compared these to healthy, age and sex matched controls [4]. Bandla et al. in at least one setting speculated that diminished flow may be beneficial. In this work they examined 15 healthy human subjects and explored the use of continuous flow, limb hypothermia to limit the delivery of chemotherapeutic agents to peripheral nerves. No further studies have been reported with this specific model yet it serves to broach the theory that reduced delivery of toxins may be protective [5]. And In another suggestive study, perfusion effects in patients with established neuropathic pain were examined and compared to healthy controls using dynamic contrast-enhanced magnetic resonance imaging. Time-signal intensity

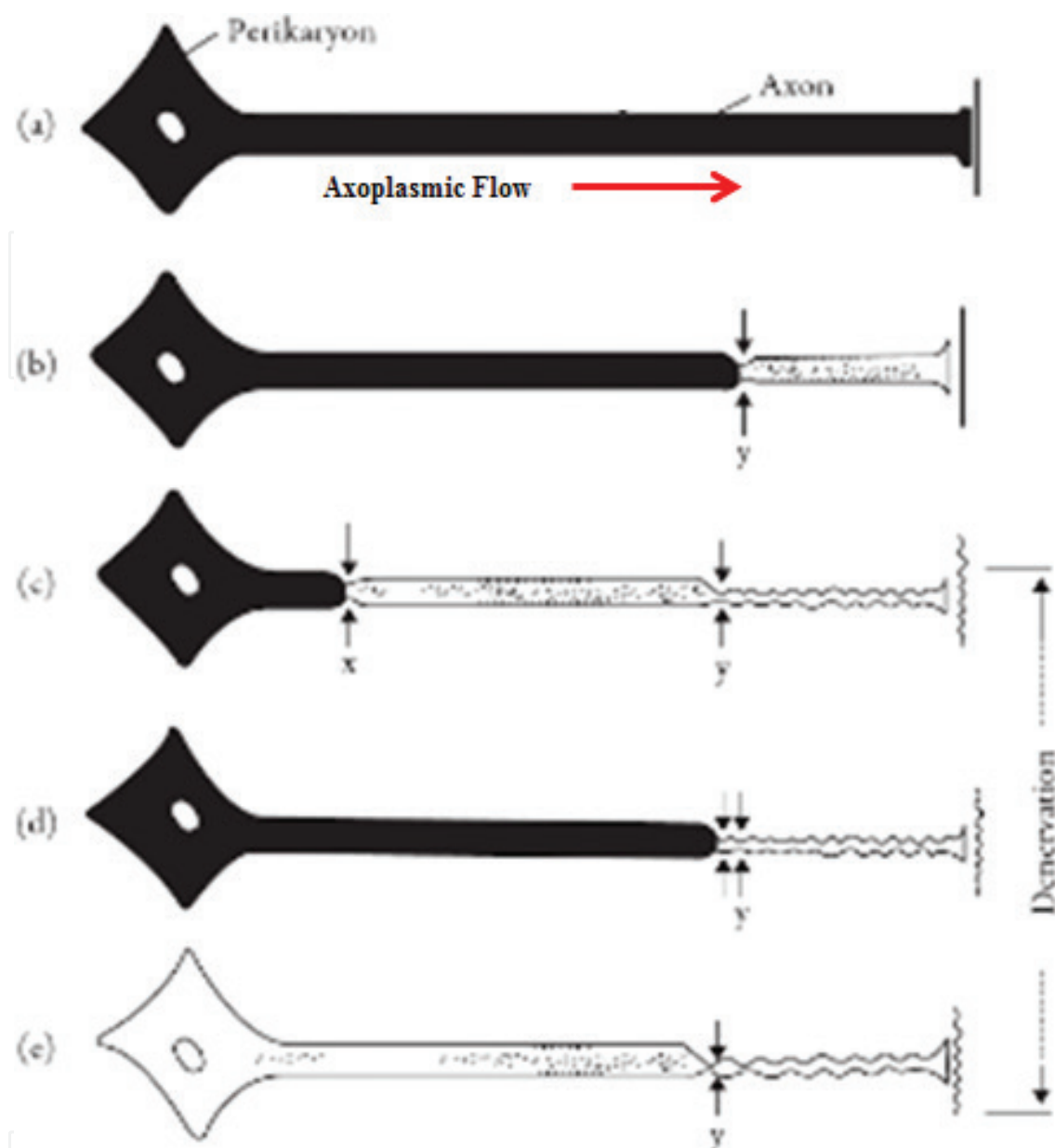


Figure 1. Different types of neural lesions that can lead to denervation. Axoplasmic material is represented by the density of the shading. Completely healthy neuron (a) axoplasmic flow is complete. (b) In a healthy neuron with one area of mild compression flow is maintained distal to a compressive point indicated by "y". (c) In a healthy neuron with two mild compressions, disruption of flow and thus denervation occurs distal to "y" which is the point of compression. (d) Denervation.

analysis showed significantly increased contrast uptake in patients with neuropathy and was determined to be the result of increased blood-nerve permeability [6].

Finally the chapter will focus upon interventions that may allow for not only treatment of these neuropathies at the earliest stages of their presentations but also preventive measures in patients at risk.

It is our hope that this chapter will not only elucidate these mechanisms of disease but also stimulate discussions which will lead to further research into this component of neuropathic disease in the hope that better patient treatment options may be developed.

Neuropathies Associated with Increased Risk of Second Crush Injury				
Neuropathy	Vasa Nervorum Mechanism	Perfusion Dependent	Axonal Transport Defect	Baseline Flow Characteristics of Neural Environment (Goals)
Diabetes	Microvascular cell loss occurs, progressive capillary occlusion	Yes	Yes	Maintain
Rheumatoid Arthritis	Reduction in number of vessels of vascular supply of nerves due to endothelial apoptosis	Yes	Yes	Maintain
Inflammatory Bowel Disease	Microvascular ischemic demyelination	No	Yes	Maintain
Vitamin B ₁₂ Deficiency	Not known	No	Yes	Maintain
Alcoholic	Not known	Unclear	Yes	Maintain
Hypertension/ Hypotension	Diminished flow	Yes	Yes	Maintain
Uremia	Degradation of Na ⁺ / K ⁺ Pumps Disrupts Neuronal Integrity	Unclear	Yes	Maintain
Platinum	↓ in vascular endothelial cells	Yes	Yes	Maintain

Table 1. Neuropathies associated with risk of double crush injury.

3. Causes of peripheral neuropathy

3.1. Diabetic neuropathy

Diabetic Peripheral Neuropathy is a common neurological manifestation of both type I and type II diabetes, affecting up to 50% of diabetics with an even greater incidence in those with subclinical manifestations. The peripheral neuropathy can involve both motor and sensory

nerves and the complexity of the metabolic and vascular factors involved has still not been fully elucidated. The sensory loss is classically described as a “stocking and glove distribution” involving both hand and legs. The underlying pathology causing this neuropathy appears to involve both macro and microvascular processes.

3.1.1. Galactose neuropathy

As far back as 1984 galactose was implicated as a cause for peripheral neuropathy in a murine, diabetic model. Using C14 iodoantipyrine as a radioactive tracer of tissue perfusion, the group noted a significant decline in nerve blood flow in animals that had ingested galactose for 6 months vs. controls. There was also a positive correlation between galactose ingestion, endoneurial edema, increased tissue pressure, and ultimate demyelination of nerve fibers. The group also found that Schwann cells showed significant glycogen accumulation in regions in which there was edema. This bolstered the argument that edema, rather than neural hyperactivity in the sorbitol pathway was responsible for the pathological changes in galactosemic neuropathy [7].

3.1.2. Diabetes and autonomic function

Another study examined peroneal nerve conduction velocity as a primary outcome of neural function and correlated this to the severity of diabetic neuropathy. Mallamaci et al. studied autonomic function in uremic patients and were able to show a weak non-statistical relationship between an improvement in neurologic function and post-renal transplant status [8].

Dillon et al. concluded that slow-healing of neuropathic ulcers was associated with a loss of cholinergic nerve function, that cholinergic stimulation will increase capillary blood flow and indirectly suggested that improved blood flow to the neural supply of the region may have an overall beneficial effect to the insulted tissue [9]. In 1997 the same group advanced their work to conclude that peripheral blood flow is inversely related to the degree of peripheral neuropathy [10].

3.1.3. Obstructive sleep apnea and oxidative stress

The role of oxidative stress in the pathogenesis of diabetic peripheral neuropathy as it was related to obstructive sleep apnea was studied. There was a 65% incidence of OSA in diabetic patient with DPN. In patients with diabetes and OSA, there was a prevalence of 60% of diabetic peripheral neuropathy. However, in diabetic patients without OSA, the prevalence was 27% of diabetic peripheral neuropathy ($p < 0.001$) [11]. A theory for the precise mechanism of this correlation was not discussed.

3.1.4. Role of angiotensin

Angiotensin-converting enzyme was considered as early as 1998 as playing a role in the treatment of human diabetic neuropathy in a randomized trial. In this work 41 patients with normotension, “mild” diabetic neuropathy and a diagnosis of type I or type II diabetes were placed in the randomized double-blind placebo-controlled trial. Assessments of treatment efficacy were made using the endpoint of neuropathic symptoms, deficit scores, vibratory perception threshold, peripheral-nerve electrophysiology, and cardiovascular autonomic function at 6 and 12 months of treatment with the primary endpoint of change in peroneal

motor nerve conduction velocity. The study revealed a significant increase in peroneal motor nerve conduction velocity, M-wave amplitude and sural nerve action potential amplitude ($p = 0.03$). However vibration-perception threshold, autonomic function and the symptoms of neuropathy and deficit score showed no improvement in either group. Yet the question remains whether neural functional impairment can ultimately lead to symptomatic improvement and further clinical study is needed to make this determination [12].

3.1.5. Glycochelates and transition metals

The role of transition metals was argued in a review article by Qian et al. in 2000. They presented data that heavily glycosylated proteins known to accumulate in individuals suffering from diabetes gain an increased affinity for transition metals such as iron and copper. This affinity results in the accumulation of bound metal by elastin and collagen within the arterial wall. The bound metal is believed to cause the catalytic destruction of endothelium-derived releasing factor (nitric oxide or a nitric oxide derivative). The loss of vasodilatory ability (or chronic vasoconstriction) impairs blood to peripheral nerves with resultant deprivation of oxygen and critical nutrients. The authors cite initial studies that suggest the administration of chelators such as desferrioxamine may prevent or reverse slower peripheral nerve conduction and neuronal blood flow [13].

3.1.6. Endothelial control of microcirculation

The role of endothelium-dependent and endothelium-independent microvasodilation and their relationships to neural microcirculatory control was examined in type I and type II diabetic patients by Kilo et al., in 2000. They used iontophoresed acetylcholine and nitroprusside studied in a dose-response technique to elicit C-fiber mediated vasodilation. As expected, endothelium-dependent vasodilation of the cutaneous microcirculation was attenuated in type II diabetic subjects vs. control; however there was no significant difference between the endothelium-dependent vasodilation in type I diabetics vs. controls. There was no difference between either diabetic group (type I or type II) regarding endothelium-independent vasodilation. They also found that the C-fiber-mediated axon reflex was impaired in both type I and type II diabetics, which the group stated was consistent with a small fiber neuropathy. The study led to the conclusion that endothelial function and nitric oxide play a significant role in the pathogenesis of peripheral neuropathy in type II diabetic patients and that this disease process is the result in part of significant C-fiber impairment. Again, the function of C-fibers, the neural component of peri-neural hemodynamics, and the peri-neural chemical milieu may begin to suggest a common pathway for the perfusion of peripheral nerves and the development of peripheral neuropathy [14].

3.1.7. Axon reflex vasodilation

Axon reflex vasodilation was induced by histamine iontophoresis to assess cutaneous afferent C-fiber function in a diabetic human model. In 2000, Schuller et al. used this approach to measure cutaneous vasoconstrictor responses. The group also used two other neurophysiological methods to assess small nerve fiber function in patients with non-diabetic peripheral neuropathy: heart rate variation tests to assess cardiac parasympathetic small fiber function,

and cutaneous vasoconstrictor response (sympathetic C fibers) induced by deep inspiration measured by laser Doppler flowmetry. Based on the study results the authors implied that functionally different systems (parasympathetic, sympathetic, and sudomotor) may be affected separately and can and should be tested separately. This consideration may be of use in constructing experimental human models to test various neuropathy treatment interventions [15].

3.1.8. Genetic therapy of diabetic neuropathy

Reversal of experimental diabetic neuropathy in a murine model induced by two different techniques was explored by Schratzberger et al. in 2001. Both streptozotocin- and alloxan-induced diabetes models were employed and nerve blood flow was assessed by laser Doppler imaging or direct detection of a locally administered fluorescent lectin. In both models intramuscular gene transfer of plasmid DNA encoding VEGF-1 or VEGF-2 resulted in increases in vascularity and nerve blood flow to levels found in control animals. The group also reported that constitutive over expression of both transgenes resulted in restoration of large and small fiber peripheral nerve function as measured by motor and sensory nerve conduction velocities. Similar findings in a lapine model are also reported. There is accumulating evidence, then, that genetic therapy may have a role in the treatment of peripheral neuropathy of diabetic origin. Unlike the observed efficacy of this gene therapy in chemotherapy-induced neuropathy considerations for induction of related angiogenesis would not be a factor in the decision to institute plasmid DNA therapy; however a concern for possible retinal angiogenesis and a question of initiating or worsening diabetic retinopathy may be a concern. In this regard further research is needed first to assess the associated angiogenicity of this treatment in animals and second to establish whether any benefit of the therapy can be extrapolated to a human model [16].

3.1.9. Protein kinase

Protein kinase inhibition was examined in a work by Casselini. In this study they reported that over-activation of the enzyme and microvascular dysfunction resulted in the disordered skin changes observed in diabetic peripheral neuropathy. Their study concluded that in patients with DPN ruboxistaurin-enhanced skin blood flow at the distal calf reduced sensory symptoms and improved quality of life (QoL) as measured by the Norfolk QoL-DN [17].

The role of inhibition of protein kinase C (PKC) in the study of experimental diabetes in a human model was discussed by Sasase et al. 2006. Specifically they emphasize the effects of hyperglycemia-induced PKC activation and the subsequent altered hemodynamics, angiogenesis, vasoconstriction, endothelial permeability, cell growth, cytokine activation and leukocyte adhesion. Their discussion asserts that PKC β inhibitors were well-tolerated in clinical trials and that this inhibition may therefore represent a promising approach to the treatment of diabetic complications [18].

3.1.10. Nitrosative stress

The nitrosative stress argument was further discussed in a 2007 paper by Obrosova et al. In this work they found that streptozotocin-induced diabetic rats that were maintained with the

peroxynitrite decomposition catalyst FP15 exhibited a dose-dependently corrected improvement in the neuropathic disorders that occurred secondary to experimental diabetes. These disorders were sensory and motor nerve deficits; mechanical hyperalgesia, and tactile allodynia in the absence of small sensory nerve fiber degeneration. FP15 was also found to correct endoneurial nutritive blood flow and nitrotyrosine fluorescence in aorta and epineurial arterioles, indicating that it helped maintain vessel integrity. In addition FP15 alleviated diabetes-induced decreases in acetylcholine-mediated relaxation of coronary and mesenteric arteries. The findings iterate the significance of nitrosative stress in the development of neuropathy as well as vasculopathy and suggest that further studies of PDCs in the treatment of experimental diabetes are needed [19].

The role of peroxynitrite-mediated nitrosative stress in the development of diabetic neuropathy was studied in a murine model by Negi et al. in 2010 [20]. In this work the effect of a combination of peroxynitrite decomposition catalyst (PDC), FeTMPyP [21], and a poly (ADP-ribose) polymerase (PARP) – a nuclear enzyme activated after detection of DNA damage-inhibitor [22]. The rationale for the use of the PARP inhibitor was the role that overactivation of this enzyme is believed to play in the development of diabetic neuropathy [23]. The group studied the following endpoints: motor conduction velocity and nerve blood flow for evaluating neural function; malondialdehyde and peroxynitrite levels to detect oxidative stress-nitrosative stress; and NAD concentration in sciatic nerve to assess NAD overproduction of PARP. Treatment with combination of FeTMPyP and 4-ANI led to improvement in neural function and also attenuated the oxidative-nitrosative stress markers. The combination also reduced the overactivation of PARP which was demonstrated by increased levels of NAD and by the demonstration of decreased PAR immunopositivity in sciatic nerve microsections. The authors concluded that treatment with a combination of a PDC and a PARP inhibitor attenuates alterations in peripheral nerves in experimental diabetic neuropathy.

3.1.11. *Resistin*

Serum levels of the adipokine resistin were shown to correlate with systolic blood pressure, diastolic blood pressure and endothelium (ET); and to negatively correlate with nitric oxide. More recently [25] resistin was shown to actively induce hypertension and insulin resistance in wild type mice believed to occur by the upregulation of angiotensin (Agt) toll-like receptor 4 expression. In toll-like receptor 4 (tlr4) negative mice or in mice treated with the angiotensin-converting enzyme inhibitor, perindopril resistin had no effect. The authors concluded from this that resistin activates the renin- NF angiotensin system via the TLR4/P65-NFkB subunit/Agt pathway which links insulin resistance to hypertension. The higher serum resistin levels in patients with diabetic neuropathy vs. diabetics without peripheral neuropathy suggests that resistin may play a role in the pathogenesis of type II diabetes and diabetic peripheral neuropathy. The question is also raised regarding whether hypertension secondary to resistin is a causative factor in this neuropathy (**Figure 2**) [24, 25].

3.1.12. *Endothelial dysfunction*

The relationship between endothelial and neural control of skin blood flow (SkBF) in patients with diabetic peripheral neuropathy was studied by Brooks et al. in 2008 [27]. It is worth noting here that in this study, which examined the effect of the isoform protein kinase C

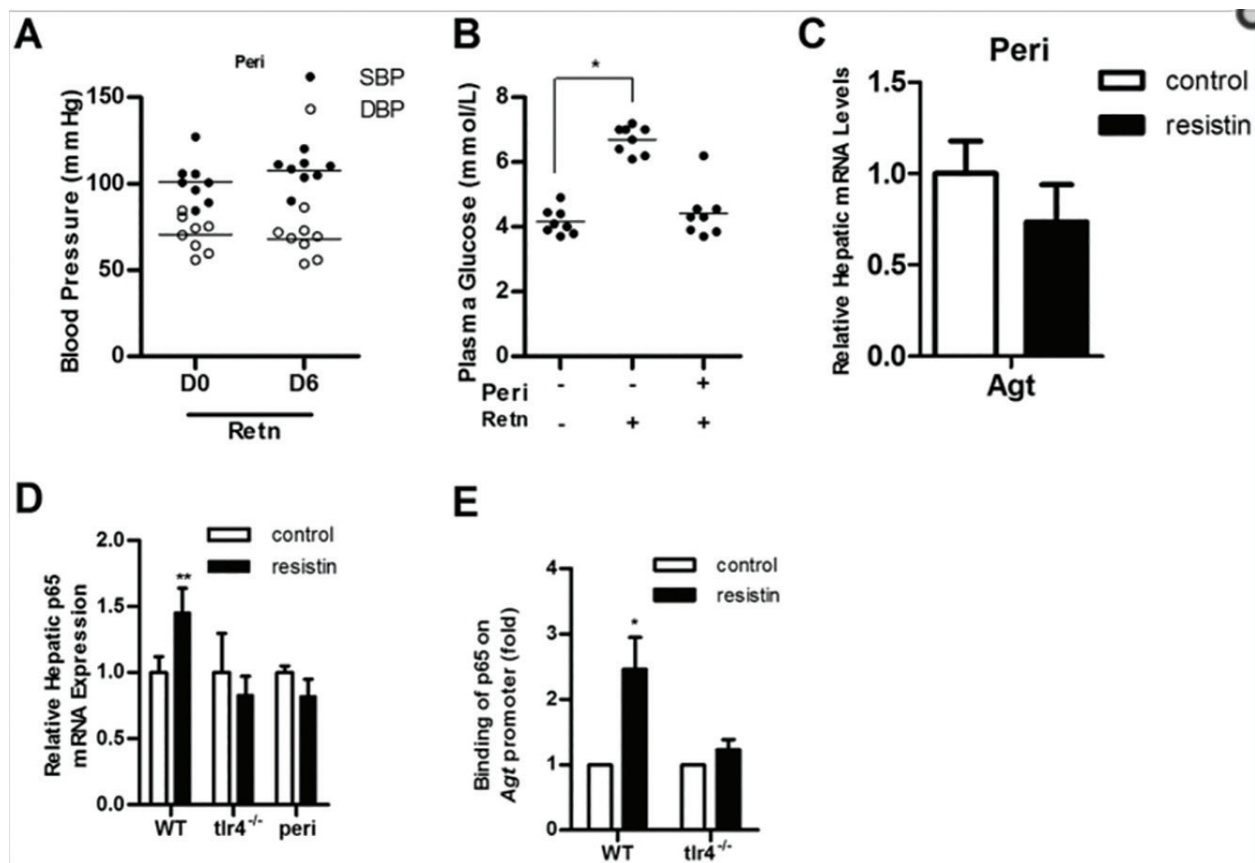


Figure 2. Perindopril blocks the action of resistin. (A) BP in wild-type mice pre-treated with perindopril (Peri). BP was measured before resistin treatment (day 0, D0) and after 6 days of resistin treatment (day 6, D6); (B) plasma glucose levels in mice exposed to different treatments; (C) Agt and (D) p65 expression in mice exposed to different treatments and in different mouse lines; (E) binding of p65 to the Agt promoter was determined by chromatin immunoprecipitation. The resistin group (Retn) was injected with 400 ng/day resistin; while the control group was injected with PBS (control-vehicle). Perindopril (5 mg/kg/day) was administered orally for 7 days (animals were treated as described in Materials and Methods). Data are presented as mean \pm SD ($n = 8$). * $p < 0.05$, ** $p < 0.01$ (adapted from Jiang et al., [25]).

inhibitor ruboxistaurin (which has been shown to slow or reverse the progression of diabetic neuropathy) [26]; the group found that while RBX had no direct effect of skin blood flow they did find correlation between C-fiber mediated and endothelium-dependent skin blood flow at baseline. The importance of this finding was that it suggested that improving endothelial function could positively affect microcirculation via the neurovascular arcade [27]. Zakareia et al. in 2008 concluded that the rise in vascular endothelial growth factor (VEGF) in diabetic neuropathy may be protective and preserve neural blood flow, and that the significant rise in soluble fatty acids may be causative in the advancement of neuropathy [28].

Pek et al. in 2015 further studied the relationship between endothelial dysfunction and arterial stiffness and diabetic neuropathy [29]. This group collected data on blood chemistry, arterial stiffness by carotid-femoral pulse wave velocity (PWV) and endothelial function by laser Doppler flowmetry. The group recruited 2054 patients 2014 of whom met the criteria for a diagnosis of diabetic peripheral neuropathy (DPN). The presence of DPN in this work was defined as either impaired light touch sensation tested using the 10 g monofilament ($<7/10$ on either foot) or a neurothesiometer (which compares vibration perception thresholds) (Young, 1993) reading of ≥ 25 V. Patients with DPN were significantly older (60.1 ± 9.9 vs.

57 ± 10.8 years); had a longer duration of diabetes (15.8 ± 10.0 vs. 10.9 ± 8.6 years); had a higher systolic blood pressure (146 ± 20.6 vs. 137.6 ± 18.7 mmHg); and a higher pulse wave velocity (11.5 ± 3.5 vs. 9.5 ± 2.7 m/s); poorer endothelium-dependent vasodilation (73.4 (33.9–141.3) vs. 105.7 (51.2–175)%); and poorer endothelium-independent vasodilation (54.6 (31.2–80.6) vs. 68.3 (38.2–108.2)%).

These findings contribute to the argument that hypertension and poor vascular compliance are risk factors for peripheral neuropathy in clinical diabetes. It should be noted that it may prove an ever more daunting task to extrapolate findings from non-human, experimental diabetic neuropathy models to the human disease process.

3.1.13. *Sodium-hydrogen exchanger*

In 2013, Lupaychyk et al. examined the neuropathic endpoints of motor and sensory nerve conduction velocities in sciatic motor and sensory nerves, endoneurial nutritive blood flow, vascular reactivity of epineurial arterioles, thermal nociception tactile allodynia and intraepidermal nerve fiber density in a streptozotocin-diabetic murine model following administration of cariporide. The Na⁺/H⁺ exchanger-1 inhibitor partially reversed the diabetes induced motor and sensory nerve conducting deficits; thermal hyperalgesia; tactile allodynia and intraepidermal nerve fiber loss. Cariporide was also associated with reduction of diabetes-induced accumulation of advanced glycation end-product, oxidative stress and nitrated proteins in the sciatic nerve. The study did not proffer a mechanism for the action of the drug in this role; however NHE activation has been known to result in calcium overload in some cell types while inhibition of NHE appears to prevent reperfusion injury. Of particular interest with the use of this class of drugs, is their potent scavenging capacity of oxidizing free radicals which can proceed to damage many cellular components including phospholipid A- containing cellular membranes [30–32].

3.1.14. *Puerarin*

The effect of the isoflavone, Puerarin, was assessed in a review by Wu et al. in 2014. The evaluation of relatively low quality studies involving 1664 via meta-analysis showed that Puerarin injection combined with western medications was more effective than conventional therapy for diabetic peripheral neuropathy in terms of nerve conduction velocity and hemorheologic index. Although suggested by the review: it is not specifically indicated that pressure dependent neurovascular blood flow correlates with symptomatic improvement through use of this vasodilator [33].

3.2. Rheumatoid disease

The existence of neuropathic pain in rheumatic disease has been described in the literature. Most of these discussions have involved rheumatoid arthritis, systematic lupus erythematosus and systemic vasculitis, and the incidences of neuropathic pain in these populations have been limited. In variants of rheumatoid disease with cryoglobulinemia there have been more frequent reports. Ferri et al. evaluated the prevalence of neuropathy in 33 unselected patients with mixed cryoglobulinemia (age 45–71, 25 female). Using electrophysiologic assessment

including sensory nerve conduction velocities in combination with F wave (or the second of two voltages observed following electrical impulses applied to the distal aspect of a sensory nerve distribution) and H-reflexes (the reaction of the associated musculature following the application of an electrical stimulus to the distal region of a sensory nerve) [34]; they were able to detect neuropathy in 82% of subjects. They determined that F-wave alterations specifically were the most reliable technique to determine neurologic involvement. They then found a strong correlation with significantly elevated Cryocrit levels in patients with F-wave alterations ($p < 0.008$) and determined that hemorheological abnormalities seem to contribute to the pathogenesis of nerve injury [35].

3.3. Systemic lupus

Capillaroscopic evaluation was used to assess the association between Raynaud's phenomenon (RP) and systemic lupus erythematosus (SLE). In this work Pavlov-Dolijano et al. studied 79 total patients who suffered from SLE [36]. Forty four of them (43 women) with RP, and 35 (32 women) matched for age, sex, and disease duration with SLE without RP were studied. Central nervous system involvement and peripheral neuropathy were significantly more common in SLE patients with RP while Sjogren's syndrome was more common in SLE patients without RP. Of particular note was that enlarged capillaries ($p = 0.0482$), presence of avascular areas ($p = 0.0476$) and granular blood flow ($p = 0.0482$) were more common in patients with SLE who also suffered from RP, than in patients with SLE without RP.

In this work there is no causative relationship neuropathy and SLE with RP proffered, but it is a curious finding that micro-vascular dysfunction occurred in close correlation with neuropathic symptomatology.

3.4. Inflammatory enteropathies

Celiac disease is a chronic inflammatory enteropathy that has an associated neurologic disease in about 10% of all cases. These include psychiatric illness dementia, seizures, ataxia, but most often peripheral neuropathy. In this syndrome it is the celiac disease that may remain subclinical and it is the neuropathy that is the prominent clinical presentation. In this work nerve biopsy studies revealed loss of large diameter myelinated fibers, regenerative clusters of myelinated nerve fibers and a few isolated thinly myelinated fibers. There were no indications in the work that hemodynamic influences affected the development of the related neuropathy [37].

In 2005, Gibbons et al. presented a case series in which they described four patients who presented with presyncope and postural nausea. They stated that the four patients had biopsy proven celiac disease with dysautonomia present on autonomic evaluation, iterating the likelihood of neuropathy, autonomic or otherwise, being a possible presenting sign in patients with coeliac disease. Indeed the group stated that the patients comprised 2.4% of patients referred for autonomic testing in one year. While this is greater than the reported prevalence of celiac disease in the United States of 0.71% (1 in 144) [38], it is consistent with the reported incidence found in peripheral neuropathy [37]. The relationship of hemodynamic alterations upon celiac disease-related neuropathy, as in the above work, remains unstudied.

3.5. Cobalamin deficiency-related neuropathy

Beitzke et al. investigated hemodynamic and autonomic nervous system dysfunction in patients with cobalamin deficiency, comparing autonomic responses to 60° passive head up tilting in controls vs. patients with the deficiency. Their work revealed that in the experimental or cobalamin deficient group, there was a significant fall in systolic blood pressure, a blunted fall of stroke index and cardiac index; and a lack of increase of total peripheral resistance. The results suggested that vitamin B₁₂ deficiency causes autonomic dysfunction which may be the cause for orthostatic hypotension [39]. In this description the causal or contributory mechanism is not definitive since any role blood pressure changes may have upon the initial development of the neuropathy is not asserted.

3.6. Transient receptor potential cation channel subfamily V and substance P receptor

In 2011, Fangyan et al. investigated the cardioprotection of methylcobalamin therapy against ischemia/reperfusion injury in isolated hearts of diabetic mice and the involvement of the transient receptor potential cation channel subfamily V (TRPV1). In their work they examined two models: the intact animal; and isolated hearts from streptozotocin (STZ)-induced diabetic murine models. In the isolated heart model they measured hemodynamic parameters and release of lactate dehydrogenase (LDH), calcitonin gene-related peptide (CGRP) and substance P (SP) in coronary effluent during reperfusion. The study revealed that in the isolated heart preparations the DM hearts that had received the methylcobalamin regimen yielded higher concentrations of SP in the coronary effluent ($p < 0.01$); higher expression of TRPV1 ($p < 0.01$); and higher expression of substance P receptor (SPR) in myocardium digests. Normal hearts also yielded higher release of CGRP and SP in the effluent as well as higher expression of myocardial TRPV1, calcitonin receptor-like receptor (CRLR) and SPR than in DM preparations. They concluded that the cardioprotective effect of Methylcobalamin therapy in isolated DM murine hearts is related to the expression of TRPV1 and SPR [40].

3.7. Nerve and axonal regeneration

In murine models methylcobalamin has been shown to have central neuronal protection capabilities which include the promotion of injured nerve and axonal regeneration and protection of glutamate induced neurotoxicity [41–43]. However no direct relationship between peripheral neuropathy, hypotensive-ischemia, and glutamate has been studied to date. It has been speculated that in certain neuronal subpopulations such as hippocampal field CA-1 and neocortical layers 3, 5, and 6 which are characteristically destroyed after sub-maximal hypoxic-ischemic exposure that central neurotoxicity is the result of the endogenous exertion amino acid neurotransmitter, glutamate, released into the extracellular space. Whether this is a mechanism of neuronal protection in the periphery is unknown. Glutamate in the periphery has been shown to be important for sensory input transduction particularly along nociceptive pathways [44]. Complete characterization of the glutamatergic system in the peripheral nervous system is necessary, and its changes under varying pathological conditions are necessary. Clearly studies of any protective effects of Methylcobalamin in the periphery need to be conducted before speculation upon any directed therapeutic intervention with methylcobalamin can be used.

3.8. Alcohol

3.8.1. Cardiac autonomic neuropathy and peripheral neuropathy

The link between alcohol and peripheral neuropathy has been described as recently as 2010, but the 1998 work by Agelink et al., emphasized the occurrence of autonomic neuropathy, and in particular a cardiac autonomic neuropathy (CAN) associated with chronic alcoholism [45]. This alcoholic CAN was also statistically significantly associated with peripheral neuropathy to the extent that the group reported that no evidence of CAN was found without a concomitant, clinically manifest peripheral neuropathy. The group also reported that the neuropathy was likely related to the total lifetime dose of alcohol as well as the duration of alcohol dependence; and that these components were the most important factors contributing to the pathogenesis of both the autonomic as well as the peripheral components of the disease. No distinct relationship of hypertension to the peripheral neuropathy *per se* was reported by any of these groups. Ayad et al. did assert, however, that the cardiac neuropathy/hypertension profile was consistent with a deleterious effect on vascular hemodynamics and structure [46]. This might suggest impairment of the microvasculature as a possible mechanism of nerve injury and subsequent peripheral, neuropathic processes.

3.9. Hypertension/hypotension (blood flow)

3.9.1. Hemodynamic correlates

Regarding hemodynamic correlates of blood pressure and neuropathy, Cho et al. referred to a cross-sectional study of age-associated peripheral neuropathy (AAPN) in which they determined that a history of hypertension was protective. In the work they designed, they collected baseline data from 584 patients in a longitudinal study of primary care patients 65 years of age and older. The patients were selected on the basis of having none of the 10 medical conditions known to cause peripheral neuropathy. The patients were assessed for any associations between peripheral neuropathy by examination and the following criteria: history of hypertension, number of anti-hypertensive medications, systolic blood pressure, diastolic blood pressure, pulse pressure and orthostatic hypotension. The group concluded that the negative correlation between hypertension and AAPN was unexplainable. They noted that the positive association between pulse pressure and neuropathy in diabetic subjects supported findings from earlier studies and suggested AAPN and diabetic neuropathy may be distinct entities [47].

3.9.2. Cuban epidemic neuropathy

In a 1999 report, the Cuban epidemic neuropathy (CEN) outbreak which occurred from following an outbreak from January 1, 1992 through January 14, 1994 was described. During this health crisis, 50,862 Cuban residents were affected. The neuropathy included an optic form as well as a peripheral form with both types characterized by weight loss and easy fatigability [48]. In 2002, Gutierrez et al. studied autonomic cardiovascular reflexes in patients with CEN. They found that affected patients had significantly less heart rate variability during paced breathing. They reported that this suggested reduced cardiac parasympathetic innervation. While this study examined blood pressure changes in the setting of peripheral neuropathy no causative or influential relationship between the two was described [49].

3.9.3. *Chronic venous insufficiency*

Chronic venous insufficiency (CVI) as a correlate of peripheral neuropathy was examined in a 2000 study by Reinhardt et al. [50] This group compared 30 patients with CVI and 20 healthy controls using motor and sensory nerve conduction studies, vibration testing and thermotesting, the quantitative, sudomotor axon-reflex test, and Doppler flowmetry. In the CVI group distal motor latency of the peroneal nerve was prolonged ($p = 0.02$); there were increased limits for warm ($p = 0.016$) and cold detection ($p = 0.016$); and there was reduced vibration sense ($p = 0.008$). The group goes on to state that the results demonstrate a disturbance of A-alpha, A-beta, and A-delta fibers; as well as thermoafferent C-fibers. The mechanism of these disorders, they assert, is neural ischemia caused by a venous microangiopathy and increased endoneurial pressure.

3.9.4. *Ischemic monomelic neuropathy*

The relationship between chronic and critical leg ischemia was studied by Weinberg, et al. Nineteen patients suffering from chronic and critical leg ischemia were studied [51]. All patients experienced pain only 16% (3) were completely free of neuropathic symptoms. They concluded that there is a predominantly sensory neuropathy associated with chronic and critical limb ischemia, that measures of blood loss correlate with neurologic symptom scores and the suggest that the underlying pathophysiology is a distal axonopathy affecting nerve fibers of all sizes. This study implicates a perfusion dependent neuropathic pathogenesis exist in this syndrome.

3.9.5. *Sympathetic denervation*

The role of regional blood flow was further emphasized in a study that examined whether painful diabetic neuropathy is associated with abnormal sympathetic nervous function in affected limbs. Positron emission tomography (PET) scanning was used after intravenous injection of the sympathoneural imaging agent 6-[(18)F]-fluorodopamine to visualize sympathetic innervation and [(13)N]-ammonia to visualize local perfusion. Compared with non-neuropathic patients and diabetic patients with unilateral neuropathy in whom comparisons were made between the involved limb and the non-involved limb, PET scanning revealed decreased flow-corrected 6-[(18)F]- fluorodopamine derived radioactivity in patients with painful diabetic neuropathy as well evidence suggesting partial loss of sympathetic innervation [52].

The role of hypertension in the development of peripheral neuropathy was studied by Gregory et al. in 2012. They asserted that current rodent models did not adequately replicate all pathological features of diabetic neuropathy. Based upon this assertion they tested the hypothesis that combining hypertension with insulin-deficient diabetes produces a more pertinent model of peripheral neuropathy. In their work behavioral, physiological and structural indices of neuropathy were measured for up to 6 months in spontaneously hypertensive and age-matched normotensive rats with or without concurrent streptozotocin-induced diabetes. They found that hypertensive rats developed nerve ischemia thermal hyperalgesia nerve conduction slowing and axonal atrophy. In addition they observed the presence of thinly myelinated fibers with supernumerary Schwann cells which occur during cycles of degradation and production of myelin. The group also noted reduced levels of myelin basic protein. In streptozotocin-induced

diabetic rats similar findings were noted save for the absence of thinly myelinated fibers and the fact that there were normal levels of myelin basic protein [53]. Hence in the murine model, at least in the presence of diabetes, hypertension is not associated with a protective effect against the development of peripheral neuropathy seen in at least one human study [47].

3.9.6. *Alpha lipoic acid*

In an important work written in 2000, Haak et al. studied the beneficial effects of alpha-lipoic acid (ALA) is known to have on diabetic polyneuropathy. The work focused upon the effect of ALA on microcirculation in patients with diabetes mellitus and peripheral neuropathy. Two groups were compared: eight patients (age 60 ± 3 years) with diabetes of 19 ± 4 years who received a 6 week course of ALA, 1200 mg each day orally; and a second group of nine patients (age 65 ± 3 years) with diabetes of 14 ± 4 years duration. The groups had similar sex (~50%) and BMI (24.8 ± 1.3 – 23.6 ± 0.7 kg/m²) distributions. The second group was studied before and after they had received 600 mg ALA or placebo intravenously over 15 minutes in order to investigate whether ALA has an acute effect on microcirculation. Capillary blood cell velocity was examined at rest and during post reactive hyperemia. They found that the oral ALA group showed a significant decrease in the time to peak capillary blood cell velocity (tpCBV). The intravenous infusion of ALA also decreased the tpCBV in patients with diabetic neuropathy. The group determined that in patients with diabetic polyneuropathy ALA improves microcirculation via an increased perfusion reserve. They asserted that their improvement in the symptoms of diabetic polyneuropathy may be occurring by virtue of improvements in microcirculatory blood flow at the level of the vasa nervorum [54].

3.9.7. *Hypertension vs. hypotension*

In a 2005 study Jarmuzewska et al. sought to determine which component of the blood pressure is responsible for a perceived link between hypertension and sensorimotor peripheral neuropathy [55]. To examine this relationship they took 55 consecutive outpatients with type II diabetes and measured blood pressure and 10 neurophysiological parameters: nerve conduction velocity at the median, ulnar, posterior tibial, and peroneal nerves; and sensory amplitude (AMP) and latency (LAT) at the median, ulnar and sural nerve. The results of this analysis showed that age, diabetes duration, systolic blood pressure and pulse pressure are negatively correlated with nerve function. Their regression analysis showed that after correction for age, disease duration, glycated hemoglobin, BMI, microalbuminuria, and SBP: PP was independently and negatively associated with nerve conduction and signal AMP; and positively correlated LAT. At least two considerations raised with this work: first there is no suggestion of any mechanistic relationship with the neurophysiologic changes and, second, there is presentation of the strength of the correlation between the acquired data and any regression line, i.e. R², despite the group reporting on what the analysis showed. The approach in the study, however, was important in that it specifically delineated quantifiable components of nerve function that should be used in clinical models for future works on the relationship of flow and pressure dynamics on the development of neuropathic processes.

The relationship between hypotension and sensory motor peripheral diabetic neuropathy was further studied in a 2007 work by this same group [56]. Here they studied the connection

between cardiovascular risk factors, parameters of metabolic control and the presence of sensorimotor peripheral neuropathy. They examine blood pressure, glycated hemoglobin, lipid profile, and the presence of micro- and macro-vascular complications in 31 consecutive outpatients with type II diabetes age 60.7 ± 7.5 who had been diagnosed within 10 years of the study. Their work revealed that the prevalence of hypertension- defined as a blood pressure $\geq 140/90$ - was higher in sensorimotor peripheral diabetic neuropathy-positive patients. They went a step further and performed regression analysis on the data which revealed that after correction for age, gender, disease duration, glycated hemoglobin and serum lipids there was a correlation between hypertension and sensorimotor diabetic peripheral neuropathy. The group states that there is a strong association between hypertension and sensorimotor diabetic peripheral neuropathy but they report an R^2 – or the statistical measure of how close the data are to the fitted regression line- of 0.17 (17%), In other words the model explains relatively little of the variability of the data about the mean or the incidence of sensorimotor diabetic peripheral neuropathy. In this light the question of the relationship of hypertension with peripheral neuropathy, at least in the setting of type II diabetes remains equivocal. This is especially so in comparison to at least one study in non-diabetic patients which indicates that hypertension may be protective against the development of peripheral neuropathy [47]. In addition any question of a causal mechanism between hypertension and peripheral neuropathy remains unanswered.

Another attempt to correlate hemodynamics with peripheral neuropathy sought to use brachial-ankle pulse wave velocity, which is considered to be a valid marker of clinical atherosclerosis. The brachial-ankle pulse wave velocity is a measure of arterial stiffness and can be measured by peripheral tonometry, Doppler ultrasound and catheter tip manometry. Park et al. assessed 692 patients with type II diabetes (314 men, 376 women) with a mean age of 56.9 ± 10.9 years and a mean duration of diabetes of 7.9 ± 6.3 years [57]. The group chose the endpoints of neuropathic pain intensity on the numeric visual analog scale, the neurological assessment using ankle reflexes and the 10 g monofilament test; and the brachial-ankle pressure wave velocity. They found a positive correlation between the presence of peripheral neuropathy and maximal baPWV ($r = 0.127$, $p < 0.001$). After applying the independent t test the group then reported that the patients with peripheral neuropathy had higher maximal baPWV, systolic blood pressure, subject number of female sex; and older age compared with controls.

The role of hypertension in the development of peripheral neuropathy was not necessarily clarified in this work as the authors offered no such explanation, however the existence of peripheral artery disease as measured by baPWV and neuropathy raises the question of whether similar compliance changes occur in the microvasculature and specifically impact perfusion of peripheral nerves via the vasa nervorum.

The relationship between hypertension and diabetic peripheral neuropathy remains unclear and a consistent correlation (either positive or negative) between the two entities is yet to be found in the literature. Ozaki et al. in 2016 used a murine model to further examine this question [58]. Specifically their goal was to analyze the effects of hypertension on diabetic neuropathy. They studied morphologic features of peripheral nerves in rats with hypertension. They divided Male rats into two groups: alloxan-induced diabetic rats who received deoxycorticosterone acetate salt (DOCAS-salt) and non-diabetic rats who also received DOCA-salt. Sciatic, tibial (motor) and sural (sensory) nerves were then studied histomorphologically.

Systolic blood pressure was maintained above 140 mmHg in both groups and endoneurial vessels in both groups showed endothelial hypertrophy and vessel lumen narrowing (**Figure 3**). However electron microscopic analysis revealed duplication of the basal lamina surrounding the endothelium and pericytes of the endoneurial vessels, a lesion the group stated that was more frequent and severe in the diabetic group (**Figure 4**). They also reported that on morphometric analysis of the tibial nerve there was a shift to smaller fiber and myelin sizes in the diabetic group than in the control group (**Figure 3**).

3.9.8. Superoxides

The role of superoxides in relationship to peripheral nerve damage caused by microvascular dysfunction in a murine model was examined in an important work by Jin et al. in 2012 [59]. In this study the group examined the effect of the sulfated polysaccharide complex sulodexide. This drug is known to induce acceleration of spontaneous fibrinolysis-thrombolysis of preformed thrombi [34]; to inhibit leukocyte activation and endothelial adherence [60]

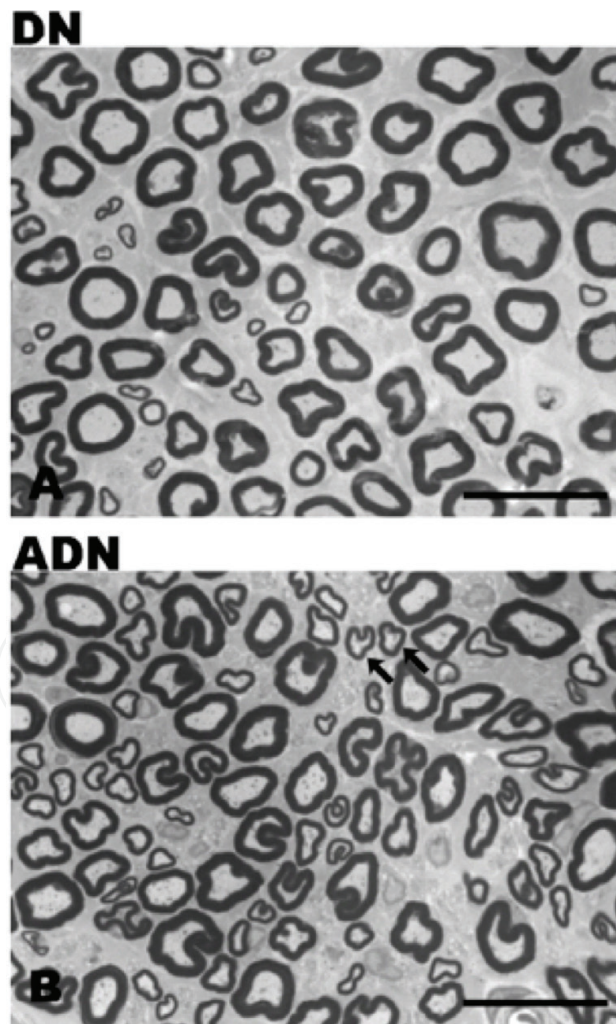


Figure 3. Representative sections of sural nerve in the control (A) and diabetic (B) groups. The small- sized myelinated fibers are increased in the diabetic group (arrows). Endoneurial fibrosis is observed in both groups (adapted from Ozaki et al. [58]).

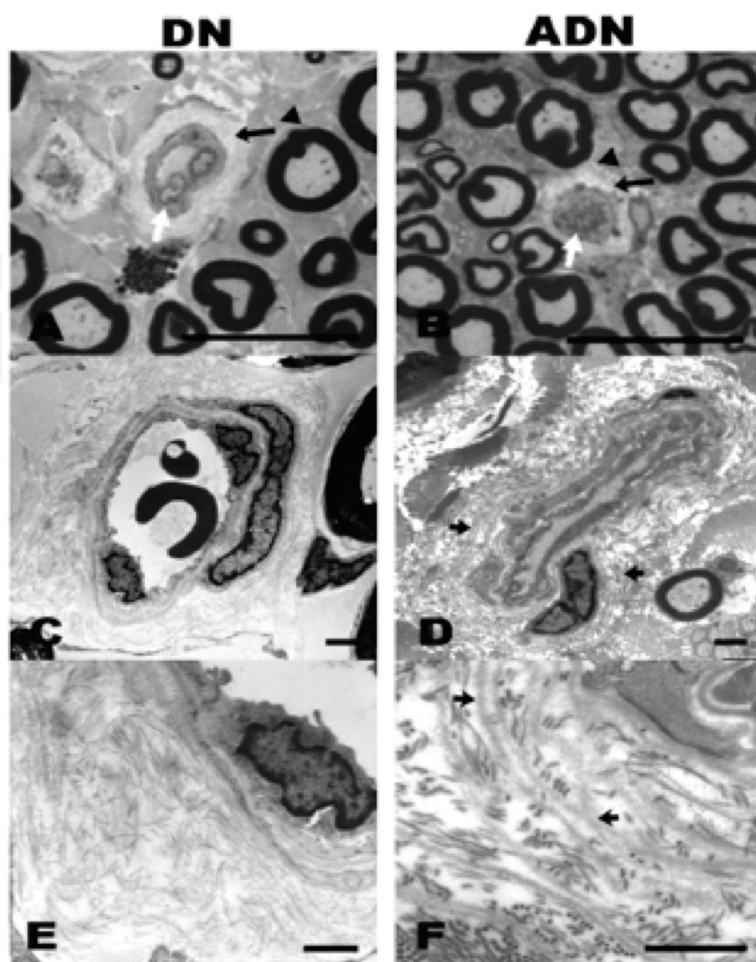


Figure 4. Representative sections of sciatic nerve in the diabetic (ADN) and control groups (DN). (A, B) in endoneurial vessels (white arrows), narrowing of the lumen with endothelial hypertrophy is observed in both groups. Both nerves show edema (black arrow) and fibrosis (arrowhead) in the endoneurium. (C, D) Electron microscopically, duplication of the basal lamina (arrows) surrounding the endothelium and pericytes of endoneurial vessels is seen in the ADN group. Many collagen fibers are also present around the vessels of both groups. (E, F) high magnification of **Figure 2** (C, D) has been performed. Duplicated basal laminae (arrows) of the diabetic group are also seen between collagen fibers, but in the DN group, edema is observed among collagen fibers (adapted from Ozaki et al. [58]).

and to protect endothelial integrity in the microcirculation [61]. The group divided female Sprague–Dawley rats into four groups normal, normal + SDX; DM; DM + SDX. They found that superoxide dismutase activity in the blood and sciatic nerve were increased significantly after sulodexide treatment. They also found that electrical current perception threshold was reduced, and that skin blood flow was improved in the DM + SDX group compared to the DM group ($p < 0.005$). They also found that the mean myelinated axon area was significantly larger in the DM + SDX group vs. the DM group. The results of this work suggest not only the beneficial role of SDX in treating the peripheral neuropathy of DM but also that the drug may be useful in neuropathies of other origins. The work also supports the possible role of microneurovascular dynamics in the development of the disease.

3.9.9. Alpha adrenoceptor agonists

Small fiber neuropathy in diabetic patients treated with alpha-adrenergic agonists was the subject of a study by Schmiedel et al. in 2008 [62]. The emphasis of this work was on the impairment

of 0.1 Hz microvascular vasomotor. It tested the hypothesis that dermal vasoconstriction-induced microvascular oscillations are reduced in diabetic patients with peripheral and/or autonomic neuropathy; and whether this method could be used as a non-invasive surrogate marker to assess diabetic small fiber neuropathy. The work examined four matched groups: diabetic patients without neuropathy; with peripheral neuropathy; with peripheral and autonomic neuropathy; and non-diabetic controls. Following iontophoretic administration of phenylephrine 0.1 Hz oscillations recorded at the foot were significantly attenuated in diabetic patients with peripheral and/or autonomic neuropathy compared to diabetic patients without peripheral neuropathy. Oscillation measures correlated significantly with all markers of peripheral neuropathy ($p < 0.001$) but not with markers of microvascular endothelial function of metabolic syndrome markers. In a logistic regression model, reduced microvascular oscillations at the foot were a strong predictor for the presence of peripheral neuropathy.

The findings of this work suggest that attenuation of oscillations, an indicator of vascular compliance, is reduced in the presence of diabetic neuropathy. The question then arises: is there a loss of such compliance in other or all described peripheral neuropathies. These studies are yet to be performed.

3.10. Uremia

Peripheral neuropathy in chronic kidney disease (CKD) or uremic neuropathy affects 90% of CKD patients [63]. There are multiple causes of CKD, the majority of which result from primary renal disorders. Among the CKD variants that occur as a complication of systemic disease, diabetes mellitus is the most common cause worldwide. It is noteworthy that regardless of the cause, patients afflicted with CKD have a high prevalence of neurologic complications. Initial work on the disease suggested that uremic neuropathy only occurred when the glomerular filtration rate (GFR) was consistently 12 mL/minutes. Recent studies, however, have demonstrated that uremic neuropathy occurs in about 70% of patients prior to their requiring hemodialysis [64]. The characteristic symptoms, which include pain, loss of sensation, and weakness, can be disabling. Uremic neuropathy commonly affects large motor neurons and sensory fibers. Small nerves are commonly involved as well. Early signs and symptoms include distal sensory loss and reduced tendon reflexes in the lower extremities. As the neuropathy progresses, the loss of sensation extends proximally in the lower extremities. Similar symptoms can occur in the upper extremities. In the advanced stages, motor nerves of the lower extremities are affected leading to muscle atrophy and resulting weakness. The effects of systemic uremia on peripheral nerves can be demonstrated by the generalized decrease in conduction velocity in both motor and sensory nerves. This is caused by structural changes along the length of the peripheral nerves. In addition to structural changes, there is likely an unknown uremic toxin that is neurotoxic.

Studies have identified several compounds that are now considered to be possible neurotoxins. Creatinine, urea, uric acid, guanidine, methyl guanidine, guanidinosuccinic acid, oxalic acid, phenols, aromatic hydroxyacids, indican, amines, myoinositol, beta-2 microglobulin, parathyroid hormone, amino acids, and neurotransmitters all fall into this group. None of these compounds, however, have moved beyond the speculative consideration and been definitively proven to be a cause of peripheral neuropathy.

Recent evidence suggests that hyperkalemia plays a major role in uremia related peripheral neuropathy. Hyperkalemia has been shown to cause axonal dysfunction in a dose-dependent

manner. This dysfunction can be reversed with the treatment of hyperkalemia suggesting that maintaining normal potassium level in CKD patients can help prevent uremic peripheral neuropathy [65]. There is no evidence to suggest that normalizing serum potassium levels can reverse the peripheral nerve dysfunction in patients with existing uremic peripheral neuropathy at any stage. It is known that uremic toxins are likely to be direct or indirect causes of central nervous system neurodegeneration. Uremia indirectly contributes to systemic inflammation, endothelial dysfunction and atherosclerosis leading to neurodegeneration and cognitive dysfunction. Several compounds including uric acid, indoxyl sulphate, rho-cresyl sulphate, interleukin-1beta, interleukin-6, and tumor necrosis factor-alpha have been suggested as likely contributors to the development of neurodegeneration [66]. Interestingly, crystalin-C has recently also been attributed to neurodegeneration through amyloid plaque formation [67]. The possible direct causes of neurodegeneration have been mentioned previously. Intuitively, it is possible to suggest that neurodegeneration directly or indirectly, centrally and/or peripherally is multifactorial. It involves multiple causative agents that may act either as direct neurotoxins or via the induction of systemic inflammation, endothelial dysfunction, and atherosclerosis. Each of these processes may lead to the disruption of pressure-dependent blood flow, and ultimately lead to neuropathy and cell death.

3.11. Chemotherapeutic agents

Chemotherapy-induced peripheral neuropathy (CIPN), as the name implies, occur in oncology patients who have been exposed to neurotoxic chemotherapeutic agents. CIPN is debilitating and often develops after several treatments in a dose dependent fashion. Interestingly, a few of the newer chemotherapeutic agents can cause CIPN in an idiosyncratic way unrelated to the accumulated dose of the agents. In a 2007 work Kannarkat et al. reviewed the literature regarding complications of common chemotherapeutic agents and chemotherapeutic agents that had been recently developed [68]. While their main emphasis was upon the cognition-impairing effects of the therapy they also looked at the occurrence of neuropathic pain with the drug Bortezomib which was the first therapeutic proteasome inhibitor to be used in humans. The group found that the drug has a propensity toward causing a largely sensory but reversible peripheral neuropathy. The group found from the literature that the infusion of magnesium and calcium pre- and post- oxaliplatin infusion reduces the neuropathy associated with this specific drug but that it may actually interfere with clinical response to oxaliplatin. They stated that no other known interventions at the time reduced the incidence or severity of neuropathy related to platinum compounds, taxanes (taxoids), or thalidomides. They did suggest that regional neural blood flow, DNA damage, mitotic dysfunction, defects in neural repair, and oxidative stress may play roles in the effects of chemotherapeutic agents upon the nervous system.

CIPN affects approximately 30 to 40% of patients receiving neurotoxic chemotherapeutic agents [69]. Common groups of agents with established associations with CIPN are platinum based drugs, vinca alkaloids, taxanes (taxoids), thalidomide, and proteasome inhibitors. Cyclophosphamide, methotrexate and immune check point inhibitors have also been reported to cause CIPN. CIPN is often caused by primary direct neurotoxic effect on the neurons often with a predilection for sensory over motor and autonomic neurons causing anatomic and/or physiologic changes. Symptoms are likely amplified by hyper-excitability and central sensitization. The anatomic changes are mainly targeted at the dorsal root ganglion neurons or

their axons leading to peripheral sensory loss, ataxia, and pain. A significant exception to this mechanistic tendency of chemotherapeutic agents is the likely mechanism by which platinum compounds cause neuropathy. This is based upon the fact that, typically, only a sensory neuropathic component is observed. Regarding thalidomide and its newer analogues, recent evidence of its toxicity pathway suggests that anti-angiogenesis may play a significant role in the cause of CIPN. Anti-angiogenesis may not be unique to the thalidomide class but indeed may contribute to a common pathway to CIPN for all chemotherapeutic agents [70, 71].

Platinum-based chemotherapeutic agents commonly used include cisplatin, oxaliplatin, and carboplatin. Of these, the most toxic compound is cisplatin. All of the platinum-based chemotherapeutic agents cause permanent sensory CIPN. They are believed to inflict damage upon the dorsal root neurons. This is the result of adduct formation with nuclear and mitochondrial DNA which ultimately leads to cellular apoptosis. There is also evidence to suggest that cisplatin-linked anti-angiogenesis causes peripheral neuropathy [71]. Direct mitochondrial damage also occurs and is postulated to the coasting phenomenon in which the symptoms of CIPN continue to worsen several months after the discontinuation of therapy [72].

The role of platinum-based chemotherapeutic agents in the development of neuropathy was evaluated in a prospective study by Boogerd et al. in which the group examined the occurrence and degree of central peripheral and autonomous neuropathy. Twelve patients were examined before, during and after initiation of cisplatin treatment. Their evaluations included neurologic examination, nerve conduction studies of median and peroneal nerves, and short latency somatosensory evoked potentials (SSER) after median and tibial nerve stimulation. They noted that SSER appeared to be the most sensitive method for the detection of peripheral nerve impairment [73].

In 2011, Cunningham et al. stated that chemotherapy induced peripheral neuropathies (CIPN) developed from unknown mechanisms but that symptoms could be reduced by manual therapy (massage) implying that digital augmentation of blood flow may provide symptomatic relief from neuropathic pain [74].

Yeo et al. in 2016, using a murine model, showed that clonidine dose-dependently reduced oxaliplatin-induced allodynia and spinal p-p 38 mitogen activated protein kinase (MAPK) expression. When given in combination with the MAPK inhibitor SB203580, reduced dose clonidine decreased allodynia without significant, undesirable motor or cardiovascular effects [75].

3.11.1. Antimicrotubule agents

This class of chemotherapeutic agents includes taxanes (or taxoids), vinca alkaloids, and the newer agents, eribulin, ixabepilone, brentuximab, vedotin, and ado-trastuzumab emtansine. Taxanes, paclitaxel, docetaxel, and cabazitaxel are used commonly and cause painful, dose and length-dependent sensory neuropathy. The mechanism for this is likely due to the ability of taxanes to cause target interference with microtubule-based axonal transport function [76]. Vinca alkaloids, vincristine, vinblastine, vindesine, and vinorelbine destabilize microtubule formation interfering with axonal transport and mitochondrial function. The compounds can lead to length-dependent sensory neuropathy with some motor neuron involvement. The degree of neuropathy may be long term or permanent. Epothilones, eribulin and ixabepilone, have the same mechanism of action as taxanes, causing axonal sensorimotor CIPN [77].

Brentuximab vedotin and ado-trastuzumab emtansine are biologic hybrid agents created by the conjugation of tumor specific antibody to a chemotherapy agent. They both interfere with microtubule function and the use of these agents results in a high incidence of CIPN.

In a 2000 study Ekholm et al. *examined* the taxoid chemotherapeutic agent Paclitaxel in order to determine if it changed cardiovascular regulation in breast cancer patients previously treated with anthracyclines. They concluded that Docetaxel treatment did not cause deterioration of vagal cardiac control in breast cancer patients after exposure to epirubicin. They also determined that the observed changes in blood pressure response suggested that docetaxel changes sympathetic vascular control; however the changes appeared to be related to changes in cardiovascular autoregulation as opposed to neuropathic changes in the peripheral sympathetic fibers [78].

Later, in 2007, Kirchmair and his group studied Paclitaxel as used in the treatment of breast, lung, and ovarian cancers; and thalidomide as used to combat multiple myeloma and other bone marrow cancers [70]. Again, the rationale for the study was the dose limiting effect of the development of peripheral neuropathy when these drugs are used. The group hypothesized that the toxic neuropathies resulting from the destruction of vasa nervorum and that the neuropathy could be reversed by administering an angiogenic cytokine. The group used a murine model and employed intramuscular gene transfer of naked plasmid DNA encoding VEGF-1 administered in parallel with Taxol injections. They found that in this setting there was complete inhibition of nerve function deterioration and inhibition of peripheral nerve vasculature diminution. A similar result was seen when the study was repeated using thalidomide. The work iterates the implication of microvascular damage as the basis for toxic neuropathy and, again, regional blood flow and vascularity appear to be critical components in the development as well the prevention of peripheral neuropathy.

Gracias et al. in 2011 studied peripheral neuropathy secondary to paclitaxel exposure in a murine model [79]. Paclitaxel targets tubulin and stabilizes the microtubule polymer and protects it from disassembly and blocks mitotic progression at the spindle checkpoint which delays the onset of anaphase and triggers apoptosis [80]. In their work, Gracias et al. dosed male Sprague–Dawley rats with 1 mg/kg paclitaxel for four doses over 8 days and examined hind paw vasodilation as an indirect measure of calcitonin gene-related (CGRP) release. When compared to rats that were injected only with vehicle, capsaicin- or electrical stimulation of the sciatic nerve- induced vasodilation, paclitaxel-treated rats demonstrated significantly attenuated vasodilation. Paclitaxel did not affect direct vasodilation induced by intradermal injection of methacholine or CGRP which demonstrated that blood vessels' ability to dilate remained intact. These results suggest that paclitaxel affects the peripheral endings of sensory neurons to alter transmitter release, and this may contribute to the symptoms seen in neuropathy. Further we may possibly query whether the diminished vasodilation from more central stimulation may inhibit blood flow to the degree that consistent vasa nervorum- mediated perfusion becomes impaired leading to peripheral nerve compromise and subsequent peripheral neuropathy.

3.11.2. Proteasome inhibitors

The proteasome inhibitor, bortezomib, causes length-dependent small fiber neuron axonal sensory neuropathy. Fortunately, it is a reversible phenomenon. Additionally, bortezomib may also cause severe immune-mediated polyradiculoneuropathy in some patients. Newer generation

proteasome inhibitors, carfilzomib and ixazomib, have a lower incidence of CIPN compared to bortezomib [81, 82]. The mechanism by which proteasome inhibitors cause CIPN is thought to be the result of their effects on the microtubules and mitochondria of sensory neurons. This effect results in decreased axonal transport and function [83, 84].

Bortezomib is used in the treatment of multiple myeloma and is known to result in peripheral neuropathy [85], Tsukaguchi et al. [86] employed the use of lafutidine an H₂-blocker with gastroprotective activity which is believed to function via a similar mechanism as capsaicin, i.e., increasing mucosal blood flow via capsaicin-sensitive afferent neurons, and selective blockade of afferent sensory neurons. An example of this function is the ability of lafutidine to reduce the pain of glossodynia and taxoid-induced peripheral neuropathy [86].

Peripheral neuropathy (PN) caused by bortezomib was studied in eight patients twice a week for 2 weeks followed by 1 week without treatment for up to four cycles. Lafutidine was administered orally at 10 mg twice daily. The total occurrence of PN was four out of the eight patients. They found from this limited study that although the total occurrence of PN after the first course and in no cases was bortezomib treatment discontinued because of PN. It may be speculated that lafutidine is useful for the amelioration of bortezomib-induced PN. Bortezomib is a 20S proteasome complex inhibitor that acts by disrupting various cell signaling pathways leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis. Bortezomib causes mitochondrial changes resulting in swollen and vacuolated mitochondria in axons, opening of mitochondrial permeability transition pore (mPTP) with release of intracellular calcium; and activation of caspase and apoptotic pathways [87]. The anti-angiogenesis activity of this drug may have implications upon the pressure and flow development component of peripheral neural blood supply and the evolution of neuropathic changes.

Speculation upon the role of a capsaicin-like intervention in this neuropathy must of necessity consist of consideration of interactions at a number of sites in the molecular pathways of nerve injury and death. Studies, then, are needed to dissect these interactions and shed light upon the effect of this treatment.

3.11.3. Antiretroviral chemotherapeutic agents

Patients treated with antiretroviral medications of the nucleoside analogue reverse transcriptase inhibitors (NRTIs) class of drugs can develop myopathy and neuropathy of varying severity after prolonged therapy with the neuropathy characterized as painful, sensory and axonal [88]. NRTIs cause mitochondrial DNA (mtDNA) dysfunction and impaired oxidative phosphorylation. There is evidence that the resultant mitochondrial toxicity is due to a new category of acquired mitochondrial toxins, azido groups that compete as substrates of DNA pol-gamma and terminate mtDNA synthesis and thus lead to axonal degradation [89].

In a 2005 case report Fodale et al. *describe* a fatal exacerbation of peripheral neuropathy in which iatrogenic mitochondrial damage occurred. They describe a 57 year old man with mild neuropathy with hepatitis B and C virus treated with the antiretroviral lamivudine 300 mg per day. The causal relationship was implied when at 3 months of therapy he presented with dysphoria and progressive muscle weakness. He subsequently developed quadraparesis, acute respiratory failure and sudden cardiac arrest with successful resuscitation. The lamivudine was discontinued

and respiratory capacity improved. The patient subsequently died suddenly despite hemodynamic, ventilator and metabolic support. Electrophysiological studies prior to death revealed sensory-motor axonal neuropathy. Biochemical and mitochondrial DNA molecular genetics suggested possible widespread iatrogenic mitochondrial damage. The group speculated that mtDNA dysfunction could be a potential cause of the sudden cardiac arrest [90].

3.12. Antibiotics and antifungals

Antibiotics are commonly used agents in both inpatient and outpatient settings. They are generally well tolerated but may cause peripheral neuropathy in idiosyncratic as well as dose-dependent fashions. The incidence of peripheral neuropathy associated with antibiotics is drug dependent and is relatively rare compared to the incidence seen with chemotherapeutic agents. It has been demonstrated that clinically appropriate doses of bactericidal antibiotics can cause mitochondrial dysfunction that leads to leakage of toxic reactive oxygen species (ROS) from the mitochondrial electron transport chain (ETC) in mammalian cells [91]. The ROS can interact with cellular components such as lipids, protein and DNA. The end result is oxidative stress with subsequent tissue damage. The oxidative stress produced by bacteriostatic antibiotics is significantly less. Similar to the chemotherapeutic agents, antibiotics have been shown to inhibit angiogenesis [92], which has been proposed as a major mechanism of chemotherapeutic-related neurotoxicity and peripheral neuropathy [70]. The antibiotic classes that are known to cause peripheral neuropathy are: aminoglycosides, tetracyclines, fluoroquinolones, oxazolidinones, and polymyxins. Clinical observations however suggest that the malady is not limited to these antibiotic groups alone.

3.12.1. Aminoglycosides

The ototoxicity associated with aminoglycosides is well described. The role of this antibiotic in causing peripheral neuropathy and encephalopathy is less commonly discussed. The mechanism leading to peripheral neuropathy is unclear. Gentamycin has been linked to peripheral neuropathy and microscopic examination of involved neural tissue have reveals lysosomal abnormalities that as of yet have no clear cause [93]. Current evidence appears to suggest that this group of antibiotics causes nerve damage via the activation of NMDA receptors and subsequent release of oxidative radicals. It is postulated that the excitotoxicity activation of NMDA receptors within the cochlear leads to the formation of ROS causing ototoxicity [94, 95]. Intrastriatal neomycin leads to gliosis. It is noteworthy that this effect is attenuated in the presence of NMDA antagonists. Neuromuscular blockade, commonly associated with aminoglycosides, is a temporary form of peripheral neuropathy. These agents inhibit the quantal release of acetylcholine pre-synaptically and bind to the acetylcholine receptors post-junctionally at the neuromuscular junction causing weakness.

3.12.2. Tetracyclines

Tetracyclines have been associated with neuropathy of the cranial nerves [96]. However, the cause and incidence are unclear.

3.12.3. Fluoroquinolones

Fluoroquinolones have been known to cause peripheral neuropathy. Oral fluoroquinolones are associated with an increased risk of developing peripheral neuropathy of up to 30% [97], and an overall incidence of 1% of developing this disorder [98]. Of all the cases of fluoroquinolones associated peripheral neuropathy, 9% of these patients had Guillain-Barre syndrome [98]. The three fluoroquinolones commonly implicated in peripheral neuropathy are ciprofloxacin, levofloxacin, and moxifloxacin [97, 98]. Fluoroquinolones are associated with neurotoxicity of central nervous system possibly through their inhibition of GABA receptors [99]. Peripheral nerves also express GABA receptors. Whether the interaction of fluoroquinolones with GABA receptors of peripheral nerves or Schwann cells or whether it is a combination of an interaction with both classes of cells that leads to peripheral neuropathy still remains unknown.

3.12.4. Oxazolidinones

Oxazolidinones is a unique class of antibiotics that is completely different from any other antibiotic group. The only oxazolidinone available for clinical use is linezolid. Little is known about the mechanism by which linezolid causes peripheral neuropathy or the incidence of this peripheral neuropathy. There are reports of linezolid causing Bell's palsy and optic neuropathy [100, 101]. and there is at least one report that details four cases of linezolid causing peripheral neuropathy with concomitant use of a selective serotonin re-uptake inhibitor (SRI) [102]. In a retrospective analysis of 75 patients receiving treatment with a combination of six drugs including linezolid and pyridoxine, 13% of the patients were found to have sensory peripheral neuropathy [103].

3.12.5. Metronidazole

Metronidazole has been reported to cause both motor and sensory peripheral as well as optic and autonomic neuropathies [104–107]. The incidence of peripheral neuropathy is unknown and appears to be dose dependent. The precise mechanism of metronidazole causing neuropathy is unknown. It has been suggested that metronidazole-induced vasogenic edema leading to axonal swelling is a likely cause [108].

3.12.6. Polymyxins

The polymyxins, polymyxin B and colistin have an approximately 7% incidence of paraesthesias and polyneuropathy in treated patients [109]. It appears that the route of administration correlates with the severity of the incidence of neuropathy. Intravenous administration of polymyxin B incidence of neuropathy is 27% as compared to 7.3% for the intramuscular route [110]. Neurotoxicity is also dose dependent and there is a sex predilection with females having a higher rate of neurotoxicity as compared to males. The mechanism of neurotoxicity is postulated to be the interaction of polymyxins with neurons due to their high lipid content [111].

3.12.7. Nitrofurantoin

Nitrofurantoin has been implicated as the cause of sensorimotor polyneuropathy in pediatric patients, especially those with a history of renal insufficiency. This manifests as paresthesia and dysesthesia in the lower extremities [112–114]. The incidence is estimated to be about 0.0007% [115]. The precise mechanism of the polyneuropathy is unknown.

3.12.8. Isoniazid

Isoniazid causing dose-dependent, reversible sensorimotor peripheral neuropathy is a well-known phenomenon that is preventable with the administration of pyridoxine. The incidence of peripheral neuritis is from 6% to approximately 20% in patients taking exposed to a dose of 6 mg/kg daily [116, 117]. There are also reports of isoniazid in combination with ethambutol causing severe but reversible optic neuritis [118]. The mechanism by which isoniazid causes peripheral neuropathy is unknown but it has been suggested to relate to isoniazid-induced pyridoxine deficiency. The complex relationship between isoniazid and pyridoxine is unknown. In adults, pyridoxine supplement is recommended with isoniazid treatment. However, in the pediatric population, pyridoxine prophylaxis with isoniazid is not necessary [119].

3.12.9. Triazole antifungals

The triazole antifungal class of drugs includes itraconazole and voriconazole, which are currently in clinical use. These drugs associated with an increased risk of development of peripheral neuropathy. The incidence is estimated to be approximately 10%, and the symptoms are partially or fully reversible after cessation of therapy [120]. The precise cause remains unknown.

3.13. Miscellaneous

3.13.1. Oxidative stress

The role of thiobarbituric acid reacting substances (TBARs) measure of lipid peroxides in the neural blood flow abnormalities associated with diabetes and its metabolic changes in peripheral neuropathy was studied in 2005 by Migdalis et al. In this work 77 patients with type II diabetes (39 neuropathic and 38 non-neuropathic) and 38 control patients were studied. The neuropathic study group had significantly lower levels of TBARs, 3.5 $\mu\text{mol/L}$ (2.2–5.6, $p < 0.05$) compared to controls, 4.5 $\mu\text{mol/L}$ (3.08–8.05, $p < 0.001$) and to diabetics without neuropathy 4.9 $\mu\text{mol/L}$ (3.09–8.05, $p < 0.001$). In the neuropathy group there was a negative correlation between the score for nerve dysfunction with TBARs level, $r = -0.42$, $p < 0.01$.

This finding was counter intuitive since lipid peroxide levels or TBARs are typically thought to be elevated in disease states such as atherosclerosis and diabetes (Yagi, 1998). The implications of this study are unclear with the authors asserting that TBAR levels in patients with diabetic neuropathy are “abnormal” but do not offer an explanation of the negative correlation between the score for nerve function with the TBAR levels.

We submit that further studies need to be undertaken in order to clarify this relationship. Based on contemporary works in murine models a most reasonable sequel to this study

would be follow-up examinations of TBARS and anti-oxidant therapies in these same *in vivo* diabetic neuropathy preparations [121].

The oxidative stress and pro-inflammatory processes which contribute to vascular complications including endothelial dysfunction and peripheral neuropathy in diabetes mellitus was examined in a 2006 study by Nangle et al. [21] In this work the group administered eugenol – which is known to have antioxidant and anti-inflammatory properties especially in the inhibition of lipid peroxidation [122] – to streptozotocin induced diabetic rats. The group analyzed endoneurial blood flow reduction; gastric fundus maximum nitrenergic nerve-mediated relaxation reduction; and maximum endothelium-dependent relaxation reduction in renal artery rings all in diabetic animals. Eugenol significantly improved or completely reversed each of these reductions but did not affect diabetes-increased sensitivity to phenylephrine-mediated contraction. Nevertheless the study demonstrated that both vascular as well as neural complications of experimental diabetes are improved by the antioxidant/anti-inflammatory agent eugenol and reinforces the argument for the role of pressure-flow perfusion dependence on the development of oxidative stress-related peripheral neuropathy.

3.13.2. *Eosinophilic granulomatosis with polyangiitis (EGPA)*

In 2015 Boubabdalloui et al. discussed a case report of eosinophilic granulomatosis with polyangiitis (EGPA) and described a peripheral vasculitis in a 21 year old man who presented with an associated peripheral neuropathy [123].

3.13.3. *Nitric oxide*

Some studies have suggested a key role of nitric oxide in development of injuries resulting from malfunction of the microvasculature as a result of neuropathic peripheral nerves. These neuropathies may be age- or disease- related. In a 2002 article Minson et al., examined thermally induced cutaneous vasodilation capacity (% CVC max; 28 mM nitroprusside infusion) in response to the nitric oxide inhibitor NG-nitro-L-arginine methyl ester (L-NAME) which was infused throughout the protocol [124]. The study compared 2 groups using microdialysis fibers placed in the forearm skin of 10 young subjects (age 22 ± 2 years) and 10 older subjects (77 ± 5 years) with skin blood flow subsequently measured by laser-Doppler flowmeters. The protocol entailed the heating of both sites to 42°C for approximately 60 minutes with data expressed as a percentage of maximal vasodilation. The work revealed that local heating before L-NAME infusion resulted in a significantly reduced initial peak, $61 \pm 2\%$ CVC max, in younger subjects vs. $46 \pm 4\%$ CVC max in older subjects; and a reduced plateau CVC in younger subjects ($93 \pm 2\%$ CVC max) as well as in older subjects ($82 \pm 5\%$ CVC max). When the nitric oxide synthetase (NOS) inhibitor was infused following 40 minutes of heating CVC declined to the same value in the young and older adults. They concluded from the work that the overall contribution of nitric oxide to the plateau phase of the SkBF response to local heating was less in the older subjects. Further they concluded that age-related changes in both axon reflex-mediated and NO mediated vasodilation contributed to attenuated cutaneous vasodilator responses in the elderly [124]. In 2010, Fromy et al. focused upon mechanosensitivity and vasodilation or pressure-induced vasodilation (PIV) or the dilation of the cutaneous microvasculature when a non-nociceptive external pressure is locally applied to

the skin [125]. PIV is mediated by mechanical stimuli (pressure) applied to sensory C-fibers which subsequently release neurotransmitters that cause the release of endothelial factors which cause smooth muscle relaxation of the cutaneous microvessels. This response has been documented in both murine as well as in human models. Based on earlier studies in which this group demonstrated that PIV is altered in the skin of old mice without neuropathy, the group then hypothesized that older humans would have reduced PIV as well. Their study examined two age groups: older subjects (60–75 years) and younger subjects (20–35 years). They determined that there were statistically significant changes in percentage vasodilation in response to local pressure application among all (young, non-neuropathic older, and neuropathic older) groups (**Figure 5**).

The group states that there is altered physiological ability to protect the skin against localized in 60–75 year old subjects and that older subjects who present with a severe sensory deficit, i.e., neuropathy are particularly at risk for pressure ulcer occurrence because of a loss of local PIV [125]. One important aspect of this work is that it implies a role of nitric oxide both from this group's previous murine model work and implications from related thermosensitivity studies by Minson et al... [124] Another important aspect is the possibility that nitric oxide may play a role in pressure-induced vasodilation. Indeed some low-threshold mechanoreceptors as well as some thermoreceptors fall into the class of unmyelinated C-fibers which release the aforementioned neurotransmitters that initiate the cascade which may result in the expression of nitric oxides and the resultant microvasodilation.

3.13.4. Environmental toxins

Other toxicities have been described as causing neuropathy. In a 1999 report, Fung et al., described the development of severe neuropathy in a 57-year-old man who developed signs and symptoms of peripheral following a 2-day exposure to styrene. During this time the patient had been applying the styrene this time applying the styrene which was contained in a fiberglass resin to the

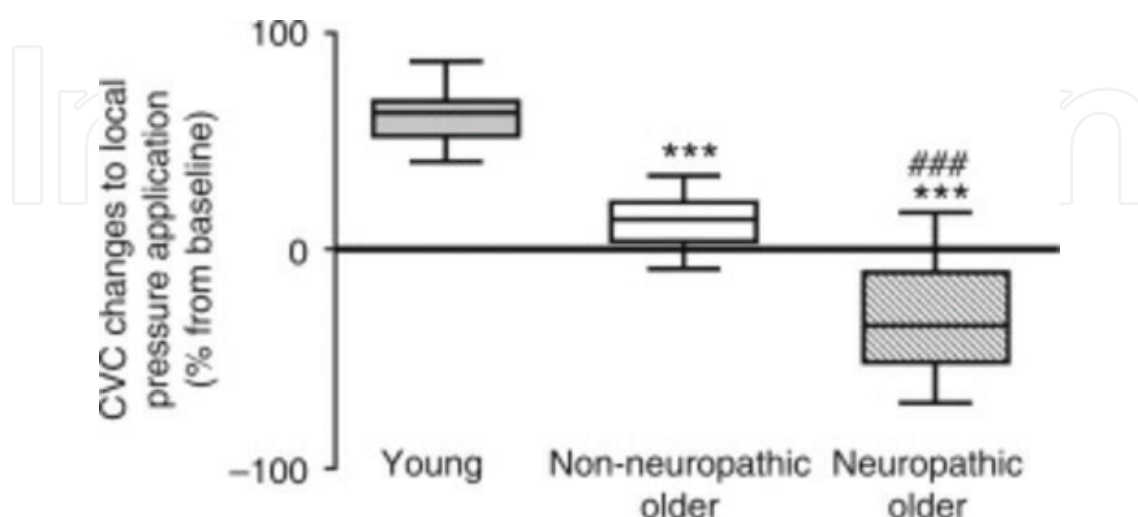


Figure 5. Percentage of vasodilation in response to local pressure application (4.2 kPa) in young ($n = 12$), non-neuropathic older ($n = 12$), and neuropathic older ($n = 10$) subjects. Statistically significant changes relative to young subjects ($***p < 0.001$) and non-neuropathic older subjects ($###p < 0.001$) CVC is cutaneous vascular conductance. The line drawn across the box is the median. The lower and upper edges of the box are drawn at the first and third quartiles, respectively. The whiskers represent the maximal and minimal value (adapted from Fromy et al. [125]).

inside of the septic tank. The neuropathy was documented by signs and symptoms consistent with a neuropathic process which was later confirmed by nerve conduction studies [126].

Abnormalities of peripheral nerves have also been observed as a result of exposure to the highly toxic industrial cleaner and insecticide, carbon disulfide. In a 2004 work, Huang et al. examined the effects of CS on the central and peripheral nervous system 3 years following cessation of exposure. They found that abnormalities of the PNS persisted and included clinical symptoms and electrophysiological findings. They also determined that central nervous system changes occurred and persisted with brain magnetic resonance images showing changes in the basal ganglia and the subcortical white matter that were suggestive of vascular events, particularly in the small vessel. The group also noted in one patient diffuse cerebral hemispheric demyelination. In their conclusion they stated that the cardiovascular system involvement may be due to thrombotic effects as opposed to atherogenic effects [127]. This raises the question of the genesis of the demyelination seen in the central nervous system. Was this the result of microangiopathy, and if so was there a similar genesis in the peripheral nerves with demyelinating changes there as well? No microscopic exams of the peripheral nerves were reported at that time, which leaves perfusion dependence of the development of peripheral neuropathy subject to speculation which necessitates further study.

4. Conclusion

The causes of peripheral neuropathy are many as we have encountered in the preparation of this chapter. Perhaps the most pronounced theme occurred at the molecular level where it appeared that oxidative stress and angiogenesis played possibly the most prominent roles in the development of perfusion dependent peripheral neuropathy. It is at this level that we believe extensive research must be performed both at the bench as well as at the bedside in order to find possible correlation with any basic science breakthroughs. It is certainly apparent to our group that interventions specifically at those points, i.e., control of the production and removal of free radicals as well as the manipulation of differential angiogenesis are essential. Completion of the latter task can only be described as daunting since many disease processes including several malignancies are promoted by angiogenesis. To differentially promote neuroprotective angiogenesis while inhibiting pathogenic angiogenesis and controlling concomitant beneficial perfusion pressures may lead to optimal results as we seek to alleviate suffering from peripheral neuropathy.

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