*Send Orders for Reprints to reprints@benthamscience.net*

*Current Diabetes Reviews,* XXXX, *XX,* 000-000 

**REVIEW ARTICLE**

# Adaptive Autonomic and Neuroplastic Control in Diabetic Neuropathy: A Narrative Review

Francesca Marsili[1], Paul Potgieter[1] and Corlius Fourie Birkill[1,*]

[1]*Research Department, Algiamed Technologies, Burnaby, Canada*

**ARTICLE HISTORY**

Received: April 14, 2023
Revised: August 31, 2023
Accepted: September 28, 2023

*DOI:*
*10.2174/0115733998253213231031050044*

**Abstract:** ***Background*:** Type 2 diabetes mellitus (T2DM) is a worldwide socioeconomic burden, and is accompanied by a variety of metabolic disorders, as well as nerve dysfunction referred to as diabetic neuropathy (DN). Despite a tremendous body of research, the pathogenesis of DN remains largely elusive. Currently, two schools of thought exist regarding the pathogenesis of diabetic neuropathy: a) mitochondrial-induced toxicity, and b) microvascular damage. Both mechanisms signify DN as an intractable disease and, as a consequence, therapeutic approaches treat symptoms with limited efficacy and risk of side effects.

***Objective*:** Here, we propose that the human body exclusively employs mechanisms of adaptation to protect itself during an adverse event. For this purpose, two control systems are defined, namely the autonomic and the neural control systems. The autonomic control system responds *via* inflammatory and immune responses, while the neural control system regulates neural signaling, *via* plastic adaptation. Both systems are proposed to regulate a network of temporal and causative connections which unravel the complex nature of diabetic complications.

***Results*:** A significant result of this approach infers that both systems make DN reversible, thus opening the door to novel therapeutic applications.

**Keywords:** Diabetes, diabetic neuropathy, adaptive control systems, autonomic control system, neural control system, Type 2 diabetes mellitus.

## 1. INTRODUCTION

Type-2 diabetes mellitus (T2DM) is a systemic disorder characterized by the combination of resistance to and inadequate secretion of insulin, and by an impaired regulation of blood glucose levels [1, 2]. T2DM is a worldwide burden to many individuals as well as to socio-economic and healthcare systems, affecting around 7% of the global population with a major impact on developed regions, such as USA, Mexico, and Western Europe [1]. In a similar manner, Western Pacific areas, including China, Indonesia, and Malaysia, constitute over a third (38%) of the total number of adults with diabetes worldwide and its prevalence is estimated to rise from 11.9% (2021) to 27% by 2045 [2]. Both the prevalence and incidence of T2DM are fast growing in the aging population, with peaks at 55-59 years old, and in individuals with obesity, dyslipidaemia, smoking habits, sedentary lifestyles, and low-grade inflammation [3]. The maladaptive progression from *normal* (fasting blood glucose level: 80-100 mg/dl) glycaemic control due to acute glucose spikes is followed by a *pre-diabetes* phase (fasting: 101-125 mg/dl) where individuals are considered highly at risk of developing diabetes due to a combination of existing factors including weight gain, age, rate of insulin response. Finally, *diabetes* will be established at fasting blood glucose level above 126 mg/dl [4]. The long-established view on diabetes associates T2DM with a wide variety of complications ranging from metabolic to hemodynamic disorders, followed by the onset of microvascular injuries (*e.g.*, retinopathy and nephropathy), and chronic neural damage/maladaptation, more commonly referred to as neuropathy [5]. Diabetic neuropathy, or diabetic peripheral neuropathy (DPN), is a disorder caused by environmental and/or genetic factors affecting 40-50% of individuals with T2DM [6]. DPN initially manifests as a sensory nerve dysfunction characterized by a distal-to-proximal, also known as a 'stocking-glove'-like, distribution and is commonly accompanied by symptoms including pain and loss of sensation [7].

Discrepancies in the literature and the limited efficacy of therapeutic solutions suggest that the pathogenesis and chronification of DPN are, to this day, largely elusive. This area of research remains pertinent due to the significant impact on the quality of life for individuals affected by DPN [8]. One of the biggest challenges when conducting research regarding complex biological systems is avoiding correlation bias. Researching DPN is no exception, especially when the temporal characteristics of its pathogenesis are investigated.

*Address correspondence to this author at the Research Department, Algiamed Technologies, Burnaby, Canada; Tel: +1 (778) 956-6540;
E-mail: corlius@algiamed.com

1573-3998/XX $65.00+.00 

Standard practice in DPN research is to depict neuropathy as a microvascular complication, based on the evidence of compromised vasculature in patients with T2DM. However, a sufficient body of research confirms that a cardiovascular condition does not necessarily precede a neural impairment, suggesting that the two events might coexist without dictating causation [7]. Following the vasculature hypothesis, the second most common cause of diabetic neuropathy is hypothesized as being related to mitochondrial-induced toxicity causing axonal programmed death, also known as axonal apoptosis [9]. This present view implies the body's inability to protect itself from harmful events and, as a result, rather contribute to its own demise. The current understanding of diabetic-related dysfunctions involves the synergistic activation of several mechanisms viewed together as a unified response to the pathogenic assault.

Contrary to the hypothesis mentioned above, our argument is based on the premise that the body innately responds by maintaining homeostasis in a way that allows it to protect itself. This proposition supports the notion that systems subsist uniquely to benefit the overall organism, and not to self-destruct, even in the presence of a toxic assault. Our review of the literature leads us to propose there are two separate control systems (*i.e.*, the autonomic and neural control systems) that respond to the pathogenesis of diabetes, creating symptoms *via* concomitant adaptative responses. These autonomic and neural responses follow distinct pathways that may occur synchronously but may also not be temporally aligned.

In this paper, diabetes is presented as a disease with a distinct chronological progression: from (a) acute glucose spikes, then to (b) a pre-diabetes phase and ultimately degenerating into (c) diabetes. Throughout these phases, the autonomic and neural control systems respond *via* two separate modes of action. The autonomic control system adjusts the inflammatory and immune responses leading to micro- and macrovascular complications, while the neural system controls the behaviour of neural signalling, both at peripheral and central levels. Despite using separate biological cascades, the autonomic control system does play, at times, a role in reinforcing the maladaptation of the neural control system.

In section 2, the paper describes the chronological progression of the autonomic control system where diabetic complications ensue through immune and inflammatory responses with systemic degenerative consequences (*e.g.*, infections of respiratory system and vascular damage). Section 3 discusses the maladaptive cascades regulated by the neural control system which lead to the occurrence of diabetic neuropathy (section 3.3).

## 2. AUTONOMIC CONTROL SYSTEM

### 2.1. Phase I – Acute Glucose Spikes (Normoglycemic)

Acute glucose spikes in healthy individuals are usually resolved through insulin secretion without clinical consequences [10]. Glucose levels are generally regulated by means of increased glycogen storage in the liver and muscle tissue, along with a controlled fat resolution [11]. The excessive presence of systemic glucose is known to cause activation of exacerbated responses during which systemic hyperinsulinemia ensues and generates an efflux of calcium ions from vascular muscle cells [12].

Calcium is a fundamental constituent in the maintenance of vascular contractile ability and insulin-mediated loss of intracellular $Ca^{2+}$ is generally associated with vasodilation in peripheral blood flow [13]. Both hyperinsulinemia and vasodilation lead to a significant increase in circulatory blood volume, expression of a sympathetic activation, which supports our proposed hypothesis on the role that the autonomic control system plays in reducing glucose spikes in the bloodstream [14]. Unresolved glucose imbalance and sympathetic-mediated vasodilation create a feedforward mechanism through a persistent systemic circulation of hyperglycaemia and hyperinsulinemia which ultimately progresses into an early diabetic phase [15].

Along with hyperinsulinemia, the body further reacts to acute blood glucose spikes by producing advanced glycation end-products (AGEs): Products of failed glycolysis, which bind to their receptors (RAGE) on cell surfaces. The coupling AGE/RAGE is known to generate a cascade of pro-inflammatory responses *via* the NF-κB pathway [16], leading to further implications involving the autonomic nervous system in handling the acute-phase of early diabetic assaults.

### 2.2. Phase II – Pre-diabetes

Should the hyperglycaemia persist, hyperinsulinemia evolves into insulin resistance and leads to vascular damage and platelet hyperreactivity, both events linked with prothrombotic insults [17]. The inability of vascular cells to respond to insulin is a common condition preceding the development of diabetes and is significantly correlated with impaired vascular dilatation and with the secretion of vasoconstriction molecules (*i.e.*, endothelin-1) leading to persistent vasoconstriction and, thus, vascular paralysis [18]. In support of our view, vasodilation is rapidly replaced by vasoconstriction through the activation of protective control systems, causing further vasculature disruption [19].

Further evidence of vascular damage is linked to the molecular compound, advanced glycation end products (AGEs), and their respective receptor (RAGE) [16]. The AGE/RAGE coupling in diabetes is a consequence of failed glucose resolution in hyperglycaemia, as mentioned above, and is known to contribute to a gene regulatory network exacerbating inflammatory responses in cardiovascular disease, retinopathy, and nephropathy. As suggested by our current model, the AGE/RAGE compound, together with other sympathetic responses, has no reported effects on the occurrence of diabetic neuropathy [20].

Persistent inflammatory processes generate a cascade of parasympathetic activation releasing immune responses (*i.e.*, increased levels of mast cells and macrophages) and anti-inflammatory responses *via* expression of cytokines and chemokines [21]. One cytokine in particular, interleukin-6 (*i.e.*, IL-6), was first described as an anti-inflammatory mediator during infections and is now thought to be involved in the inflammatory responses present in diabetes [22]. IL-6 is characterized by a bivalent behaviour with either anti-inflammatory or pro-inflammatory action, namely *via* classic or trans-signalling processes, respectively (Fig. **1**). In the pre-diabetes phase, IL-6 *classic signalling* (*i.e.*, anti-

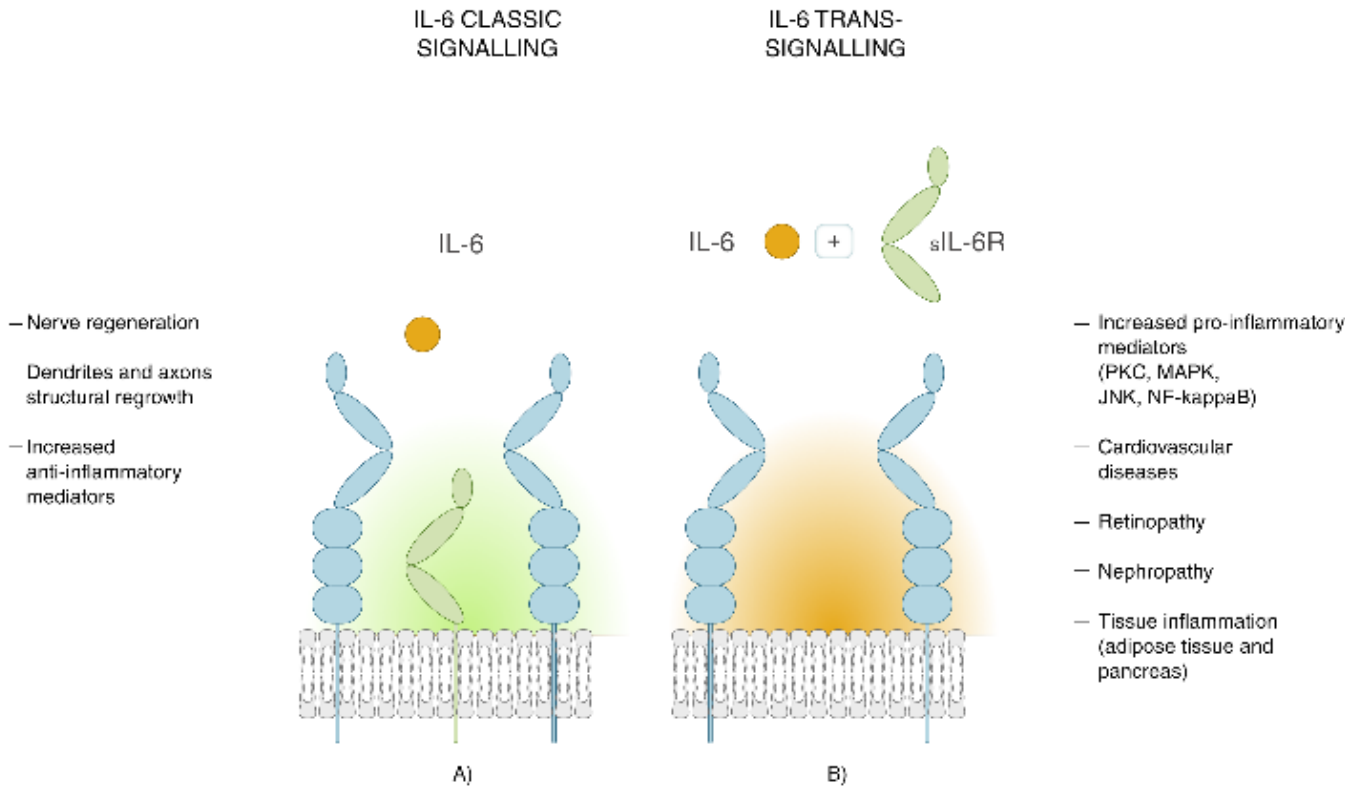


**Fig. (1).** Bivalent behaviour of Interleukin-6 (IL-6) in the human body. (**A)** IL-6 *classic-signaling* action has an anti-inflammatory role, protecting organs and tissue from inflammation and other trauma. In the peripheral nervous system, IL-6 *classic signaling* promotes dendrites and axonal structural regrowth. (**B)** IL-6 *trans-signaling* acts through an excessive amount of plasma IL-6 levels and soluble forms of IL-6 receptors. IL-6 *trans-signaling* action has pro-inflammatory effects on tissue and organs and is involved in the progression of diabetic-related complications such as retinopathy and nephropathy. **Adapted from** "The role of IL-6 in host defence against infections: Immunobiology and clinical implications" by S. Rose-John, K. Winthrop and L. Calabrese, 2017, *Nature Reviews Rheumatology, 13: p.399-409*. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

inflammatory action) produces chemokines which prevent inflammation by sending out warning signals to various types of tissue, such as the liver, kidneys, and skeletal muscles, and triggering an adaptive cascade to prevent tissue damage [23]. Further studies have established a physiological involvement of IL-6 in peripheral nerve cells, where it seems to be involved in enhancing regenerative processes after local insults or inflammation [24]. Contrary to previous views, we propose here that, at the level of the peripheral nervous system (PNS), IL-6 acts exclusively *via* classic signalling and helps regenerating nerves following trauma by clearing axons and myelin from debris. This is the first overlap between the proposed autonomic- and neural control systems (Fig. **1A**) [25].

### 2.3. Phase III – Diabetes

Established view on diabetes suggests the coexistence of adaptive and maladaptive inflammatory and immune responses with a stochastic effect on diabetic complications. Instead, we contend that the adaptive cascades of the parasympathetic system, in place during pre-diabetic phases, rapidly exacerbate into maladapted inflammation, causing a sustained production of acute-phase proteins, haptoglobins, cytokines and chemokines which is no longer counterbalanced by defensive mechanisms [26]. Parasympathetic responses soon become maladapted and release metabolic stressors (*i.e.*, cytokines and chemokines) and immune cells (*i.e.*, mast cells and macrophages). At this stage, diabetes starts manifesting as a metabolic disorder through pro-inflammatory responses with permanent systemic repercussions such as end organ damage [27].

An excessive amount of circulating cytokines is often evidence of a chronic low-grade inflammatory state, involved in the promotion of cell apoptosis and in the case of diabetes, impaired insulin degradation, tissue inflammation, and demyelinating neurodegenerative diseases, such as aging, Alzheimer's and Parkinson's diseases [28, 29].

During this phase, IL-6 is involved in the exacerbation of diabetic pathologies [30]. Similar to other chronic inflammatory diseases, maladapted processes *via* soluble forms of the IL-6 receptors (*i.e.*, sIL-6R) trigger IL-6 *trans-signalling* (*i.e.*, pro-inflammatory action), a known mechanism for the pathogenesis of pro-inflammatory cascades leading to positive feed-forwarding loops and amplified inflammatory effects (Fig. **1B**) [31]. When sIL-6R exceeds the levels of IL-6, the trans-signalling action prevails, and pro-inflammatory cascades dominate. Evidence from Zhou *et al*. (2014) and Jin *et al*. (2017) shows sIL-6R as an independent predictor of diabetes: in these patients, sIL-6R plasma levels escalate through the action of adipocytes and macrophages from adipose tissue and corroborate the presence of a chronic inflammatory state causing systemic pathology. It should be

noted that, in these papers, IL-6, IL-1, and TNF-α are not directly involved in the occurrence of peripheral neuropathy but rather contribute to the exacerbation of neuropathic symptoms by exerting chronic inflammatory pathological processes, a corroboration to our proposed model [30]. Strong evidence suggests that a correlation exists between comorbidities present in diabetic patients and cytokine IL-6 overexpression: For example, elevated plasma levels of IL-6 is associated with increased risk of atherosclerosis, as well as pancreatic and adipose tissue-derived inflammation in diabetes [32, 33].

The systemic action of sIL-6R occurs by binding with surface gp130, a transmembrane protein enhancing cytokine action via signal transducing [34]. The ubiquitous presence of gp130 to various cell types increases the number of potential inflammatory targets in the body of a diabetic individual [35]. For example, the binding of sIL-6R and gp130 on endothelial cells and vascular smooth muscle cells has deleterious effects leading to atherosclerosis and macrovascular complications (*i.e.*, vascular calcification, microvascular complications) [36]. Increased levels of sIL-6 serum, along with IL-1, TGF-β, and TNF-α, can be detected in diabetic patients and affect the kidneys *via* trans-signalling pathways. Nephropathy is a renal failure strongly correlated to chronic inflammation and a prevalent manifestation in diabetic individuals: Diabetes in the kidney is known to trigger an overproduction of sIL-6 and an overexpression of binding molecule gp130, which further amplifies gp130-sIL-6 production in a positive feed-forward, pro-inflammatory loop [31]. This augmented IL-6 level in the kidneys has further effects on TGF-β signalling, a key cytokine involved in the progressive damage of renal function by affecting the glomerular endothelial barrier [37]. These inflammatory molecules cause an overall elevation in blood pressure, leading to not only a glomerular impairment at the kidney level, but also to retinal pathology in the eyes [38]. Despite the protective action exerted on the peripheral nervous system in the pre-diabetes phase, increased levels of IL-6 and macrophages in the brain are associated with trans-signalling actions. This maladaptive response is in support of our proposed model where diabetic patients display a reduction in axonal sprouting and an anti-regenerative environment, which in turn progress to neurodegenerative diseases [39, 40].

The coexistence of both positive and negative immunomodulatory responses is a distinctive characteristic of the human immune system. As a demonstration of this bivalent nature, the immune response in diabetes is also characterized by the ability to prevent atherosclerotic attacks, supporting evidence to our proposed model where protective mechanisms act to preserve the body and maintain homeostasis [41,42]. Evidence demonstrates that the body responds to compromised vasculature by elevating systemic levels of vascular endothelial growth factor (VEGF), an immune-regulated angiogenic molecule, indicating the existence of a defence mechanism which promotes neo-vascularization as an attempt to arrest the atherosclerotic assault [43]. In our model, we propose that the immunomodulatory regulation is mediated by an innate, inflammatory reflex circuit present in the body and mediated by the activity of the vagus nerve. In the presence of short-term tissue injury or acute inflammation, the vagus nerve has the ability to balance out pro-inflammatory and anti-inflammatory circuits and its efferent arc, also known as the cholinergic anti-inflammatory pathway (*i.e.*, CAP), seems to play the role of protecting organs from damage in case of an excessive cytokine release (Fig. **2**).

According to our view, the CAP balance between anti-inflammatory and pro-inflammatory cytokines is disrupted in most diabetic individuals, leading to a persistent inflammatory cascade, culminating in morbidity and mortality [44]. As confirmed by standard models, diabetes is, among other definitions, an inflammatory disease with the secretion of pro-inflammatory cytokines and decreased anti-inflammatory mediators [45]: This feed-forward mechanism is further corroborated by the activation of signalling pathways, such as PKC, MAPK, JNK, and NF-κB, that reinforce post-transcriptional cytokine and chemokine expression [46-48]. Diabetes induces an immunocompromised state which represents a risk factor for a wide range of inflammatory diseases of the respiratory, urinary, and gastrointestinal systems [49]. This was demonstrated during the recent SARS-CoV-2 pandemic, where chronic inflammatory states in diabetic individuals reinforce the cytokine storm generated by the COVID-19 virus in a feedforwarding inflammatory loop which leads to increased risk of severe illness, respiratory complications, or death [50].

As previously mentioned, DPN is accompanied by early signs of sensory impairments. Some diabetic individuals are prone to develop, alongside DPN, chronic inflammatory demyelinating polyneuropathy (CIDP): An inflammatory-induced disease which affects the myelin sheath around motor nerves and thus impairs their conduction velocity. The exact correlation between diabetes and CIDP is still unknown, but diabetes seems to contribute as a risk factor in CIDP occurrence with 9-fold higher prevalence in diabetic individuals compared to healthy subjects [51]. According to our hypothesis, the bivalent nature of the autonomic control system has adaptive characteristics which either regulate or deregulate inflammatory and immune responses in diabetes. The occurrence of CIDP in diabetic individuals should be seen as a direct consequence of an overregulated immune response leading to inflammatory storms. This represents the second overlap between the autonomic- and neural control systems linking inflammation to demyelination on motor nerves through the overproduction of immune-mediated macrophages: By means of phagocytosis, macrophages consume the myelin sheath around motor nerves, as demonstrated by the presence of myelin debris inside the macrophages' cytoplasm during electron microscopy investigations [52, 53]. Amplification of demyelinating processes occurs in the presence of autoimmune biomarkers which bind to oligodendrocytes on myelin sheaths, inducing their death and resulting in blood-brain barrier breakdowns. The oligodendrocyte disruption, and consequent demyelination, is a common event for most immune-mediated neurological disorders, including multiple sclerosis, encephalomyelitis, and other antibody associated disorders [54-57].

### 2.4. Therapeutic Solution for Autonomic Control System

Therapeutic solutions to diabetes-induced inflammation include administration of anti-cytokine agents which have shown contrasting results and critical adverse events such as infections, rare demyelinating disorders of CNS, as well as liver and cardiac injuries [58]. Current standard of care med-

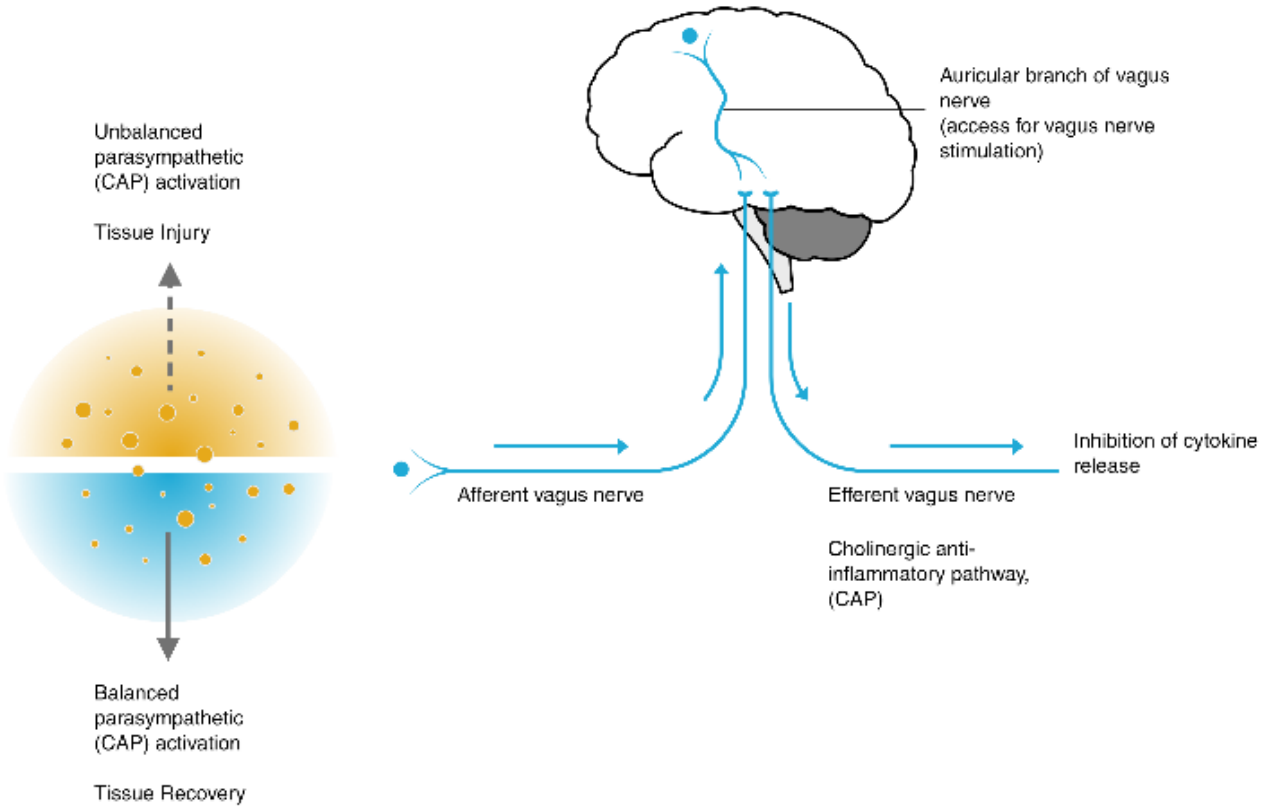


**Fig. (2).** The vagus nerve and the cholinergic anti-inflammatory pathway. In the presence of pathology, injury, or trauma, a cascade of inflammatory mediators (*i.e.*, cytokine) is activated. An unbalanced cytokine production can cause long-term organ and/or tissue disruptions. The efferent arc of the vagus nerve, also known as the cholinergic anti-inflammatory pathway, inhibits cytokine production for an anti-inflammatory effect. **Adapted from:** "Physiology and immunology of the cholinergic anti-inflammatory pathway" by K. J. Tracey, 2007, *The Journal of Clinical Investigation, 117(2): p.289-296. c*. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ication, which focuses on suppressing the inflammatory part of the neuropathy, has shown limited efficacy [59]. This paper focuses on exploring vagus nerve (VN) control to facilitate the regulation of the diabetic-induced chronic cytokine storm causing a long-term hyperinflammatory state followed by impaired immunity [60]. VN is the cranial nerve in charge of triggering inflammatory reflexes and regulating cytokine levels: Vagus Nerve Stimulation (VNS) through electrical therapies has shown the ability to deregulate chronic cytokine storms and thus inhibit inflammation [61, 62]. When CAP is stimulated with VNS, the brain activates biochemical cascades which oppose the occurring inflammation and deregulate the IL-6 storm (Fig. **2**) [63]. A novel therapeutic approach may involve regulating the vagus nerve *via* electromagnetic stimulation in order to mediate the CAP and, hence, contain the inflammation. Several studies have demonstrated the efficacy of VNS to reduce cytokine production in inflammatory syndromes such as rheumatoid arthritis, respiratory complications from COVID-19, sepsis, and other related conditions [64-68]. The use of VNS might represent an interesting solution for the treatment of diabetes-induced autonomic inflammation and for prevention of cardiovascular disease in diabetic individuals [69]. A further consideration regarding VNS treatment is the limited, if not absent, side effects. Should the model proposed in the present paper be substantiated with further research, VNS could strongly complement current standard of care.

## 3. NEURAL CONTROL SYSTEM

Previous literature suggests that increased glucose concentrations around sensory nerves influence mitochondrial behaviour. In diabetic individuals, mitochondria ostensibly fail to respond using protecting mechanisms and instead react by generating toxic agents fatal to axons and dendrites (*i.e.*, axonal apoptosis). We alternatively propose that the responses to glucose imbalance, through neural control are considered to be adaptive and protective mechanisms.

### 3.1. Phase I – Acute Glucose Spikes (Normoglycemic)

Parallel to the autonomic control system, acute spikes of glucose generate changes to the extracellular milieu of peripheral nerves with effects on transmembrane channels: glucose binds to membranes and induces fluctuations in cellular behaviours. Among the most susceptible cells to glucose-induced ion imbalances are C-fibres: Thin, unmyelinated, polymodal fibres responding to thermal, mechanical, and chemical stimuli [70]. Contrary to motor neurons, sensory neurons and their cell bodies are exposed to systemic glucose fluctuations due to the lack of a myelin barrier and being located outside the blood-brain barrier (BBB) and blood-nerve barrier (BNB) (Fig. **3**) [71]. Sensory dysfunction in diabetes occurs prior to motor neuron involvement - it uses separate mechanisms at distinct anatomical sites - and is the

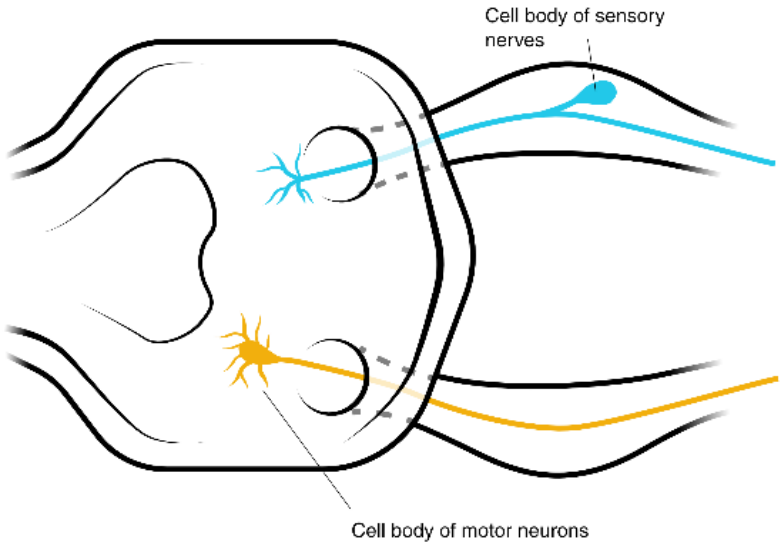


**Fig. (3).** Cell body of sensory and motor neurons. The cell body of sensory neurons is located outside the spinal cord, while the cell body of motor neurons is located on the ventral side of the spinal cord inside the grey matter. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

first clinical event of diabetic peripheral neuropathies (DPN) [72].

The lack of myelin and the systemic glucose fluctuations expose C-fibre dendrites to an ionic imbalance which impairs the functionality of transmembrane ion channels and has an influence on the depolarization threshold of the nerve. This fact is often overlooked in standard DPN models. Here, we propose it as a key mechanism triggering diabetic neuropathy and neural control. Sensory neurons react to the excess of glucose levels in the extracellular milieu by decreasing the action of potassium ($K^+$) and sodium ($Na^+$) ion channels (*i.e.*, channelopathy), known to play a role in action potential repolarization [72-75]. Glucose spikes have the consequence of closing channels, leading to longer action potentials (*i.e.*, longer width of peak) and to membrane depolarization with effects on firing frequency [76, 77].

### 3.2. Phase II – Pre-diabetes

In our proposed model, when channelopathy ensues, sensory nerves develop into a persistent hyperexcited state. As a result, biological reactive cascades trigger mechanisms of peripheral neural plasticity, such as nerve remodelling and regeneration [78]. The regeneration attempt regulated by the neural control system is further supported by the presence of IL-6, as mentioned above (see section 2.2). Here, the autonomic control system closely supports the neural control system in halting the sensory nerve maladaptation caused by glucose. To support this notion, clinical evidence of new dendrite growth in patients with diabetic neuropathy is present in the literature where morphological changes to dermal and intraepidermal small sensory fibres are reported, namely axonal swelling, increased branching and sprouting [79, 80]. Swelling, for example, is a common manifestation of newly generated epidermal nerve fibres following wounds and degenerative events and, even in diabetes and pre-diabetes, it is an early marker of nerve fiber lesions [81].

During this phase, the dendrites of sensory C-fibres undergo functional changes while proliferating at fast rates; these regeneration attempts from the neural control system are often accompanied by a sensation of burning pain [82]. This is an appropriate response when considering that one or more dendrites may be defective due to injury or other aetiologies: new healthy dendrites would generally increase the overall activation threshold of surrounding areas through spatial summation which should have inhibitory effects on the hyperexcited signals [83, 84]. This neuroplastic response, also known as synaptic scaling, can be found in existing literature as a common adaptive mechanism of the neural system [85]. In diabetic individuals, this adaptive compensation through newly formed dendrites seems to be quickly replaced by a persistent ionic imbalance, leading to a feedforward loop of amplified neural signalling and consequent hyperexcitability (Fig. **4**).

Standard physiological testing for sensory neural dysfunction is subjective, thus making early diagnosis of sensory hyperexcitability challenging [72, 86]. By the time objective symptoms can be observed, dendrites and axons exhibit functional and structural modifications and regrowth is obstructed [87]. DPN often manifests as increased axonal conductivity and neurotransmitter release, along with disruption of sensory afferent nerves already at early stages of the diagnosis.

### 3.3. Phase III – Diabetes

This paper contends that chronic neuropathy may not be caused by mitochondrial toxicity, but it is rather a reversible process, a consequence of maladapted spinal and supraspinal neuroplasticity, and triggered by prolonged peripheral sensory hyperexcitability; a novel concept to the best of found knowledge.

In healthy individuals, local insults to peripheral sensory neurons trigger central mechanisms of readaptation leading to elimination of redundant neural connections and regrowth

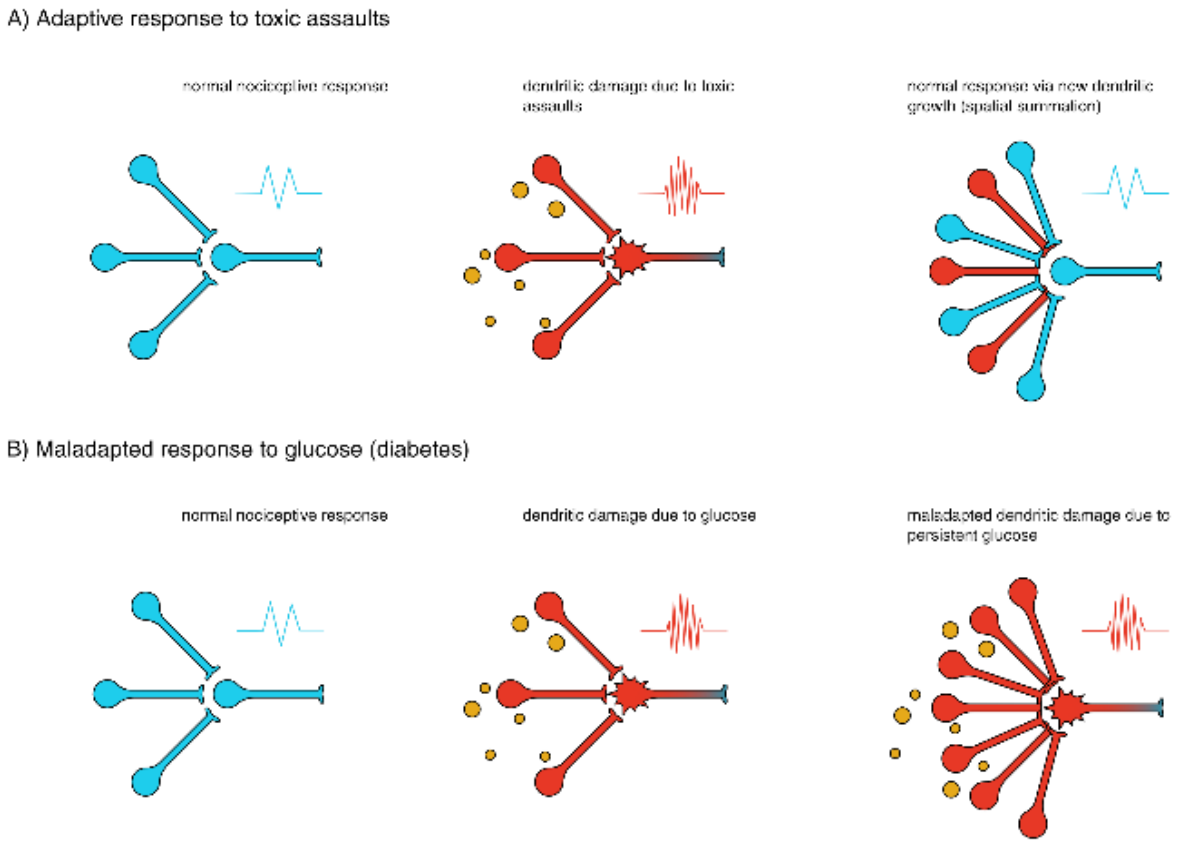


**Fig. (4).** Neuroplastic response of peripheral sensory nerves to assaults. (**A**) Adaptive neuroplastic response to short-term toxic assaults or injury. When peripheral sensory nerves are exposed to toxic assaults or trauma, they undergo dendritic damage causing hyperexcitability and thus prolonged nociception transmission. Generation of new, healthy dendrites is a common adaptive response which helps lowering the overall synaptic transmission. (**B**) Prolonged exposure to glucose, as seen in diabetic individuals, cause the adaptive regenerative attempts to become maladapted in a long-term hyperexcited state. Glucose damage to sensory nerves impede new dendritic and axonal regrowth to be an effective neuroplastic mechanism. **Adapted from:** "The self-tuning neuron: synaptic scaling of excitatory synapses" by G. G. Turrigiano, 2008, *Cell, 135(3): p.422-435*. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

of new, more relevant neural circuits [88, 89]. This selective response is a common adaptive event in many biological processes, and it occurs without causing the death of the parent neurons, also referred to as apoptosis [90]. In the brain, synaptic pruning is most often not a degenerative process, but it is rather an essential step to the formation of complex cortical networks that play a crucial role in consciousness, learning, and in cortical refinement for the creation of long-term memory [88]. In rare instances, cortical maladaptation, also known as synaptic degeneration, occurs and is thought to play a crucial role in the pathogenesis of complex behavioural, psychiatric, and cognitive disturbances such as during the death of primitive neurons in multiple sclerosis [90, 91].

In diabetes, chronic hyperexcitability causes structural changes to axons and the elimination of dendrites at the periphery with simultaneous adjustments to synaptic connections in the brain. Among these processes, the pruning of dendrites in the periphery generates the inhibition of sensory pathways with significant consequences for the individuals regarding motility and sensitivity (*i.e.*, insensate foot, diabetic foot, lack of proprioception) [88]. The effects of long-lasting peripheral neural excitability on the central nervous system cause central sensitization and subsequent changes at spinal and supraspinal centres: A fundamental process of neurodegenerative diseases [92,93]. It is plausible to hypothesize that similar mechanisms are responsible for the chronification of diabetes-induced neuropathy, which leads to the interruption of peripheral neural regrowth [94]. Similar to phantom-limb syndromes, the long-term diabetic neural altered communication from the periphery to the central nervous system evolves into neural adaptations which in turn lead to the creation of somatosensory "pain memory", promoting the inhibition of descending pathways, the development of maladapted cortical networks and the detriment of healthy networks [95, 96].

Contrary to what current literature suggests, the central adaptation occurring in DPN is possibly not the primary cause of neuropathic manifestations at the periphery but is rather a consequence of a bottom-up amplifying mechanism generated by pre-existing peripheral hyperexcitability (Fig. **5**) [97,98]. To corroborate this hypothesis, existing research confirms structural reduction of cortical thickness and cortical remapping, proportional to the severity of DPN symp-

toms, which lead to altered functionality only subsequent to compromised peripheral neural excitability, especially at the primary somatosensory cortex [99,100]. Brain imaging studies have found significant changes in cortical representation (*e.g.*, primary somatosensory cortex, dorsolateral prefrontal cortex, motor cortex, thalamus, orbitofrontal cortex) which is strongly proportional to symptom chronicity in chronic low-back pain patients [101]. Such neuroplastic changes occur as well in patients with phantom-limb pain and complex regional pain syndrome, suggesting that remapping is driven by peripheral inputs and is associated with any chronic pain syndrome regardless the aetiology [102].

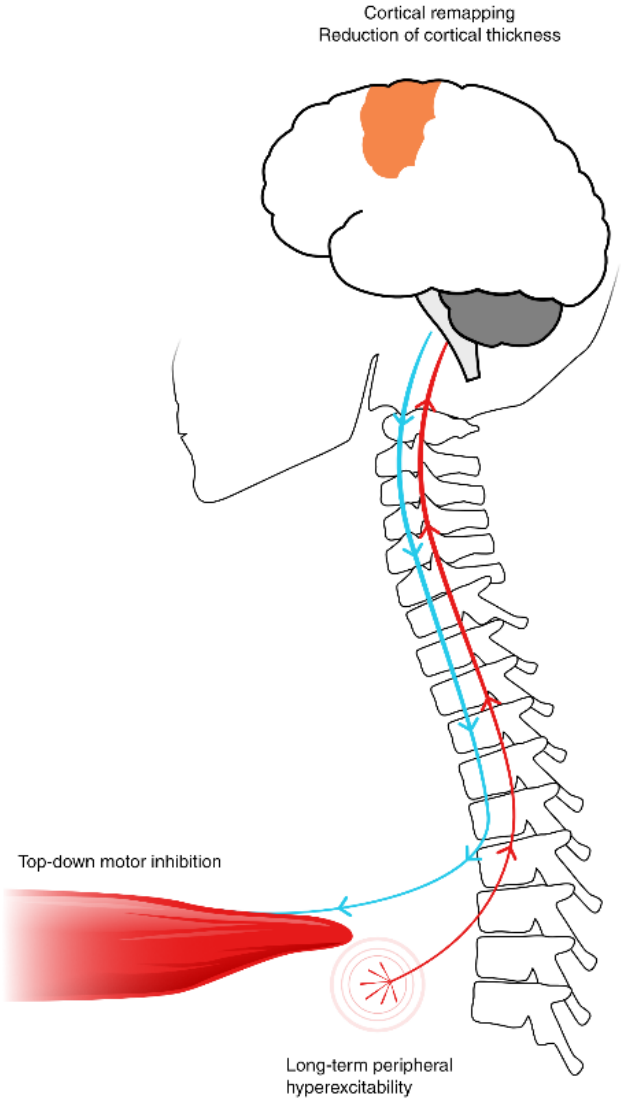


**Fig. (5).** Cortical adaptations in individual with diabetes follow a bottom-up mechanism triggered by peripheral hyperexcitability. Motor inhibition (or facilitation) is instead a top-down mechanism triggered by cortical remapping and/or reduction of cortical thickness. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In diabetic patients, there is also evidence of reduced cortical thickness within motor cortex regions which triggers long-term potentiation (LTP)-like mechanism, a process of frequent neural firing, known to induce central sensitization of motor neurons [103]. Insulin resistance seems to also play an active role in the diabetic brain, governing neuroplastic changes in the motor cortex [104]. The role of insulin resistance in cortical remapping is still unclear and requires further investigation, which is out of the scope of our paper.

Individuals with DPN suffer reorganization at the cingulate cortex, insular cortex, prefrontal lobe, and thalamus: for example, altered connections among prefrontal cortex, anterior cingulate cortex, and the medial thalamus correlate significantly with unpleasant sensations from non-noxious stimuli (*i.e.*, allodynia) in DPN [105]. When combined, these adaptive processes evolve into motor neuron dysfunction which, together with impaired sensory signalling, significantly impact on the quality of life of individuals with diabetes [7].

Remapping on motor cortex regions is generally not driven by peripheral inputs: Motor neurons are not exposed to hyperglycaemia in the same way as sensory neurons since their cell bodies are located within the ventral horn of the spinal cord, inside the BBB and BNB [71]. Nonetheless, early manifestations of motor neuron maladaptation are not uncommon, and we propose they could be expression of a demyelinating process, which is not mediated by neural control, but it is rather a consequence of immunocompromised states under autonomic control, as mentioned above (see section 2.3). In accordance with our proposed model, myelin sheath disruptions due to phagocytosis are solely a consequence of an autonomic maladapted control with no evident neural involvement [106]. Another theory formulated by Lund *et al*. (1991), known as the "pain adaptation model", suggests that a centrally-mediated limitation on biomechanics could occur early in the disease (Fig. **6**). By means of motor inhibition in and around the site of pain, this theory may explain how sensory neuropathy sometimes manifests as muscle pain, especially when unmyelinated nociceptors innervate and surround muscles [107,108].

Motor disorders in diabetes more frequently occur as a consequence of changes at the central nervous system, which explains the later onset in individuals with diabetes [109]. As mentioned above, neuroplasticity is related to remapping of cortical areas as an unsuccessful protective mechanism aimed at reducing painful inputs from sensory neuropathies [105,110]. Decreased motor strength is among one of the latest clinical manifestations of diabetes: Found exclusively on patients with failures to sensory nerves, it is considered a direct consequence of central readaptations from sensory dysfunctional processing [111,112]. The progressive sensory impairment and motor inhibition often result in muscle weakness, loss of balance, increased falling – a typical manifestation in individuals with diabetes [16].

In summary, sensory neuropathy is caused at first by peripheral and local events, while its chronicity and progression are caused by long-term spinal and supraspinal adaptation processes. This adaptation is a consequence of sensitization in the spinal cord and is triggered from the periphery by increased firing of nociceptors [113]. Overall, the neural control system presented above follows a bottom-up amplifying pathway which leads to neuropathic pain symptoms in diabetic individuals. This paper proposes that these mecha-

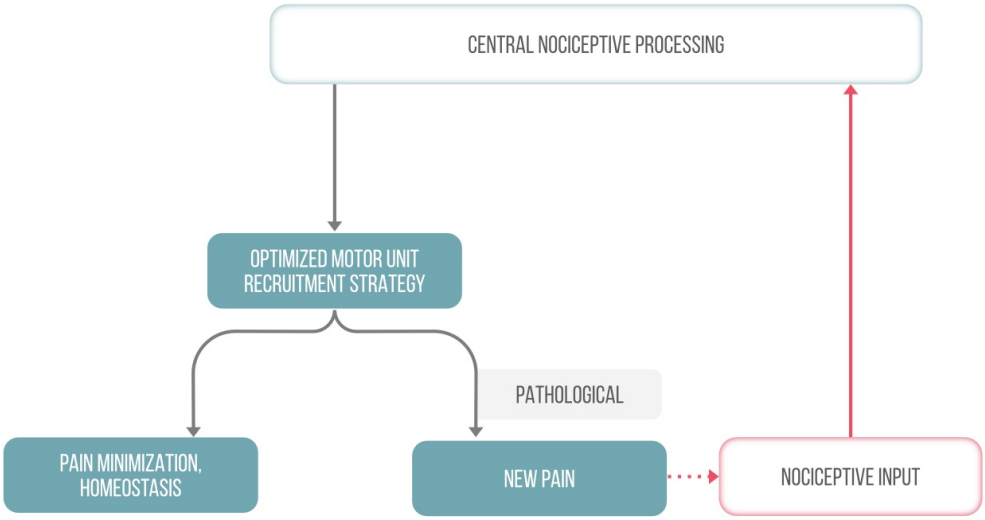


**Fig. (6).** The "pain adaptation model" by Lund *et al*. (1991). Nociceptive inputs from sensory nerves innervating areas of or around muscles can cause centrally-mediated adjustment such as motor inhibition or new motor neuron recruitment. **Adapted from:** "How does pain affect jaw muscle activity? The integrated pain adaptation model" by C.C. Peck, G.M. Murray and T.M. Gerzina, 2008, *Australian Dental Journal, 53(3): p.201-207*.

nisms are not pathogenic, but are rather neuroplastic (mal)adaptive responses, consequences to the significant ionic imbalances caused by unresolved blood glucose levels. The ability to counteract and/or prevent progression of these (mal)adaptive cascades would lead to normalised homeostasis and the ability to restore the neural control system to its normal functionality.

### 3.4. Therapeutic Solution for Neural Control System

The standard of care for treating pain caused by DPN includes pharmacologic interventions such as anticonvulsants, antidepressants, and opioids, which exhibit little pain relief or functional improvement but have many associated adverse effects [114]. Non-invasive electromagnetic therapies have been tested and investigated for the treatment of sensory and motor neuropathies [115,116]. The clinical efficacy of electromagnetic therapies in generating analgesic effects have been proven and is one reason behind the growing interest on electromagnetic therapies as a therapeutic solution for DPN. For example, two clinical trials on individuals with diabetic neuropathy (n = 80 and n = 34, respectively) have applied transcutaneous peripheral nerve stimulation using Stimpod NMS460 (Algiamed Technologies, Canada) and NMS300 (precursor to the NMS460) respectively and obtained significant reduction of DN4 and VAS pain scores, emphasizing the role that electromagnetic therapies might play in resolving neuropathic syndromes [117,118]. While the underlying mechanism of electromagnetic therapies is still under investigation, it is thought to be involved with pain modulation, nerve excitability changes, cellular energy production, cell metabolism enhancement and gene expression changes [119–121]. Should the model proposed in the present paper be substantiated with further research, electromagnetic therapies might play a crucial role in corrective readaptation of neurological pathways, and as such it may have a positive impact on patient outcomes as a therapeutic solution.

## 4. PAINFUL AND PAINLESS DIABETIC NEUROPATHY

Pain is a common feature of many diabetic neuropathies, but its prevalence and epidemiology are not yet well established [122]. The underlying mechanism of diabetic neuropathy is still unclear and predicting whether an individual will experience a painful or painless neuropathy is beyond current knowledge [123]. Up to 50% of diabetic patients will develop some sort of chronic pain condition during their life, while the larger portion will present some clinical manifestations of diabetic neuropathy at peripheral and central levels without reporting any pain [124].

Efforts have been made to define the characteristics of diabetic individuals with painful neuropathy (*e.g.*, more depression, anxiety, poor self-reported quality of life, and poor glucose control [124]) and, from a physiological point of view, pain is significantly correlated with increased neovascularization and nerve regeneration processes (*e.g.*, increased vascular endothelial growth factor (VEGF) and increased nerve growth factor [125-127]). Pain is also accompanied by a significant increase of pro-inflammatory molecules, such as IL-6 and TNF-α.

Painful and painless diabetic neuropathy share similarities at peripheral, spinal and supraspinal levels with only few discrepancies [124]. A major focus should be drawn to the absence of regeneration attempts in painless DPN, suggesting failures at both neural and autonomic levels. As mentioned above, peripheral dendrites regenerate as a consequence of sensory hyperexcitability through the mediation of the neural control system. The consequent swelling and sprouting are events known to generate painful experiences [128]. In case of painless DPN, regeneration attempts fail to

occur and therefore, also the associated pain. The lack of an inflammatory response in painless DPN is suggestive of impaired autonomic control which halts the exacerbation of symptomatology caused by metabolic stressors (*i.e.*, chemokines and cytokines) [123].

In our proposed model, the detection of hyperexcited sensory nerves and the delivery of warning signals to the central nervous system are both responsibility of the neural control system. Missing warning signals from the neural pathway delay protective efforts and thus silently accelerate disease progress without the manifestation of pain symptoms. These events suggest that pain is actually part of a functional defence mechanism – it is only experienced as a consequence of regenerative efforts from the autonomic and the neural control systems, and the lack of it may be an indication of the inability of both systems to continue adaptation. The model discussed in this paper unravels some of the ambiguities surrounding painless and painful DPN: though the discussions on these ambiguities are limited, further investigation on the matter is beyond the scope of the present paper.

## 5. SHARED FEATURES BETWEEN DPN AND OTHER NEUROPATHIES

Diabetes, despite being the most common cause of peripheral neuropathy, is not the only disease triggering neuropathic conditions. Inflammatory conditions, infections, autoimmune diseases, and chemotherapy all originate peripheral neuropathies [129]. Similar to the glucose imbalance in diabetes, other peripheral neuropathies are first triggered by the exposure of sensory nerves to external agents (*i.e.*, chemotherapic agents, medication) and/or other viral infections which, due to the lack of a myelin sheath, and of the BBB and BNB, cause systemic or local ionic imbalances and sensory hyperexcitability. In chemotherapy-induced peripheral neuropathy, antineoplastic agents on sensory nerves act in a 'glove and stocking' conformation, followed only at later stages by motor dysfunction. In addition to the sensory hyperexcitability, most agents used in chemotherapy cause neuroinflammation due to their ability to activate microglia, astrocytes and immune cells, which, in turn, increase the release of cytokines (*i.e.*, IL-6) by the autonomic control system [130]. Besides chemotherapy and diabetes, autoimmune and inflammatory diseases are common aetiologies of peripheral neuropathy. Around 40% of patients suffering HIV develop distal symmetrical polyneuropathy and a similar prevalence is observed in individuals with rheumatoid arthritis or Guillain-Barré syndromes [131,132]. These pathologies present compromised immune systems which trigger maladaptive processes at the level of the autonomic nervous system, as observed in chronic inflammatory demyelinating neuropathies [133].

A point of interest lies in observing the shared similarities between diabetes and other types of pathology which corroborate the involvement of two parallel control systems in inducing neuropathic conditions. The autonomic nervous system is characterized by an immediate response and a feed-forwarding cascade of metabolic reactions at systemic levels with disruptive consequences on several organs. In contrast, the neural control system is resilient, adaptive, and plastic. In chemotherapy-induced neuropathy, analogous to diabetic neuropathy, first manifestations of the disease occur at later stages, weeks after completion of the therapy [130]. The slow adjustment of the nervous system during pathological conditions is indicative of the inherent ability of the neural control system to respond to pathological changes by creating an adjusted and (mal)adapted homeostasis, where survival and functionality is optimized despite the unfavourable conditions.

## CONCLUSION

The clinical presentation of diabetic-related pathologies such as DPN is complex and layered and its pathogenesis remains largely elusive. Two schools of thought exist regarding the pathogenesis of DPN. The first motivates for neuronal dysfunction as being the result of a microvascular complication, similar to other associated pathologies such as retinopathy and nephropathy. The second associates neuropathy with axonal apoptosis, caused by mitochondrial ROS toxicity. Mitochondrial toxicity and microvasculature failures have ostensibly played a critical role in the chronicity of the disease, by instituting self-damaging and sabotaging mechanisms that enhance and amplify the symptomatology without possibility of recovery. For these reasons, the predominant hypothesis holds that chronic diabetic syndromes are intractable and irreversible. This is underscored by current therapeutic approaches which are mainly focused on suppression of symptoms, with limited efficacy and an increased risk of side effects. This paper proposes that the complexities introduced when considering the temporality and causality of diabetes and its complications may be described by considering the roles of two distinct control systems [autonomic, (Fig. **7**), and neural, (Fig. **8**)]. This approach offers new tools to unravel the complexity of this multi-layered condition, from the acute to the chronic phases. By introducing two separate control systems, multiple events may coexist without necessarily sharing a common mode of action, as seen in individuals with diabetes. These two control systems generate parallel, synchronous and, at times, overlapping cascades which constitute the complex, multifaceted nature of diabetes. In some individuals the response of the two control systems may be asynchronous and not temporally aligned, accounting for some enigmatic occurrences, such as painless diabetic neuropathy. The proposed model may revolutionize the way we understand and treat diabetes. While limitations do apply, this model accounts largely for anomalies making diabetic complications difficult to diagnose and even more difficult to treat. The notion that the neural control system responds through plastic changes opens up possibilities for previously minimalized therapies such as electromagnetic therapies. Electromagnetic therapies offer an innovative approach to modulate or even re-model neural control systems which could impact on:

- Maladapted autonomic responses through accessing the cholinergic anti-inflammatory pathway utilizing the vagus nerve.
- Re-modelling the characteristics of peripheral nerves
- The former leading to central re-adaptation by stimulating restoration of spinal excitability, leading to the creation of more favourable cortical networks.

Under these assumptions, diabetic complications could well be reversible.

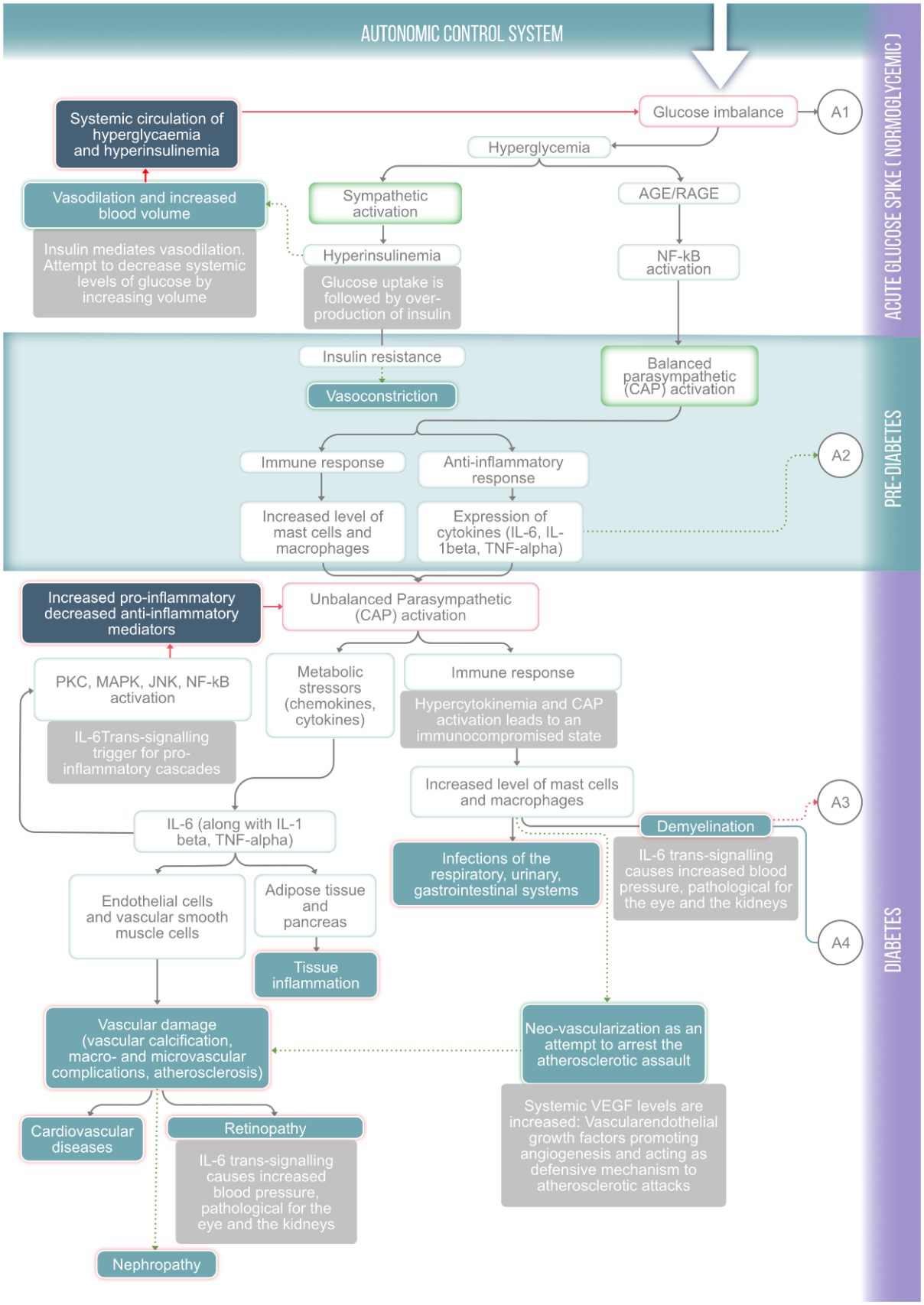


**Fig. (7).** New model explaining the mechanism underlying diabetic-induced complications. The autonomic control system regulates the adaptive and maladaptive responses *via* inflammatory and immune mediators leading to cardiovascular, renal and kidney complications. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

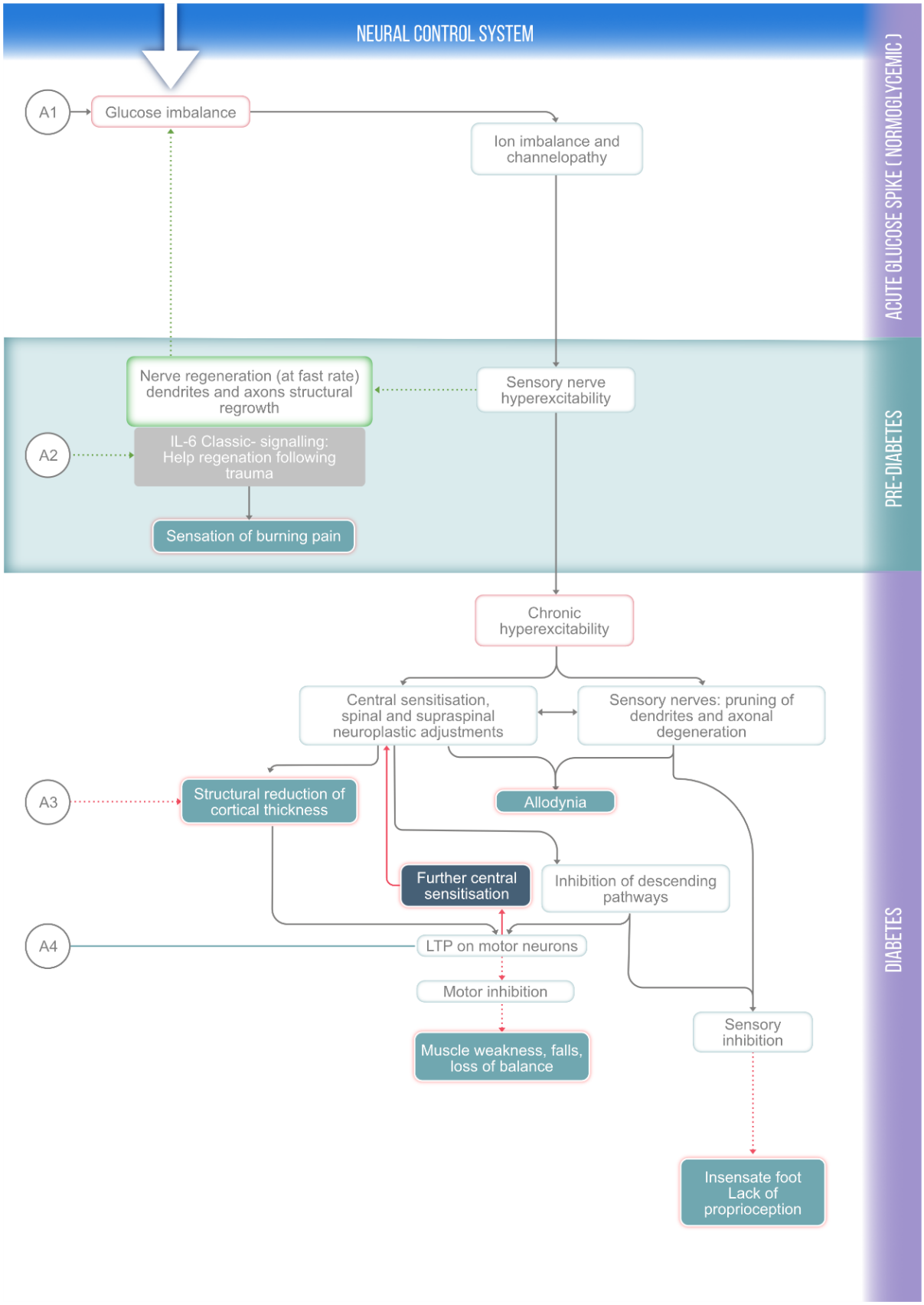


**Fig. (8)** The neural control system regulates the responses leading to diabetic neuropathy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Here, it is proposed that the structural and anatomical dysfunction of peripheral nerves may be restored through gene expression changes, while spinal excitability and supraspinal cortical reorganization can be reversed using restorative neuroplasticity mechanisms as seen in the recovery of brain injuries. Similarly, inflammatory flares could be deregulated using targeted therapeutic solutions on vagus nerve responses. Ongoing research on electromagnetic therapies seems to suggest their efficacy as a long-term therapeutic solution for the treatment of both diabetic neuropathies and inflammatory complications, through their intervention on both the autonomic and neural control systems. In conclusion, diabetes is a complex disease involving multiple interdependent mechanisms which affect peripheral and central networks as well as autonomic responses. Research has been conducted to unravel the underlying mechanisms of diabetic complications, with focus on the maladapted metabolic pathways generated by mitochondrial toxicity and microvascular dysfunction. Despite a significant body of research and clinical evidence, a knowledge gap still exists that prevents these observations from being translated into effective therapeutical solutions. Here, diabetic complications are viewed as a clinical condition that can be reversed both at autonomic, peripheral, and central levels. Electromagnetic therapies offer an innovative approach to modulate control systems in order to initiate mechanisms (a) for the modulation of adaptive autonomic responses, (b) for the regeneration of peripheral nerve fibres, (c) for the restoration of spinal excitability, and (d) for the creation of more favourable cortical networks.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| DN | = | Diabetic Neuropathy |
| T2DM | = | Type-2 Diabetes Mellitus |
| AGEs | = | Advanced Glycation End-products |
| VEGF | = | Vascular Endothelial Growth Factor |
| CIDP | = | Chronic Inflammatory Demyelinating Polyneuropathy |

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declared the following potential conflicts of interest with respect to the research authorship, and/or publication of this article: Corlius Fourie Birkill, Francesca Marsili are employed by Algiamed Technologies as part of the research and development department. Paul Potgieter has received consultancy fees from Algiamed Technology.

## ACKNOWLEDGEMENTS

The authors acknowledge all Algiamed study team members and coinvestigators.

## REFERENCES

[1] Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of type 2 diabetes-global burden of disease and forecasted trends. J Epidemiol Glob Health 2019; 10(1): 107-11. http://dx.doi.org/10.2991/jegh.k.191028.001 PMID: 32175717

[2] International Diabetes Federation. IDF Diabetes Atlas 10th ed.. 2021. Available from:https://www.diabetesatlas.org

[3] Bo A, Thomsen RW, Nielsen JS, *et al.* Early-onset type 2 diabetes: Age gradient in clinical and behavioural risk factors in 5115 persons with newly diagnosed type 2 diabetes-results from the DD2 study. Diabetes Metab Res Rev 2018; 34(3): e2968. http://dx.doi.org/10.1002/dmrr.2968 PMID: 29172021

[4] Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care 2009; 32(Suppl. 2): S151-6. http://dx.doi.org/10.2337/dc09-S301 PMID: 19875543

[5] Forbes JM, Cooper ME. Mechanisms of diabetic complications. Physiol Rev 2013; 93(1): 137-88. http://dx.doi.org/10.1152/physrev.00045.2011 PMID: 23303908

[6] Hicks CW, Selvin E. Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. Curr Diab Rep 2019; 19(10): 86. http://dx.doi.org/10.1007/s11892-019-1212-8 PMID: 31456118

[7] Kobayashi M, Zochodne DW. Diabetic neuropathy and the sensory neuron: New aspects of pathogenesis and their treatment implications. J Diabetes Investig 2018; 9(6): 1239-54. http://dx.doi.org/10.1111/jdi.12833 PMID: 29533535

[8] Feldman EL, Callaghan BC, Pop-Busui R, *et al.* Diabetic neuropathy. Nat Rev Dis Primers 2019; 5(1): 41. http://dx.doi.org/10.1038/s41572-019-0092-1 PMID: 31197153

[9] Gundogdu BM. Diabetic peripheral neuropathy: An update on pathogenesis and management. Curr Neurol Neurosci Rep 2006; 6(1): 1-4. http://dx.doi.org/10.1007/s11910-996-0001-3 PMID: 16469264

[10] Rahman MS, Hossain KS, Das S, *et al.* Role of insulin in health and disease: An update. Int J Mol Sci 2021; 22(12): 6403. http://dx.doi.org/10.3390/ijms22126403 PMID: 34203830

[11] Ohishi M. Hypertension with diabetes mellitus: Physiology and pathology. Hypertens Res 2018; 41(6): 389-93. http://dx.doi.org/10.1038/s41440-018-0034-4 PMID: 29556093

[12] Clark MG, Wallis MG, Barrett EJ, *et al.* Blood flow and muscle metabolism: A focus on insulin action. Am J Physiol Endocrinol Metab 2003; 284(2): E241-58. http://dx.doi.org/10.1152/ajpendo.00408.2002 PMID: 12531739

[13] Limberg JK, Soares RN, Power G, *et al.* Hyperinsulinemia blunts sympathetic vasoconstriction: A possible role of β-adrenergic activation. Am J Physiol Regul Integr Comp Physiol 2021; 320(6): R771-9. http://dx.doi.org/10.1152/ajpregu.00018.2021 PMID: 33851554

[14] Kim J, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction. Circulation 2006; 113(15): 1888-904. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.563213 PMID: 16618833

[15] Scherrer U, Sartori C. Insulin as a vascular and sympathoexcitatory hormone: Implications for blood pressure regulation, insulin sensitivity, and cardiovascular morbidity. Circulation 1997; 96(11): 4104-13. http://dx.doi.org/10.1161/01.CIR.96.11.4104 PMID: 9403636

[16] Feldman EL, Nave KA, Jensen TS, Bennett DLH. New horizons in diabetic neuropathy: Mechanisms, bioenergetics, and pain. Neuron 2017; 93(6): 1296-313. http://dx.doi.org/10.1016/j.neuron.2017.02.005 PMID: 28334605

[17] Hadi HAR, Suwaidi JA. Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag 2007; 3(6): 853-76. PMID: 18200806

[18] Zhou MS, Schulman IH, Zeng Q. Link between the renin–angiotensin system and insulin resistance: Implications for cardiovascular disease. Vasc Med 2012; 17(5): 330-41. http://dx.doi.org/10.1177/1358863X12450094 PMID: 22814999

[19] Rask-Madsen C, King GL. Vascular complications of diabetes: Mechanisms of injury and protective factors. Cell Metab 2013; 17(1): 20-33.

http://dx.doi.org/10.1016/j.cmet.2012.11.012 PMID: 23312281
[20] Ramasamy R, Yan SF, Schmidt AM. Receptor for AGE (RAGE): Signaling mechanisms in the pathogenesis of diabetes and its complications. Ann N Y Acad Sci 2011; 1243(1): 88-102. http://dx.doi.org/10.1111/j.1749-6632.2011.06320.x PMID: 22211895
[21] Pongratz G, Straub RH. The sympathetic nervous response in inflammation. Arthritis Res Ther 2014; 16(6): 504. http://dx.doi.org/10.1186/s13075-014-0504-2 PMID: 25789375
[22] Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta Mol Cell Res 2011; 1813(5): 878-88. http://dx.doi.org/10.1016/j.bbamcr.2011.01.034 PMID: 21296109
[23] Akbari M, Hassan-Zadeh V. IL-6 signalling pathways and the development of type 2 diabetes. Inflammopharmacology 2018; 26(3): 685-98. http://dx.doi.org/10.1007/s10787-018-0458-0 PMID: 29508109
[24] Rothaug M, Becker-Pauly C, Rose-John S. The role of interleukin-6 signaling in nervous tissue. Biochimica et Biophysica Acta (BBA) -. Molecular Cell Research 2016; 1863(6): 1218-27.
[25] Cox AA, Sagot Y, Hedou G, *et al.* Low-dose pulsatile interleukin-6 as a treatment option for diabetic peripheral neuropathy. Front Endocrinol 2017; 8: 89. http://dx.doi.org/10.3389/fendo.2017.00089 PMID: 28512447
[26] Chen L, Deng H, Cui H, *et al.* Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2018; 9(6): 7204-18. http://dx.doi.org/10.18632/oncotarget.23208 PMID: 29467962
[27] Tsalamandris S, Antonopoulos AS, Oikonomou E, *et al.* The role of inflammation in diabetes: Current concepts and future perspectives. Eur Cardiol 2019; 14(1): 50-9. http://dx.doi.org/10.15420/ecr.2018.33.1 PMID: 31131037
[28] Banerjee M, Saxena M. Interleukin-1 (IL-1) family of cytokines: Role in type 2 diabetes. Clin Chim Acta 2012; 413(15-16): 1163-70. http://dx.doi.org/10.1016/j.cca.2012.03.021 PMID: 22521751
[29] Lyra e Silva NM, Gonçalves RA, Pascoal TA, *et al.* Pro-inflammatory interleukin-6 signaling links cognitive impairments and peripheral metabolic alterations in Alzheimer's disease. Transl Psychiatry 2021; 11(1): 251. http://dx.doi.org/10.1038/s41398-021-01349-z PMID: 33911072
[30] Zhou J, Zhou S. Inflammation: Therapeutic targets for diabetic neuropathy. Mol Neurobiol 2014; 49(1): 536-46. http://dx.doi.org/10.1007/s12035-013-8537-0 PMID: 23990376
[31] Feigerlová E, Battaglia-Hsu SF. IL-6 signaling in diabetic nephropathy: From pathophysiology to therapeutic perspectives. Cytokine Growth Factor Rev 2017; 37: 57-65. http://dx.doi.org/10.1016/j.cytogfr.2017.03.003 PMID: 28363692
[32] Lieb DC, Parson HK, Mamikunian G, Vinik AI. Cardiac autonomic imbalance in newly diagnosed and established diabetes is associated with markers of adipose tissue inflammation. Exp Diabetes Res 2012; 2012: 1-8. http://dx.doi.org/10.1155/2012/878760 PMID: 22110481
[33] Weitz J, Diaz RR, Almaca J, Makhmutova M, Caicedo A. Anti-inflammatory cholinergic signals inhibit islet resident macrophage responses to ATP in living pancreatic tissue slices. Diabetes 2018; 67(Supplement_1) http://dx.doi.org/10.2337/db18-197-OR
[34] White UA, Stephens JM. The gp130 receptor cytokine family: Regulators of adipocyte development and function. Curr Pharm Des 2011; 17(4): 340-6. http://dx.doi.org/10.2174/138161211795164202 PMID: 21375496
[35] Qu D, Liu J, Lau CW, Huang Y. IL -6 in diabetes and cardiovascular complications. Br J Pharmacol 2014; 171(15): 3595-603. http://dx.doi.org/10.1111/bph.12713 PMID: 24697653
[36] Montgomery A, Tam F, Gursche C, *et al.* Overlapping and distinct biological effects of IL-6 classic and trans-signaling in vascular endothelial cells. Am J Physiol Cell Physiol 2021; 320(4): C554-65. http://dx.doi.org/10.1152/ajpcell.00323.2020 PMID: 33471622
[37] Zhang XL, Topley N, Ito T, Phillips A. Interleukin-6 regulation of transforming growth factor (TGF)-β receptor compartmentalization and turnover enhances TGF-β1 signaling. J Biol Chem 2005; 280(13): 12239-45. http://dx.doi.org/10.1074/jbc.M413284200 PMID: 15661740
[38] Robinson R, Srinivasan M, Shanmugam A, *et al.* Interleukin-6 trans-signaling inhibition prevents oxidative stress in a mouse model of early diabetic retinopathy. Redox Biol 2020; 34: 101574. http://dx.doi.org/10.1016/j.redox.2020.101574 PMID: 32422539
[39] Campbell IL, Erta M, Lim SL, *et al.* Trans-signaling is a dominant mechanism for the pathogenic actions of interleukin-6 in the brain. J Neurosci 2014; 34(7): 2503-13. http://dx.doi.org/10.1523/JNEUROSCI.2830-13.2014 PMID: 24523541
[40] Recasens M, Almolda B, Pérez-Clausell J, Campbell IL, González B, Castellano B. Chronic exposure to IL-6 induces a desensitized phenotype of the microglia. J Neuroinflammation 2021; 18(1): 31. http://dx.doi.org/10.1186/s12974-020-02063-1 PMID: 33482848
[41] Lamagna C, Aurrand-Lions M, Imhof BA. Dual role of macrophages in tumor growth and angiogenesis. J Leukoc Biol 2006; 80(4): 705-13. http://dx.doi.org/10.1189/jlb.1105656 PMID: 16864600
[42] Galli SJ, Grimbaldeston M, Tsai M. Immunomodulatory mast cells: Negative, as well as positive, regulators of immunity. Nat Rev Immunol 2008; 8(6): 478-86. http://dx.doi.org/10.1038/nri2327 PMID: 18483499
[43] Castilla MÁ, Caramelo C, Gazapo RM, *et al.* Role of vascular endothelial growth factor (VEGF) in endothelial cell protection against cytotoxic agents. Life Sci 2000; 67(9): 1003-13. http://dx.doi.org/10.1016/S0024-3205(00)00693-7 PMID: 10954034
[44] Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003; 26(5): 1553-79. http://dx.doi.org/10.2337/diacare.26.5.1553 PMID: 12716821
[45] Xiao J, Li J, Cai L, Chakrabarti S, Li X. Cytokines and diabetes research. J Diabetes Res 2014; 2014: 1-2. http://dx.doi.org/10.1155/2014/920613 PMID: 24551859
[46] Kim H, Zamel R, Bai XH, Liu M. PKC activation induces inflammatory response and cell death in human bronchial epithelial cells. PLoS One 2013; 8(5): e64182. http://dx.doi.org/10.1371/journal.pone.0064182 PMID: 23691166
[47] Sabio G, Davis RJ. TNF and MAP kinase signalling pathways. Semin Immunol 2014; 26(3): 237-45. http://dx.doi.org/10.1016/j.smim.2014.02.009 PMID: 24647229
[48] Yung JHM, Giacca A. Role of c-Jun N-terminal Kinase (JNK) in obesity and type 2 Diabetes. Cells 2020; 9(3): 706. http://dx.doi.org/10.3390/cells9030706 PMID: 32183037
[49] Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab 2012; 16(Suppl. 1): S27-36. PMID: 22701840
[50] Guo W, Li M, Dong Y, *et al.* Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020; 36(7): e3319. http://dx.doi.org/10.1002/dmrr.3319 PMID: 32233013
[51] Bril V, Blanchette CM, Noone JM, Runken MC, Gelinas D, Russell JW. The dilemma of diabetes in chronic inflammatory demyelinating polyneuropathy. J Diabetes Complications 2016; 30(7): 1401-7. http://dx.doi.org/10.1016/j.jdiacomp.2016.05.007 PMID: 27389526
[52] Park HT, Kim YH, Lee KE, Kim JK. Behind the pathology of macrophage-associated demyelination in inflammatory neuropathies: demyelinating Schwann cells. Cell Mol Life Sci 2020; 77(13): 2497-506. http://dx.doi.org/10.1007/s00018-019-03431-8 PMID: 31884566
[53] Koike H, Katsuno M. Macrophages and autoantibodies in demyelinating diseases. Cells 2021; 10(4): 844. http://dx.doi.org/10.3390/cells10040844 PMID: 33917929
[54] Traka M, Podojil JR, McCarthy DP, Miller SD, Popko B. Oligodendrocyte death results in immune-mediated CNS demyelination. Nat Neurosci 2016; 19(1): 65-74. http://dx.doi.org/10.1038/nn.4193 PMID: 26656646
[55] Peschl P, Bradl M, Höftberger R, Berger T, Reindl M. Myelin oligodendrocyte glycoprotein: Deciphering a target in inflammatory demyelinating diseases. Front Immunol 2017; 8: 529. http://dx.doi.org/10.3389/fimmu.2017.00529 PMID: 28533781
[56] Skaper SD. Oligodendrocyte precursor cells as a therapeutic target for demyelinating diseases. Prog Brain Res 2019; 245: 119-44. http://dx.doi.org/10.1016/bs.pbr.2019.03.013

[57] Höftberger R, Guo Y, Flanagan EP, *et al.* The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody. Acta Neuropathol 2020; 139(5): 875-92. http://dx.doi.org/10.1007/s00401-020-02132-y PMID: 32048003

[58] Velikova TV, Kabakchieva PP, Assyov YS, Georgiev TA. Targeting inflammatory cytokines to improve type 2 diabetes control. BioMed Res Int 2021; 2021: 1-12. http://dx.doi.org/10.1155/2021/7297419 PMID: 34557550

[59] Zhou YQ, Liu Z, Liu ZH, *et al.* Interleukin-6: An emerging regulator of pathological pain. J Neuroinflammation 2016; 13(1): 141. http://dx.doi.org/10.1186/s12974-016-0607-6 PMID: 27267059

[60] Payne SC, Ward G, MacIsaac RJ, Hyakumura T, Fallon JB, Villalobos J. Differential effects of vagus nerve stimulation strategies on glycemia and pancreatic secretions. Physiol Rep 2020; 8(11): e14479. http://dx.doi.org/10.14814/phy2.14479 PMID: 32512650

[61] Caravaca AS, Gallina AL, Tarnawski L, *et al.* An Effective method for acute vagus nerve stimulation in experimental inflammation. Front Neurosci 2019; 13: 877. http://dx.doi.org/10.3389/fnins.2019.00877 PMID: 31551672

[62] Tsaava T, Datta-Chaudhuri T, Addorisio ME, *et al.* Specific vagus nerve stimulation parameters alter serum cytokine levels in the absence of inflammation. Bioelectron Med 2020; 6(1): 8. http://dx.doi.org/10.1186/s42234-020-00042-8 PMID: 32309522

[63] Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: A missing link in neuroimmunomodulation. Mol Med 2003; 9(5-8): 125-34. http://dx.doi.org/10.1007/BF03402177 PMID: 14571320

[64] Koopman FA, Chavan SS, Miljko S, *et al.* Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Natl Acad Sci USA 2016; 113(29): 8284-9. http://dx.doi.org/10.1073/pnas.1605635113 PMID: 27382171

[65] Staats P, Giannakopoulos G, Blake J, Liebler E, Levy RM. The use of non-invasive vagus nerve stimulation to treat respiratory symptoms associated with COVID-19: A theoretical hypothesis and early clinical experience. Neuromodulation 2020; 23(6): 784-8. http://dx.doi.org/10.1111/ner.13172 PMID: 32342609

[66] Kaniusas E, Szeles JC, Kampusch S, *et al.* Non-invasive auricular vagus nerve stimulation as a potential treatment for COVID-19 originated acute respiratory distress syndrome. Front Physiol 2020; 11: 890. http://dx.doi.org/10.3389/fphys.2020.00890 PMID: 32848845

[67] Asad ZUA, Przebinda A, Chaudhary AMD, Farooqui S, Youness H, Stavrakis S. The role of vagus nerve stimulation in sepsis. Bioelectron Med 2020; 3(4): 51-62. http://dx.doi.org/10.2217/bem-2020-0010

[68] Boezaart AP, Botha DA. Treatment of Stage 3 COVID-19 with transcutaneous auricular vagus nerve stimulation drastically reduces interleukin-6 blood levels: A report on two cases. Neuromodulation 2021; 24(1): 166-7. http://dx.doi.org/10.1111/ner.13293 PMID: 33063409

[69] Pavlov VA. The evolving obesity challenge: Targeting the vagus nerve and the inflammatory reflex in the response. Pharmacol Ther 2021; 222: 107794. http://dx.doi.org/10.1016/j.pharmthera.2020.107794 PMID: 33310156

[70] Dubin AE, Patapoutian A. Nociceptors: The sensors of the pain pathway. J Clin Invest 2010; 120(11): 3760-72. http://dx.doi.org/10.1172/JCI42843 PMID: 21041958

[71] Muramatsu K. Diabetes mellitus-related dysfunction of the motor system. Int J Mol Sci 2020; 21(20): 7485. http://dx.doi.org/10.3390/ijms21207485 PMID: 33050583

[72] Sung JY, Tani J, Chang TS, Lin CSY. Uncovering sensory axonal dysfunction in asymptomatic type 2 diabetic neuropathy. PLoS One 2017; 12(2): e0171223. http://dx.doi.org/10.1371/journal.pone.0171223 PMID: 28182728

[73] Sohn JW. Ion channels in the central regulation of energy and glucose homeostasis. Front Neurosci 2013; 7: 85. http://dx.doi.org/10.3389/fnins.2013.00085 PMID: 23734095

[74] De Bernardis Murat C, Leão RM. A voltage-dependent depolarization induced by low external glucose in neurons of the nucleus of the tractus solitarius: interaction with $K_{ATP}$ channels. J Physiol 2019; 597(9): 2515-32. http://dx.doi.org/10.1113/JP277729 PMID: 30927460

[75] de Campos Lima T, Santos DO, Lemes JBP, Chiovato LM, Lotufo CMC. Hyperglycemia induces mechanical hyperalgesia and depolarization of the resting membrane potential of primary nociceptive neurons: Role of ATP-sensitive potassium channels. J Neurol Sci 2019; 401: 55-61. http://dx.doi.org/10.1016/j.jns.2019.03.025 PMID: 31015148

[76] Ågren R, Nilsson J, Århem P. Closed and open state dependent block of potassium channels cause opposing effects on excitability-a computational approach. Sci Rep 2019; 9(1): 8175. http://dx.doi.org/10.1038/s41598-019-44564-x PMID: 31160624

[77] Lin YC, Lin CSY, Chang TS, *et al.* Early sensory neurophysiological changes in prediabetes. J Diabetes Investig 2020; 11(2): 458-65. http://dx.doi.org/10.1111/jdi.13151 PMID: 31563156

[78] Bönhof GJ, Strom A, Püttgen S, *et al.* Patterns of cutaneous nerve fibre loss and regeneration in type 2 diabetes with painful and painless polyneuropathy. Diabetologia 2017; 60(12): 2495-503. http://dx.doi.org/10.1007/s00125-017-4438-5 PMID: 28914336

[79] Wendelschafer-Crabb G, Kennedy WR, Walk D. Morphological features of nerves in skin biopsies. J Neurol Sci 2006; 242(1-2): 15-21. http://dx.doi.org/10.1016/j.jns.2005.11.010 PMID: 16448669

[80] Cheng HT, Dauch JR, Porzio MT, *et al.* Increased axonal regeneration and swellings in intraepidermal nerve fibers characterize painful phenotypes of diabetic neuropathy. J Pain 2013; 14(9): 941-7. http://dx.doi.org/10.1016/j.jpain.2013.03.005 PMID: 23685187

[81] Lauria G, Lombardi R, Camozzi F, Devigili G. Skin biopsy for the diagnosis of peripheral neuropathy. Histopathology 2009; 54(3): 273-85. http://dx.doi.org/10.1111/j.1365-2559.2008.03096.x PMID: 18637969

[82] Galosi E, La Cesa S, Di Stefano G, *et al.* A pain in the skin. Regenerating nerve sprouts are distinctly associated with ongoing burning pain in patients with diabetes. Eur J Pain 2018; 22(10): 1727-34. http://dx.doi.org/10.1002/ejp.1259 PMID: 29885017

[83] Li S, Liu N, Zhang X, Zhou D, Cai D. Bilinearity in spatiotemporal integration of synaptic inputs. PLOS Comput Biol 2014; 10(12): e1004014. http://dx.doi.org/10.1371/journal.pcbi.1004014 PMID: 25521832

[84] Hao J, Wang X, Dan Y, Poo M, Zhang X. An arithmetic rule for spatial summation of excitatory and inhibitory inputs in pyramidal neurons. Proc Natl Acad Sci USA 2009; 106(51): 21906-11. http://dx.doi.org/10.1073/pnas.0912022106 PMID: 19955407

[85] Moulin TC, Rayêe D, Williams MJ, Schiöth HB. The synaptic scaling literature: A systematic review of methodologies and quality of reporting. Front Cell Neurosci 2020; 14: 164. http://dx.doi.org/10.3389/fncel.2020.00164 PMID: 32612512

[86] Hossain MJ, Kendig MD, Wild BM, *et al.* Evidence of altered peripheral nerve function in a rodent model of diet-induced prediabetes. Biomedicines 2020; 8(9): 313. http://dx.doi.org/10.3390/biomedicines8090313 PMID: 32872256

[87] Sango K, Mizukami H, Horie H, Yagihashi S. Impaired axonal regeneration in diabetes. perspective on the underlying mechanism from *in vivo* and *in vitro* experimental studies. Front Endocrinol 2017; 8: 12. http://dx.doi.org/10.3389/fendo.2017.00012 PMID: 28203223

[88] Sakai J. How synaptic pruning shapes neural wiring during development and, possibly, in disease. Proc Natl Acad Sci USA 2020; 117(28): 16096-9. http://dx.doi.org/10.1073/pnas.2010281117 PMID: 32581125

[89] Faust TE, Gunner G, Schafer DP. Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS. Nat Rev Neurosci 2021; 22(11): 657-73. http://dx.doi.org/10.1038/s41583-021-00507-y PMID: 34545240

[90] Riccomagno MM, Kolodkin AL. Sculpting neural circuits by axon and dendrite pruning. Annu Rev Cell Dev Biol 2015; 31(1): 779-805. http://dx.doi.org/10.1146/annurev-cellbio-100913-013038 PMID: 26436703

[91] Geloso MC, D'Ambrosi N. Microglial Pruning: Relevance for synaptic dysfunction in multiple sclerosis and related experimental models. Cells 2021; 10(3): 686.

http://dx.doi.org/10.3390/cells10030686 PMID: 33804596
[92] Plant LD. A role for K2P channels in the operation of somatosensory nociceptors. Front Mol Neurosci 2012; 5: 21. http://dx.doi.org/10.3389/fnmol.2012.00021 PMID: 22403526
[93] Yaron A, Schuldiner O. Common and divergent mechanisms in developmental neuronal remodeling and dying back neurodegeneration. Curr Biol 2016; 26(13): R628-39. http://dx.doi.org/10.1016/j.cub.2016.05.025 PMID: 27404258
[94] Alrabayah M, Qaswal AB, Suleiman A, Khreesha L. Role of potassium ions quantum tunneling in the pathophysiology of phantom limb pain. Brain Sci 2020; 10(4): 241. http://dx.doi.org/10.3390/brainsci10040241 PMID: 32325702
[95] Flor H. Maladaptive plasticity, memory for pain and phantom limb pain: review and suggestions for new therapies. Expert Rev Neurother 2008; 8(5): 809-18. http://dx.doi.org/10.1586/14737175.8.5.809 PMID: 18457537
[96] Meyers EC, Kasliwal N, Solorzano BR, *et al.* Enhancing plasticity in central networks improves motor and sensory recovery after nerve damage. Nat Commun 2019; 10(1): 5782. http://dx.doi.org/10.1038/s41467-019-13695-0 PMID: 31857587
[97] Schwartzman RJ, Grothusen J, Kiefer TR, Rohr P. Neuropathic central pain: Epidemiology, etiology, and treatment options. Arch Neurol 2001; 58(10): 1547-50. http://dx.doi.org/10.1001/archneur.58.10.1547 PMID: 11594911
[98] Meacham K, Shepherd A, Mohapatra DP, Haroutounian S. Neuropathic pain: Central *vs*. peripheral mechanisms. Curr Pain Headache Rep 2017; 21(6): 28. http://dx.doi.org/10.1007/s11916-017-0629-5 PMID: 28432601
[99] Drewes AM, Søfteland E, Dimcevski G, *et al.* Brain changes in diabetes mellitus patients with gastrointestinal symptoms. World J Diabetes 2016; 7(2): 14-26. http://dx.doi.org/10.4239/wjd.v7.i2.14 PMID: 26839652
[100] Selvarajah D, Wilkinson ID, Fang F, *et al.* Structural and functional abnormalities of the primary somatosensory cortex in diabetic peripheral neuropathy: A multimodal MRI study. Diabetes 2019; 68(4): 796-806. http://dx.doi.org/10.2337/db18-0509 PMID: 30617218
[101] Daffada PJ, Walsh N, McCabe CS, Palmer S. The impact of cortical remapping interventions on pain and disability in chronic low back pain: A systematic review. Physiotherapy 2015; 101(1): 25-33. http://dx.doi.org/10.1016/j.physio.2014.07.002 PMID: 25442672
[102] Vartiainen N, Kirveskari E, Kallio-Laine K, Kalso E, Forss N. Cortical reorganization in primary somatosensory cortex in patients with unilateral chronic pain. J Pain 2009; 10(8): 854-9. http://dx.doi.org/10.1016/j.jpain.2009.02.006 PMID: 19638329
[103] Ferris JK, Peters S, Brown KE, Tourigny K, Boyd LA. Type-2 diabetes mellitus reduces cortical thickness and decreases oxidative metabolism in sensorimotor regions after stroke. J Cereb Blood Flow Metab 2018; 38(5): 823-34. http://dx.doi.org/10.1177/0271678X17703887 PMID: 28401788
[104] Fried PJ, Pascual-Leone A, Bolo NR. Diabetes and the link between neuroplasticity and glutamate in the aging human motor cortex. Clin Neurophysiol 2019; 130(9): 1502-10. http://dx.doi.org/10.1016/j.clinph.2019.04.721 PMID: 31295719
[105] Zhang Y, Qu M, Yi X, *et al.* Sensorimotor and pain-related alterations of the gray matter and white matter in type 2 diabetic patients with peripheral neuropathy. Hum Brain Mapp 2020; 41(3): 710-25. http://dx.doi.org/10.1002/hbm.24834 PMID: 31663232
[106] Koike H, Katsuno M. Pathophysiology of chronic inflammatory demyelinating polyneuropathy: Insights into classification and therapeutic strategy. Neurol Ther 2020; 9(2): 213-27. http://dx.doi.org/10.1007/s40120-020-00190-8 PMID: 32410146
[107] Lund JP, Donga R, Widmer CG, Stohler CS. The pain-adaptation model: A discussion of the relationship between chronic musculoskeletal pain and motor activity. Can J Physiol Pharmacol 1991; 69(5): 683-94. http://dx.doi.org/10.1139/y91-102 PMID: 1863921
[108] Hodges PW, Moseley GL. Pain and motor control of the lumbopelvic region: Effect and possible mechanisms. J Electromyogr Kinesiol 2003; 13(4): 361-70. http://dx.doi.org/10.1016/S1050-6411(03)00042-7 PMID: 12832166
[109] Bansal V, Kalita J, Misra UK. Diabetic neuropathy. Postgrad Med J 2006; 82(964): 95-100. http://dx.doi.org/10.1136/pgmj.2005.036137 PMID: 16461471
[110] Henry DE, Chiodo AE, Yang W. Central nervous system reorganization in a variety of chronic pain states: A review. PM R 2011; 3(12): 1116-25. http://dx.doi.org/10.1016/j.pmrj.2011.05.018 PMID: 22192321
[111] Sweetnam D, Holmes A, Tennant KA, *et al.* Diabetes impairs cortical plasticity and functional recovery following ischemic stroke. J Neurosci 2012; 32(15): 5132-43. http://dx.doi.org/10.1523/JNEUROSCI.5075-11.2012 PMID: 22496559
[112] Andersen H. Motor neuropathy. In: Elsevier BV, Ed. Diabetes and the Nervous System 3rd series. 2014; pp. 81-95. http://dx.doi.org/10.1016/B978-0-444-53480-4.00007-2
[113] Morgalla MH, de Barros Filho MF, Chander BS, Soekadar SR, Tatagiba M, Lepski G. Neurophysiological effects of Dorsal Root Ganglion Stimulation (DRGS) in pain processing at the cortical level. Neuromodulation 2019; 22(1): 36-43. http://dx.doi.org/10.1111/ner.12900 PMID: 30561852
[114] Snyder MJ, Gibbs LM, Lindsay TJ. Treating painful diabetic peripheral neuropathy: An update. Am Fam Physician 2016; 94(3): 227-34. PMID: 27479625
[115] Weintraub MI, Cole SP. Pulsed magnetic field therapy in refractory neuropathic pain secondary to peripheral neuropathy: electrodiagnostic parameters-pilot study. Neurorehabil Neural Repair 2004; 18(1): 42-6. http://dx.doi.org/10.1177/0888439003261024 PMID: 15035963
[116] Lei T, Jing D, Xie K, *et al.* Therapeutic effects of 15 Hz pulsed electromagnetic field on diabetic peripheral neuropathy in streptozotocin-treated rats. PLoS One 2013; 8(4): e61414. http://dx.doi.org/10.1371/journal.pone.0061414 PMID: 23637830
[117] Berger P, Landau S. Can an electrical pulsed radio frequency device relieve pain and improve function in patients with pedal diabetic neuropathy? A single blind randomized placebo-controlled trial. In: Johannesburg 2016.
[118] Goroszeniuk T, Kothari S. External stimulation: simplistic solution to intractable pain. London 2015.
[119] Weintraub MI, Herrmann DN, Smith AG, Backonja MM, Cole SP. Pulsed electromagnetic fields to reduce diabetic neuropathic pain and stimulate neuronal repair: A randomized controlled trial. Arch Phys Med Rehabil 2009; 90(7): 1102-9. http://dx.doi.org/10.1016/j.apmr.2009.01.019 PMID: 19577022
[120] Liu H, Zhou J, Gu L, Zuo Y. The change of HCN1/HCN2 mRNA expression in peripheral nerve after chronic constriction injury induced neuropathy followed by pulsed electromagnetic field therapy. Oncotarget 2017; 8(1): 1110-6. http://dx.doi.org/10.18632/oncotarget.13584 PMID: 27901476
[121] Battecha K. Efficacy of pulsed electromagnetic field on pain and nerve conduction velocity in patients with diabetic neuropathy. Bull Fac Phys Ther 2017; 22(1): 9-14. http://dx.doi.org/10.4103/1110-6611.209877
[122] Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: Epidemiology, natural history, early diagnosis, and treatment options. Pain Med 2008; 9(6): 660-74. http://dx.doi.org/10.1111/j.1526-4637.2007.00347.x PMID: 18828198
[123] Shillo P, Sloan G, Greig M, *et al.* Painful and painless diabetic neuropathies: What is the difference? Curr Diab Rep 2019; 19(6): 32. http://dx.doi.org/10.1007/s11892-019-1150-5 PMID: 31065863
[124] Baskozos G, Themistocleous AC, Hebert HL, *et al.* Classification of painful or painless diabetic peripheral neuropathy and identification of the most powerful predictors using machine learning models in large cross-sectional cohorts. BMC Med Inform Decis Mak 2022; 22(1): 144. http://dx.doi.org/10.1186/s12911-022-01890-x PMID: 35644620
[125] Llorián-Salvador M, González-Rodríguez S. Painful understanding of VEGF. Front Pharmacol 2018; 9: 1267. http://dx.doi.org/10.3389/fphar.2018.01267 PMID: 30459621
[126] Ponirakis G, Abdul-Ghani MA, Jayyousi A, *et al.* Painful diabetic neuropathy is associated with increased nerve regeneration in pa-

tients with type 2 diabetes undergoing intensive glycemic control. J Diabetes Investig 2021; 12(9): 1642-50. http://dx.doi.org/10.1111/jdi.13544 PMID: 33714226

[127] Shillo P, Yiangou Y, Donatien P, Greig M, Selvarajah D, Wilkinson ID, *et al.* Nerve and vascular biomarkers in skin biopsies differentiate painful from painless peripheral neuropathy in type 2 diabetes. Frontiers in Pain Research 2021; 2

[128] Herder C, Bongaerts BWC, Rathmann W, *et al.* Differential association between biomarkers of subclinical inflammation and painful polyneuropathy: results from the KORA F4 study. Diabetes Care 2015; 38(1): 91-6. http://dx.doi.org/10.2337/dc14-1403 PMID: 25325880

[129] Hammi C, Yeung B. StatPearls. Neuropathy 2022.

[130] Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of chemotherapy-induced peripheral neuropathy. Int J Mol Sci 2019; 20(6): 1451. http://dx.doi.org/10.3390/ijms20061451 PMID: 30909387

[131] Kaeley N, Ahmad S, Pathania M, Kakkar R. Prevalence and patterns of peripheral neuropathy in patients of rheumatoid arthritis. J Family Med Prim Care 2019; 8(1): 22-6. http://dx.doi.org/10.4103/jfmpc.jfmpc_260_18 PMID: 30911476

[132] Motwani L, Asif N, Patel A, Vedantam D, Poman DS. Neuropathy in human immunodeficiency virus: A review of the underlying pathogenesis and treatment. Cureus 2022; 14(6): e25905. http://dx.doi.org/10.7759/cureus.25905 PMID: 35844323

[133] Wulff EA, Wang AK, Simpson DM. HIV-associated peripheral neuropathy: Epidemiology, pathophysiology and treatment. Drugs 2000; 59(6): 1251-60. http://dx.doi.org/10.2165/00003495-200059060-00005 PMID: 10882161