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Diabetic neuropathy and neuropathic pain: a (con)fusion of pathogenic mechanisms?

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Abstract

Neuropathy is a common complication of long-term diabetes that impairs quality of life by producing pain, sensory loss and limb amputation. The presence of neuropathy in both insulin-deficient (type 1) and insulin resistant (type 2) diabetes along with the slowing of progression of neuropathy by improved glycemic control in type 1 diabetes has caused the majority of preclinical and clinical investigations to focus on hyperglycemia as the initiating pathogenic lesion. Studies in animal models of diabetes have identified multiple plausible mechanisms of glucotoxicity to the nervous system including post-translational modification of proteins by glucose and increased glucose metabolism by aldose reductase, glycolysis and other catabolic pathways. However, it is becoming increasingly apparent that factors not necessarily downstream of hyperglycemia can also contribute to the incidence, progression and severity of neuropathy and neuropathic pain. For example, peripheral nerve contains insulin receptors that transduce the neurotrophic and neurosupportive properties of insulin, independent of systemic glucose regulation, while the detection of neuropathy and neuropathic pain in patients with metabolic syndrome and failure of improved glycemic control to protect against neuropathy in cohorts of type 2 diabetic patients has placed a focus on the pathogenic role of dyslipidemia. This review provides an overview of current understanding of potential initiating lesions for diabetic neuropathy and the multiple downstream mechanisms identified in cell and animal models of diabetes that may contribute to the pathogenesis of diabetic neuropathy and neuropathic pain.

INTRODUCTION

Neuropathy will afflict over half of the estimated 460 million people worldwide who have diabetes[305], of whom approximately one third will also develop neuropathic pain[2]. The pathogenesis of diabetic neuropathy is uncertain and attaining and maintaining close glycemic control remains the only universal recommendation for preventing or slowing progression of the condition. While there has been considerable progress in β-cell, stem cell and whole pancreas transplantation[231] and ongoing refinement of continuous glucose monitors for maintaining consistent euglycemia[283], these advanced bioengineering

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solutions are unlikely to become available for the majority of the diabetic population worldwide in the foreseeable future[65]. Although the mechanisms driving degenerative neuropathy and pain are likely intertwined, the unpredictability of which patients with neuropathy also exhibit pain suggests as yet ill-defined pathways unique for pain generation. Treatment of painful diabetic neuropathy is limited to analgesics[9; 18] with efficacy of any given agent limited to unpredictable sub-populations of patients[113]. This somewhat bleak landscape has prompted extensive investigation of the pathogenic consequences of hyperglycemia and, more recently, glucose-independent neurotoxic mechanisms, as downstream sites for therapeutic intervention.

The most common presentation of diabetic neuropathy is as a distal symmetrical polyneuropathy with numbness in the distal extremities. Loss of sensation can lead to unattended wounds that, when combined with peripheral vascular disease and impaired wound healing, may lead to infection and ultimately amputation[161]. Indications of motor and autonomic nerve dysfunction may also be present. Early quantifiable features of distal symmetrical polyneuropathy (from herein termed diabetic neuropathy unless stated otherwise) include slowing of large sensory and motor fiber conduction velocity (SNCV and MNCV)[32] and depletion of small sensory nerves in the skin and cornea[276]. Peripheral nerves also exhibit resistance to ischemic conduction blockade/failure (RICB/RICF), which patients may become aware of as an ability to squat or kneel for lengthy periods of time without developing paresthesias and that can be confirmed using routine electrophysiology and a blood pressure cuff[137; 316]. Microvascular lesions similar to those reported in other organs during diabetes are also an early feature[223]. Biopsy studies have identified segmental demyelination in large fibers and axonal degeneration of all fiber classes [97] with clusters of regenerating fibers[223], but regeneration is clearly insufficient to overcome ongoing distal degenerative processes. It is now widely accepted that diabetes damages all components of the nervous system, not just peripheral nerves. Historical autopsy evidence of demyelination and neuronal degeneration in the spinal cord[330] has been supported by more recent non-invasive imaging studies[313] and there is emerging recognition of structural and functional impairments in the higher CNS[27; 314; 325].

Around a third of patients with diabetic neuropathy report intermittent or continuous paresthesias and/or pain[2]. The most frequent descriptors are of numbness, tingling, burning, pins and needles, electric shock and pain to cold[359]. Pain may develop during the pre-diabetic period[331; 338] or relatively early after diagnosis of diabetes[133] but tends to be associated with advanced degenerative neuropathy[350]. A separate and distinct pain condition, historically termed insulin neuritis, can also develop after instigation of tight glycemic control[122].

DISCUSSION

1. MECHANISTIC IMPLICATIONS FROM CLINICAL OBSERVATIONS

A number of deductions made from the clinical presentation of diabetic neuropathy have guided development of mechanistic hypotheses and both clinical and preclinical investigations:

1.1. Initiating lesion: The bilateral presentation of diabetic neuropathy implies a systemic primary lesion, although people with diabetes are also more vulnerable to focal neuropathies[332]. The occurrence of neuropathy in both insulin-deficient (type 1) and insulin-insensitive (type 2) diabetes has driven an overwhelming experimental focus on hyperglycemia as the initiating lesion. This was encouraged by results from the DCCT study which showed that improved glycemic control beyond the accepted standard of care slowed onset and progression of diabetic complications, including peripheral neuropathy, in a large cohort of type 1 diabetic patients [227]. The association between hyperglycemia and complications, including neuropathy, is less convincing in patients with type 2 diabetes and alternative primary pathogenic mechanisms have been proposed (see below). Data from the DDCT, its follow-up (EDIC) and preclinical studies also prompted the concept of "metabolic memory" in which initial exposure to glucose makes indelible epigenetic modifications to cells that are not amenable to acute restoration of normoglycemia[372]. To date, this has proven to be more applicable to other complications of diabetes than to peripheral neuropathy[235], although there is supportive evidence associated with autonomic neuropathy[120].

1.2. Cellular targets: As epineurial, perineurial and endoneurial blood vessels are compromised in nerves of diabetic patients with early neuropathy[223; 271], a view of diabetic neuropathy emerged as representing a secondary manifestation of microvascular disease arising from hyperglycemia-induced damage to vascular endothelial cells[218]. This aligns diabetic neuropathy with other complications of diabetes[263] and there is an association between development of neuropathy and concurrent nephropathy and retinopathy. The presence of RICB also implies an early presence of ischemic hypoxia[218], although it also suggests that nerve metabolism adapts within acceptable tolerance limits. Whether vascular insufficiency initiates peripheral neuropathy in diabetic patients or impedes the capacity of cells within the nerve to withstand direct glucotoxic or other insults remains an area of lively debate. Similarly, whether there is initial damage to Schwann cells (primary Schwannopathy) [175], to axons (primary axonopathy) [98] or independent and/or inter-dependent mechanisms of damage to each cell type[123] has also been an area of continuous investigation [351].

1.3. Degenerative neuropathy: That numbness is usually first perceived in the toes, along with the early loss of epidermal fibers in the lower extremities, suggests a length-dependent neuropathy associated with an inability to maintain the regions of the axon that are most distant from the cell body – not unlike the travails of Napoleon when invading Russia in the winter of 1812[198]. However, reports that depletion of sensory nerves in the sub-basal plexus of the cornea is an equally sensitive marker for early neuropathy in diabetic patients indicates that distal regions of the axon are most vulnerable, irrespective of length[8; 276]. Longer axons may be particularly vulnerable to accumulation of focal lesions due to size alone, but systemic insults do not appear to discriminate based on absolute axonal length.

1.4. Painful vs painless neuropathy: Why approximately only a third of diabetic patients with degenerative neuropathy develop pain[2] remains enigmatic. Studies have

sought clinical, structural, functional or metabolic biomarkers that segregate subjects otherwise well matched in presentation of diabetes and neuropathy into those with or without pain [321; 334]. Recent examples are shown in Table 1 [30; 34; 58; 59; 76; 91; 99; 114; 115; 140; 177; 178; 196; 216; 224; 226; 242; 273–276; 285; 312; 314; 315; 320; 329; 335; 343; 350; 359; 362; 386; 416]. However, interpretation of such studies is complicated by the heterogeneity of the pain state caused by diabetes and there have been few attempts to identify biomarkers that identify specific pain sub-categories identified amongst diabetic patients[20; 350]. Perhaps the best examples to date are associations of burning pain with gain of function mutations in sub-units of the $Na_v1.7$ ion channel[11; 29], although this represents a rare sub-group within those with painful diabetic neuropathy. Identification of features unique to subjects with pain could reveal potential pathogenic mechanisms specific for pain, with the usual caveat that any implied causality must be proven.

1.5. Pain generator site: It is tempting to assume that if pain is perceived in the feet, then the primary lesion site is to sensory nerves that innervate the feet. Recent studies suggesting that pain correlates with nerve regeneration markers in the skin[30; 58] have revived the old ideas that painful diabetic neuropathy may arise from instability of degenerating peripheral sensory neurons, ephaptic activation of adjacent intact peripheral fibers and/or activity of regenerating peripheral fibers[34]. Hyperactive nociceptors and recruitment of otherwise silent nociceptors have been recorded in subjects with painful diabetic neuropathy by microneurography[259] and used to pre-select subjects for clinical trial[317]. However, the “irritable nociceptor” phenotype (preserved small fiber function with hyperalgesia) formed only a small sub-set (6%) of a cohort comprising 191 subjects with painful diabetic neuropathy[350] and peripheral hyperactivity may not be the only genesis of pain. A report that onset of type 2 diabetes triggered symmetrical pain in both feet of a patient who had one leg amputated some 44 years earlier prompted the suggestion that the initiating lesion for diabetes-induced pain need not be at the site where pain is perceived[281]. In support of this, there is a growing body of data emerging from imaging studies of diabetic subjects with painful neuropathy indicating that there is CNS dysfunction and pathology in regions associated with pain processing[312; 314] while preclinical and clinical studies also suggest spinal involvement [226]. In addition, there is growing appreciation that the genesis of neuropathic pain states evolves over time, progressing from peripheral to central sites. Painful diabetic neuropathy may therefore incorporate multiple generator sites whose relative dominance waxes and wanes as concurrent degenerative pathology progresses. This complexity has implications for selecting clinical trial populations that may be more heterogenous than previously recognized[20] and result in the infrequent (NNT > 5) and unpredictable efficacy of current pain medications used to treat painful diabetic neuropathy[113].

2. GLUCOTOXIC MECHANISMS

The occurrence of neuropathy in both forms of diabetes and the success of intensive glycemic control regimens to slow progression of diabetic neuropathy in type 1 diabetes[269] naturally focused attention on hyperglycemia as the initiating event of diabetic neuropathy. Glucose enters peripheral nerve and brain via insulin-independent glucose transporters (GLUT’s). GLUT-1 is the major glucose transporter of the microvascular and

perineurial components of the blood:brain and blood:nerve barriers[337], with GLUT-3 localized to peripheral neurons[340]. Insulin dependent GLUT-4 is restricted to select neuronal populations of the brain[19]. The search for detrimental consequences of hyperglycemia has focused on modifications to protein structure and function by direct glycation or enzyme-mediated glycosylation along with excess flux through glucose metabolism pathways (FIGURE 1).

2.1 Models of diabetic neuropathy: In vitro studies allow direct environmental manipulation of individual cell types and are valuable for identifying plausible pathogenic mechanisms, with the recognized caveats that these are traumatically excised tissues in artificial environments – neurons enter an axonal injury and regeneration phenotype while Schwann cells return to their non-myelinating form[118]. Perhaps the most sophisticated studies employ cells derived from adult control and diabetic animals maintained under conditions that reflect the in vivo insulin and glycemic environment from which they were derived[134] and co-culture neurons and Schwann cells to facilitate myelination[344; 366].

Of the animal models, diabetic cats exhibit nerve pathology that most closely reflects the human condition, with prominent demyelination and axonal degeneration[239]. Rats and mice are the most commonly used animal models of diabetic neuropathy and provide the majority of data that underpins current hypotheses regarding the pathogenesis of diabetic neuropathy and neuropathic pain. Both species can be used to model pre-diabetes, type 1 or type 2 diabetes using dietary, chemical or genetic initiating events. There are variations in the neuropathy phenotype and rate of progression between specific models, species, strains, laboratories and assays [26]. The provenance of new disorders identified in streptozotocin (STZ)-diabetic rodents, the most commonly used model of type 1 diabetes, should be established to address concerns about acute STZ neurotoxicity[15; 261; 296]. This can be done using concurrent 3-O-methyl glucose injection[81; 226], using insulin to reverse established disorders[226] and by validating disorders using genetic or dietary models[404]. Rodents are frequently studied over 4–12 weeks of diabetes and are best viewed as modeling early nerve dysfunction in the absence of overt pathology[380], as structural pathology in nerve trunks (FIGURE 2) is limited to reduced axonal caliber with late (4 months+) myelin thinning, occasional segmental demyelination and minor fiber loss[158; 159; 183; 270; 290; 398]. This can be viewed as a boon, as molecular and biochemical changes in nerve may be interpreted as preceding, perhaps precipitating, degenerative neuropathy. Unfortunately, it also limits any guarantees of the translation of therapies developed using these models. Recognition that diabetic rodents develop early loss of sensory nerve terminals in the epidermis of plantar skin (frequently termed intra-epidermal nerve fibers or IENF)[23] and reduced sensory nerve density in the cornea[52] that accompany indices of both sensory loss and hyperalgesia[168] to mirror the human condition[276] have revived hopes that rodent models can be used to study the early damage to small sensory neurons that is a feature of diabetic neuropathy (FIGURE 2).

2.2. Glucose metabolism by the polyol pathway: Early observations that tissues that contained the polyol pathway enzymes aldose reductase and sorbitol dehydrogenase were prone to diabetic complications prompted extensive research into their potential

pathogenic role[96]. Within peripheral nerve, aldose reductase is localized to endothelial and Schwann cells[165] and hyperglycemia-driven flux through the polyol pathway results in accumulation of the intermediates sorbitol and fructose along with shifts in the redox balance of the associated cofactors NADPH and NADH. Downstream consequences potentially include local osmotic stress due to sorbitol accumulation[252], fructose-driven AGE formation[12] and subsequent RAGE signaling, oxidative[75] and nitrosative stress[72] and loss of neurotrophic support[237]. As reviewed elsewhere[252], pre-clinical studies showing impressive efficacy of aldose reductase inhibitors (ARI's) against many indices of diabetic neuropathy and neuropathic pain that culminated in a number of clinical trials. To date, ARI treatment has not shown sufficiently convincing efficacy in clinical trials to support approval by most regulatory agencies, although epalrestat is approved in Japan. Whether this reflects a pathogenic mechanism that is pertinent only to diabetic rodents, sub-optimal drug properties for human use or poor clinical trial design and inappropriate endpoints remains the subject of unresolved debate[252]. Polyol pathway research is currently out of vogue but the impressive preclinical efficacy of ARI's must either indicate a major contribution to downstream pathways that damage nerve or illustrate a disconcerting gulf between preclinical models and the human disease.

2.3. Non-enzymatic glycation and the AGE-RAGE axis: The post-translational modification of cellular proteins caused by non-enzymatic attachment of glucose to amino acids, causing reversible progression from Schiff base to Amadori products and then irreversible formation of advanced glycation end products (AGE's) has intermittently recurred as a mechanism of potential glucotoxicity in many organs, including nerve[352; 375]. AGE are present throughout peripheral nerve[341] and the initial focus was on modification of components of the axonal cytoskeleton that could interrupt axonal transport and axial and radial growth[230] along with modification of basement membrane and extracellular matrix proteins that could impede neuronal regeneration after injury[95; 189]. More recently, glycosylation of ion channels has been implicated in painful diabetic neuropathy[25; 258; 390], as discussed below.

Identification of a receptor for AGE (RAGE) on the surface of neurons, Schwann cells and vascular endothelial cells[377] aligned nerve with other organs prone to damage during chronic diabetes[301]. In other tissues AGE binding to RAGE activates NADPH oxidase with subsequent release of reactive oxygen species (ROS) while RAGE signaling via NF-kB modifies gene expression, promoting inflammation and dysregulation of the survival/apoptosis equilibrium. There is evidence that similar toxic events occur in nerve[358] with recent in vitro studies demonstrating that RAGE signaling potentiates TRPV1-mediated calcium signals and contribute to painful neuropathy[24; 199]. Preclinical studies of agents with anti-AGE/RAGE properties such as aminoguanidine and B vitamins show some efficacy in rodent models of diabetic neuropathy[397] and neuropathic pain[170] while a small-scale clinical trial of the vitamin B1 derivative benfotiamine suggested improvement in pain[339]. However, these agents have other potential mechanisms of action and it should also be noted that RAGE signaling is reported to have beneficial effects in nerve such as promoting neurite outgrowth[306] and that RAGE deletion attenuated indices of neuropathy in diabetic mice.[85]

2.4. Glycolysis: Hyperglycemia-driven increases in intermediates of glycolysis have been linked to diabetic complications, including neuropathy. For example, metabolism of fructose 6-phospate by the hexosamine (glucosamine) pathway produces UDP-*N*-acetylglucosamine, which is highly reactive with proteins, most notably transcription factors, in a process called O-GlcNAcylation. This pathway has been particularly linked with cardiovascular complications of diabetes[265] and a recent study indicates that O-GlcNAcylation regulates remyelination of peripheral neurons after injury so that hyperglycemia-driven abnormal O-GlcNAcylation has the potential to impact nerve structure and function in diabetes[188].

In vascular tissue, glucose-derived diacylglycerol (via glyceraldehyde-3-phophate and phosphatidic acid), is a substrate for protein kinase C β (PKC β) and excess glucose drives elevated PKC β activity which in turn promotes increased vascular permeability and dysfunction[121]. The association of diabetic neuropathy with microvascular disease led to interest in the therapeutic potential of PKC β inhibitors. Following supportive preclinical studies[45], a clinical trial of ruboxistaurin in diabetic patients with neuropathy showed some improvement in skin blood flow, the NTSS-6 questionnaire, which quantified frequency and intensity of aching, burning, prickling, lancinating pain, numbness and allodynia, and in quality of life[48]. However, there was no significant effect on other measures of large and small fiber neuropathy, diminishing enthusiasm in this therapeutic approach.

There is an increasing focus on the role of the intermediate glycation product methylglyoxal in diabetic complications, including neuropathy and neuropathic pain. Methylglyoxal is formed by non-enzymatic dephosphorylation of triose phosphate intermediates of glycolysis (fructose 1,6-biphosphate, glyceraldehyde 3-phosphate and dihydroxyacetone phosphate) and cleared by the glyoxalase pathway. Both excess glycolysis and impaired activity of glyoxalase pathway enzymes may contribute to accumulation of methylglyoxal in diabetes, which reacts with proteins to form AGE's (see above). Mice overexpressing glyoxylase 1 do not develop indices of degenerative diabetic neuropathy[156]. A gain of function property has also been proposed from studies showing that binding of methylglyoxal to the $Na_V1.8$ voltage gated sodium channel in sensory neurons increases excitability[25], while the potential for methylglyoxal to produce pain in diabetes may also be mediated via agonism of the TRPA1 channel in peripheral nerve[191] and spinal cord[126] and induction of the integrated stress response[21]. Recent studies have confirmed the pro-nociceptive properties of methylglyoxal in humans[93] and elevated plasma methyglyoxal has been identified as a risk factor for neuropathy in patients with type 2 diabetes[13]. Approaches to reducing methylglyoxal levels or blocking downstream consequences are in development.

2.5. Mitochondrial overdrive or idling?—It has been argued that increased substrate-driven glycolysis with subsequent Krebs' cycle activity and oxidative phosphorylation (OXPHOS) in mitochondria will result in formation of free radicals that may not be adequately buffered so that there is oxidative damage to local structures. This hypothesis was developed in endothelial cells exposed to short periods of hyperglycemia in vitro[246]. There is little evidence that substrate driven "overdrive" of mitochondrial OXPHOS persists and is toxic to nerve. Exposing Schwann cells to acute hyperglycemia causes an increase in

free radical buffering capacity and does not increase ROS production[374]. In neurons from diabetic rodents, basal respiration is unchanged and maximal mitochondrial respiratory capacity reduced, not increased[60; 410]. This is accompanied by reduced expression and activity of the mitochondrial proteome[7; 61] and dysregulation of mitochondrial biogenesis[49], with aberrant fission/fusion dynamics[303]. It has therefore been proposed that nutrient excess promotes downregulation of mitochondrial function and increasing reliance on glycolysis[106]. This metabolic shift supports normal neuronal function during hyperglycemia but may limit energy-intensive processes such as dynamic plasticity of peripheral terminals in the epidermis and the capacity to respond to other insults. Efficacy of diverse activators of the AMPK/PGC1α pathway, a nutrient sensor system that regulates mitochondrial activity and dynamics, in restoring mitochondrial respiration and preventing or reversing multiple indices of neuropathy and neuropathic pain in diabetic rodents [4; 43; 300; 402] supports this concept.

There is an emerging appreciation that not all cells within the nervous system utilize glucose for ATP production in a similar manner. For example, neurons of the CNS express high levels of pyruvate dehydrogenase (PDH), which controls entry of pyruvate into Krebs cycle and drives OXPHOS, whereas astrocytes have high levels of lactate dehydrogenase, which converts pyruvate to lactate[202]. Utilization of glycolysis-derived pyruvate in astrocytes is also limited by suppression of PDH complex activity via phosphorylation by pyruvate dehydrogenase kinase (PDK). Consequently, these relatively quiescent glial cells rely primarily on glycolysis-derived ATP and indeed may provide lactate to neurons as energy substrate[173]. In contrast, electrically active neurons keep the PDH gateway open and utilize the more efficient generation of ATP by OXPHOS[136]. The metabolic dependence of neurons on glia is highlighted by the report that selective damage to Schwann cell mitochondria results in a neuropathy with damage to both myelin and axons[370]. Diabetes has been reported to increase PDK expression and activity in peripheral neurons and glia, supporting the idea that during persistent hyperglycemia, neurons suppress entry to OXPHOS and rely on glycolysis for ATP production[278]. Conversely, PDK deficiency attenuated multiple indices of neuropathy in diabetic mice including overexpression of TRPV1 and neuropathic pain. How hyperglycemia impacts the distinct metabolic profiles of neurons and Schwann cells has yet to be widely explored but such studies may provide insight into cell-specific mechanisms of glucotoxicity.

3. IMPAIRED INSULIN SIGNALING

The correlation between glycemic control and neuropathy reported in the DCCT study is not overwhelming, while the follow up study (EDIC) failed to show reversal of established neuropathy upon instigation of improved glycemic control[227; 269]. Similar studies of glycemic control in type 2 diabetic subjects did not replicate the DDCT findings for neuropathy[291; 419] and indices of neuropathy are detected in patients with pre-diabetes (elevated fasting glucose levels and/or impaired glucose tolerance) and metabolic syndrome (representing a combination of risk factors for progression to overt diabetes – central obesity, high triacylglycerides and LDL-cholesterol, low HDL-cholesterol, hypertension and hyperglycemia)[266]. A recent study that sub-divided a cohort of 1105 recently-diagnosed diabetics into 5 groups based on multiple metabolic parameters found that peripheral

neuropathy was most prevalent in those with severe insulin-deficient diabetes [407]. Taken together, these observations have driven interest in non-glucotoxic insults that may either act alone or in concert with hyperglycemia[127].

Diabetes can be viewed as a disease of impaired insulin signaling due to insulinopenia and/or insulin resistance. Insulin is structurally similar to the liver-derived peptides insulin-like growth factors 1 and 2 (IGF-1, IGF-2) and shares their growth factor-like properties. Insulin receptors are found on peripheral neurons[35], signal via Akt[129] and activation promotes growth of normal sensory[112] and motor[396] neurons. Conversely, sequestration of local insulin causes peripheral neuropathy in normal rats[35]. Schwann cells also express insulin and IGF-1 receptors and their depletion results in a peripheral neuropathy phenotype with injury to both Schwann cells and axons[135]. Loss of insulin-mediated trophic support represents a primary pathogenic mechanism of diabetic neuropathy that is independent of hyperglycemia. This applies to both type 1 and type 2 diabetes, as studies in type 2 diabetic rodents indicate that insulin signaling is impaired in peripheral nerve[128], so that the nervous system can be considered insulin resistant.

A number of preclinical studies have demonstrated a role for insulin deficiency in diabetic neuropathy and neuropathic pain. Animals injected with STZ at doses that significantly reduce insulin production but do not cause hyperglycemia, go on to develop hyperalgesia in the paw pressure test[294–296]. Insulin-resistant but normoglycemic models of pre-diabetes also develop neuropathy[81] and onset of allodynia to von Frey filaments parallels onset of insulin resistance but precedes onset of hyperglycemia in a model of type 2 diabetes[297]. Conversely, insulin-deficient diabetic rodents treated with trace amounts of systemic insulin for over 1 year to maintain body weight without impacting systemic hyperglycemia showed attenuation of large fiber conduction slowing and did not progress to paw heat hypoalgesia[37]. Most notable are studies in which trace insulin was injected into the footpad[131], infused into the spinal intrathecal space[357] or applied topically to the eye[52] of STZ-diabetic rodents. In each case, treatment prevented functional and structural indices of neuropathy without impacting hyperglycemia indicating that, provided there is adequate insulin-derived trophic support, hyperglycemia is not sufficient to induce neuropathy.

A mechanism of direct insulin action on neurons may involve mitochondria. Insulin increases mitochondrial inner membrane potential when applied direct to sensory neurons derived from normal rats in vitro[150]. Moreover, the reduced inner membrane potential, protein expression and bioenergetics profile of mitochondria from sensory neurons of STZ-diabetic rodents are restored when animals received trace insulin supplementation that also impacted functional and structural indices of diabetic neuropathy without impacting hyperglycemia[3; 61; 150]. This ability to protect against both mitochondrial dysfunction and the neuropathy phenotype also extends to IGF-1[4] with the apparent redundancy perhaps reflecting the importance of the system to cells with consistently elevated energy demands.

Insulin secretion is accompanied by equimolar release of C-peptide, the other product of pro-insulin cleavage. Although initially considered inert, there is evidence that C-peptide has

biological actions in a variety of tissues, including peripheral nerve[324], possibly via an insulin-sensitizing action. As C-peptide prevents and reverses multiple indices of neuropathy[411] and neuropathic pain[180] in animal models of type 1 diabetes[171] and showed efficacy against some manifestations of diabetic neuropathy in a clinical trial[379] it should perhaps be aligned in tandem with insulin when considering primary pathogenic mechanisms of diabetic neuropathy and neuropathic pain.

4. DYSLIPIDEMIA

Major risk factors for developing diabetic neuropathy reflect exposure to impaired insulin signaling/hyperglycemia (age, duration of diabetes and long-term glycemic control) followed by vascular dysfunction (hypertension, smoking) and dyslipidemia (obesity, elevated plasma cholesterol and triacylglycerols)[31]. Clinical evidence linking changes in specific plasma lipids to neuropathy is mixed, with studies that both demonstrated, and failed to demonstrate, associations between elevated triacyglycerols, elevated LDL-cholesterol or reduced HDL-cholesterol and neuropathy. Clinical efficacy of lipid lowering agents such as statins and fibrates against neuropathy is promising, but limited[83; 245; 280; 371]. Nevertheless, there is growing interest in how dyslipidemia may damage peripheral nerves to produce degenerative and painful neuropathy that is driven by recent preclinical studies.

Indices of neuropathy and neuropathic pain are detected in rodents fed high fat diet to induce insulin resistance and dyslipidemia but not overt hyperglycemia[81; 82; 254; 373], although the neuropathy phenotype may be species and strain specific[14]. Many of these disorders are prevented or reversed by treating pre-diabetic, type 1 or type 2 diabetic rodents with diets high in n-3 polyunsaturated fatty acids (PUFA's) to adjust the plasma ratio of n-3:n-6 PUFA [68–70; 200; 318]. Adjusting high fat diets to increase the proportion of monounsaturated fatty acids shows similar efficacy[302] and there is a growing suspicion that long chain saturated fatty acids may therefore be a pro-neuropathic entity in dyslipidemia[248]. Downstream pathogenic mechanisms may include disruption of mitochondrial function and transport in sensory neurons[303]. Dyslipidemia thus joins glucotoxicity and impaired insulin signaling as a potential driver of mitochondrial dysfunction to cause peripheral neuropathy (FIGURE 3).

5. MOLECULAR PATHOLOGY

The preclinical literature on mechanisms of diabetic neuropathy and neuropathic pain is replete with studies describing increased/decreased activity, expression or mRNA of proteins in nerve from diabetic rodents frequently accompanied by data showing that preventing or reversing specific change can impact one or multiple indices of neuropathy and/or neuropathic pain. Studies relating such changes to the primary pathogenic mechanisms discussed above are less frequent. The advent of what are now politely termed unbiased studies has allowed a somewhat less fragmented approach, with technical and bioinformatics advances supporting analysis of large data sets and identification of clusters of differentially regulated genes for pathway analysis.

5.1. Gene expression and regulation: Initial approaches used oligonucleotide microarrays and target amplification to identify differentially regulated genes in autonomic and sensory ganglia of type 1 diabetic rats [47; 272] and emphasized changes that preceded onset of functional and structural damage. Studies followed characterizing expression profiles of mouse models of type 1[56] and type 2 diabetes[142; 251; 262] and pre-diabetes[249], contrasting profiles of type 1 vs type 2 diabetic mice[130; 152] or diabetic rodents with or without an intervention that corrected indices of neuropathy[78; 84; 221; 401; 409] or specifically painful neuropathy[401]. Expression profiles of nerve biopsies from humans with diabetes have also been reported[153; 210; 229]. Common themes emerging from these studies largely echo the suspected pathogenic mechanisms described above such as glucose and lipid metabolism, oxidative stress and mitochondrial dysfunction. Additional abnormal gene expression clusters implicate impaired cytoskeletal organization, nerve growth and regeneration, inflammatory/immune system activity and signaling through MAPK, JAK/STAT and AMPK pathways. These studies have also driven the growing suspicion that neuropathy in type1 and type 2 diabetes has many molecular dissimilarities and the recent heightened interest in dyslipidemia as a primary pathogenic mechanism of diabetic neuropathy[101].

Both the production and degradation of mRNA and its subsequent translation are modified by interactions between the mRNA and the RNA-induced silencing complex (RISC) which consists of assorted proteins (the RNAse DICER, argonaute family proteins etc) and single stranded non-coding microRNA's (miRNA). This mechanism of gene silencing adds additional layers of control and complexity, particularly as each gene can be silenced by many miRNA's and each miRNA can target multiple genes. Polymorphisms of specific miRNA's are associated with susceptibility to peripheral and autonomic neuropathy in patients with type 2 diabetes[63; 64] and miRNA have attracted recent interest both as potential contributors to the pathogenesis of diabetic neuropathy and as sites of therapeutic intervention[326]. Examples are shown in TABLE 2 [5; 53; 56; 105; 132; 148; 149; 164; 185; 215; 319; 381; 384; 394; 405; 412]. While changes in miRNA are frequently linked with such downstream pathogenic mechanisms of diabetic neuropathy as inflammation, oxidative stress and impaired neuronal growth and regeneration the primary events that trigger disruption of miRNA expression have yet to be defined. Manipulation of miRNA is an emerging therapeutic approach in which identifying nerve-specific targets or delivery systems will be critical for ensuring appropriate safety profiles that will allow translation to clinical use.

5.2. Structural proteins: Early interest in dysfunctional axonal transport as a cause of distal degenerative neuropathy promoted interest in proteins of the axonal cytoarchitecture, with tubulin, neurofilament sub-units and associated proteins variously reported as being over or under expressed, glycated, glycosylated, polymerized and/or phosphorylated[111; 230; 311]. Proteins of the extracellular matrix also show post-translational modifications[10; 95]. Potential structural consequences include reduced axonal caliber and associated large fiber conduction slowing [238] and delayed axonal regrowth following focal lesions as reported in diabetic rodents[172] and humans[186], although fast axonal transport velocities are unchanged[1]. Altered expression or post-translational modification of myelin structural

proteins such as myelin basic protein (MBP), myelin associated glycoprotein (MAG), myelin protein 0 (P0 or MPZ) and peripheral myelin protein 22 (PMP22) are also reported[102; 277; 299]. Unfortunately, appropriately fixed nerve of diabetic rodents does not display overt myelin pathology similar to that reported in animals were these proteins are selectively ablated.

5.3. Trophic factors: The growing repertoire of trophic factors and their receptors that modulate nerve phenotype and function has been frequently accompanied by the discovery of reduced mRNA, protein, receptor and/or signaling in peripheral neurons, Schwann cells or target organs of diabetic rodents and thereafter by reports that delivery of the trophic factor gene or protein, mimetics, inducers or agonists corrects indices of neuropathy in the same. Examples include NGF[109; 141], CNTF[40; 42; 240], NT-3[110; 238], IGF-1[4; 154; 414] GDNF[62; 212], bFGF[244], HGF[181], G-CSF[187], MMP2[10], hedgehog proteins[38]. There are also reports of diabetes-induced increased expression of trophic factors, as occurs with BDNF[108] and both HIF-1 and its target gene VEGF[50; 307], that are attributed to responses to injury or compensation for loss of other trophic support systems. VEGF delivery improves indices of neuropathy in diabetic rodents [151; 292; 310], while the role of BDNF is more complex. Acute spinal delivery of BDNF causes tactile allodynia in normal rats and sequestration of endogenous spinal BDNF alleviates tactile allodynia and restores H-wave RDD (see above) in diabetic rats[206]. In contrast, chronic spinal delivery of BDNF to diabetic rats alleviated hyperalgesia[207]. In some cases, altered neurotrophic support has been linked to downstream consequences of hyperglycemia. For example, hyperglycemia-driven increased flux though the polyol pathway leads to reduced nerve levels of the Schwann cell derived factors NGF[256] and CNTF[237] and ARI treatment prevents diabetes-induced elevated Trk-C receptor mRNA expression [322]. However, the pathogenesis of most neurotrophic factor deficits in diabetic nerve remains unknown and clinical trials using trophic factors have not been promising[16; 103; 391], with the exception of early HGF trials against neuropathic pain[6] and a neurotrophic erythropoietin analog against pain and corneal nerve loss[33].

5.4. Cytokines and inflammatory pathways: There is little evidence from human studies that diabetic neuropathy represents a typical inflammatory neuropathy. Chronic inflammatory demyelinating polyneuropathy occurs in diabetic patients but is readily distinguished from diabetic symmetrical polyneuropathy[279]. Animal models of diabetes also lack marked inflammatory infiltrates, although there are reports of transient increases in the number and activation of peripheral nerve macrophages [67; 247] and spinal microglia[363]. The absence of large increases in inflammatory cell numbers is not surprising due to the physical constraints on tissue expansion imposed by the epineurium and spinal column. Glial cells of the PNS and CNS play many roles associated with peripheral inflammatory cells following nerve injury, including release of cytokines and chemokines[92] and clearance of myelin debris[162]. As recently reviewed in detail elsewhere [289] this neuroinflammatory system is increasing recognized as being dysregulated in diabetes.

There are multiple reports of changes in both pro- and anti-inflammatory cytokines and chemokines in the nervous system of diabetic rodents. The most widely studied are increases in the pro-inflammatory cytokines IL-1β, IL-6, TNFα and interferon-γ, [420] along with changes to downstream transcription regulators such as NF-κB and Nrf2[197]. Expression of bradykinin B_1 and B_2 receptors by microglia and neurons is also increased in the spinal cord of diabetic rodents[46; 345] and receptor antagonists alleviate indices of pain[345]. Pathogenic consequences include induction of enzymes such as COX-2[182; 284] and isoforms of nitric oxide synthase[417] that can drive tissue damage via ischemic hypoxia and oxidative/nitrosative stress thereby contributing to both degenerative neuropathy and initiation or amplification of neuropathic pain[116]. For example, induction of COX-2 and subsequent release of prostaglandins from spinal oligodendrocytes[284] and release of pro-inflammatory cytokines[345] and BDNF[241] from activated microglia have been linked to spinally-mediated pain in diabetic rodents. Increased chemokine/receptor signaling, including CCL1/CCR8[422], CXCL12/CXCR4[160], CXCL13/CXCR5[214] and others[421] is also linked to neuropathic pain in diabetic rodents. The primary pathogenesis of many of the reported changes to the neuro-inflammatory system remains to be determined, although hyperglycemia driven flux through the polyol pathway may be involved in some aspects[157; 284; 336]. Therapeutic approaches around manipulation of the neuro-inflammatory system tested in diabetic rodents range from microglial inactivators[241; 420], COX inhibitors[268; 284], TNFα inactivators[399] or inhibitors[90], overexpression of anti-inflammatory cytokines[349], antagonists to pro-inflammatory cytokines[139], chemokine neutralizing antibodies[293] and chemokine receptor antagonists[176; 232]. Efficacy of stem cells [138; 387] and natural products [78; 167; 255] against aspects of diabetic neuropathy may also be at least partly due to their anti-inflammatory properties. To date, clinical trials have not been successful[176].

5.5. Death and Survival Pathways: Dysregulation of cytoplasmic calcium has been implicated in many neurodegenerative diseases, given its role in triggering autophagic, necrotic and apoptotic pathways[51; 124]. Steady state cytoplasmic calcium concentrations are regulated by pumps located in mitochondria and endoplasmic reticulum and these organelles serve as calcium stores. Steady state cytoplasmic calcium concentrations are increased in sensory neurons from diabetic rodents[369] and this is associated with impaired calcium reuptake into endoplasmic reticulum by the sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump[413]. Subsequent depletion of calcium in the sarcoplasmic reticulum produces ER stress which can precipitate cell death[308] and this mechanism has been integrated into schema of potential pathogenic mechanisms of diabetic neuropathy[250]. It is not yet known whether mitochondrial calcium pumps, such as the mitochondrial calcium uniporter (MCU) complex and voltage-dependent anion channel (VDAC) are dysfunctional in diabetes.

Reports describing marked expression of components of apoptotic death pathways in the peripheral nerve of short-term diabetic rodents[304; 309] were initially difficult to reconcile with the slowly evolving loss of neurons and axons in these models and clinical descriptions of a distal degenerative neuropathy. Later work reported that increased caspase-3 in nerve was not associated with structural features of apoptosis such as nuclear fragmentation and

that DNA-repair mechanisms were activated, suggesting that peripheral nerve utilizes endogenous defence mechanisms to block progression from caspase-3 activation to apoptosis[57]. Over-activity of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP) has itself been linked to a mechanism of nerve injury[219]. Elevated PARP and other survival and repair markers such as heat shock protein 27 (HSP27)[282; 418] and growth associated protein 43 (GAP43)[131] in the nerve of diabetic rodents has encouraged the view that peripheral nerve is exposed to chronic stress arising from one or more of mechanisms described above but can largely tolerate and repair metabolic injuries, paralleling to the way that it survives and repairs physical injury. Therapeutic approaches that strengthen endogenous survival and repair mechanisms include overexpression of HSP 27[193] and inhibition of HSP90 to induce HSP70, a molecular chaperone protein with multiple neuroprotective properties including protecting mitochondrial function and reducing inflammation and oxidative stress[221]. HSP90 inhibitors reverse multiple indices of neuropathy in diabetic rodents and are currently in clinical development[104]. Conversely, the emerging appreciation that there are endogenous systems that constrain nerve growth has provided opportunity to intervene and thereby promote nerve growth and regeneration pathways[94]. For example, the tumor suppressor molecule PTEN (phosphatase and tensin homolog deleted on chromosome 10) inhibits the PI3K-pAkt neuronal growth pathway[195] and is upregulated in sensory neurons from diabetic animals while knockdown of PTEN improved the otherwise impaired nerve regeneration following crush injury in STZ-diabetic mice[327].

5.6. Membrane pumps: NCV slowing in short-term diabetic rodents that lack overt damage to axons or myelin led to interest in changes to nodal ion pumps that facilitate saltatory conduction in myelinated fibers. Chief of these was the Na^+/K^+ ATPase, given its role in maintaining and restoring resting membrane potential. Reduced maximal pump activity in membrane fragments associated with reduced protein expression was widely studied as a potential cause of NCV slowing and is downstream of hyperglycemia driven polyol pathway activity[125]. However, Na^+/K^+ ATPase pump activity is not impaired in intact endoneurial preparations from diabetic rodents[217] so the physiological relevance is unclear. Increased expression and activity of the Na+/H+ pump has also been reported in nerve of diabetic rodents and inhibition of the pump reversed functional and structural indices of neuropathy and neuropathic pain[220]. Overactivity of this pump increases cytoplasmic pH, glucose uptake and glycolysis, thereby having the potential to trigger multiple pathogenic mechanisms.

In the spinal cord, reduced expression of the potassium-chloride co-transporter 2 (KCC2) pump, which maintains the chloride gradient across neuronal membranes, has been linked with loss of GABAergic inhibitory function and neuropathic pain in diabetic rats[205]. KCC2 expression is suppressed by the neurotrophic factor BDNF and increased BDNF levels in central projections of primary afferents in diabetic rats suggest that the primary lesion may be of peripheral origin[205], although it has also been linked to activated spinal microglia[241]. The electrophysiological consequence of disrupted spinal GABAergic inhibitory tone in diabetic rodents is loss of rate dependent depression (RDD) of the H wave[206], which is secondary to impaired insulin signaling rather than

hyperglycemia[226]. Loss of RDD may serve as a biomarker for identifying a sub-set of diabetic humans in whom painful neuropathy includes a contribution from spinal disinhibition[226].

5.7. TRP channels: Transient receptor potential (TRP) channels are a family of non-selective cation permeable channels that transduce diverse extracellular stimuli into acute and chronic neuronal responses via influx of calcium[174]. TRPA, TRPV and TRPM family members are modulated by endocannabinoids, which may contribute to the analgesic properties of these substances[243]. There is substantial preclinical evidence that dysregulation or dysfunction of TRP channels may contribute to neuropathic pain in diabetes.

The TRPV1 channel, known for transducing the burning sensation of capsaicin, is activated by a range of physiological and pathological stimuli including heat, low pH, pro-inflammatory molecules and endocannabiniods. TRPV1 currents are also enhanced by insulin and IGF-1[368] and by the TRPM8 receptor[260]. An initial report [145] indicated that membrane bound TRPV1 protein is increased in DRG from diabetic rats, along with the channel phosphorylation state and both capsaicin and proton activated currents while TRPV1 protein expression increased in large sensory neurons and decreased in small sensory neurons. The pattern of TRPV1 protein expression and whole cell currents in the DRG and spinal cord of diabetic rodents paralleled progression from heat hyperalgesia to hypoalgesia[261] and increased TRPV1 expression at peripheral and central terminals of primary afferents has been implicated in allodynia to von Frey filaments[74]. Agents that reduce TRPV1 expression, antagonize TRPV1 or ablate it also alleviate thermal hyperalgesia and tactile allodynia in diabetic rats[17; 209]. Involvement in diabetic neuropathy beyond indices of pain is suggested by a report that TRPV1 agonists given to normal mice produce multiple indices of small fiber neuropathy including IENF loss[204]. Upstream events that may drive TRPV1-mediated pain include increased insulin, RAGE and protein kinase C activity[24; 368] and hypoxia[287]. Little is known about other TRPV family members, although a recent study reported that a selective TRPV4 channel antagonist blocked mechanical, but not cold, allodynia in diabetic mice[87].

Early indications of a role for the irritant sensing TRPA1 channel in diabetes-induced hyperalgesia came from studies with TRPA1 antagonists that alleviated allodynia to von Frey filaments and mechanical hyperalgesia[388; 389]. Cold allodynia in diabetic mice has also been attributed to TRPA1 activity[143]. Diabetes enhances channel activity without inducing TRPA1 protein expression in DRG of diabetic animals[288]. As discussed above, a pathogenic mechanism linking hyperglycemia with TRPA1 channel activation via methylglyoxal binding to the channel has been proposed[100; 192] and there is also a recent report linking TRPA1-mediated hyperalgesia in diabetic rodents to local hydrogen sulfide[288].

Protein for the cold/menthol sensing TRPM8 channel is elevated in the DRG of STZ-diabetic rats with concurrent cold allodynia[403]. Conversely, agonist activated TRPM8 currents are decreased in DRG of STZ-diabetic mice[260] and in normal DRG cells following exposure to methylglyoxal[66]. While this does not appear to be consistent with a

role for methylglyoxal in diabetes-evoked pain (see above), it has been argued that loss of TRPM8 activity enhances other TRP channel activities associated with neuropathic pain[260]. There is clearly room for additional studies in this area.

5.8. Voltage gated calcium channels: Gabapentin and pregabalin, widely used to treat painful neuropathy in diabetic patients[9], target the α2δ–1 sub-unit of voltage gated Ca^2 channels[22]. This sub-unit regulates the trafficking and activation kinetics of pore-forming α1 sub-units and thus surface expression and activity of voltage gated Ca^2 channels ([264]). The plasmalemma of sensory neurons contains multiple voltage-gated Ca^{2+} channels, including L-type ($Ca_v1.2$ and Ca_v 1.3), N-type (Ca_v 2.2), R type (Ca_v 2.3) and T-type (Ca_v 3.2 and Ca_v 3.3). Of these, the most extensively studied in the context of diabetic neuropathy is the T-type (Ca_v 3.2) calcium channel [354]. This channel shows altered kinetics due to post-translational modification by glycosylation under hyperglycemic conditions accompanied by enhanced gene expression and glucose-regulated trafficking[203; 390]. A role in neuropathic pain is suggested by reports that diverse interventions that target the $Ca_v3.2$ channel reverse allodynia to von Frey filaments and thermal hyperalgesia in diabetic rodents[117; 201; 233; 253]. Clinical trials of T-type calcium channel antagonists, including one that used the innovative design of using microneurography to pre-select diabetic subjects with both pain and spontaneously active C fibers[317] have yet to show efficacy[184; 415].

Increased mRNA for sub-units of the P/Q, but not N, type calcium channels have been reported in DRG of STZ-diabetic mice[365] and a P/Q and R type channel antagonist alleviated allodyina to von Frey filaments in STZ-diabetic rats and mice[77]. Reports of increased L-type currents in both primary afferent and dorsal horn neurons of STZ-diabetic rats[194; 376] have promoted studies of efficacy of the L-type channel antagonists against hyperalgesia[323] while efficacy against other indices of peripheral neuropathy were largely attributed to indirect effects via improved blood flow[28].

5.9: Voltage gated potassium channels and HCN channels: Given the importance of potassium channels in regulating axonal excitability there are relatively few studies implicating them in the pathogenesis of diabetic neuropathy and neuropathic pain. Expression of the voltage-gated K_v channel subunits $K_v1.2$ and $K_v1.6$, but not $K_v1.1$, was reduced in small neuronal cell bodies of the DRG in STZ-diabetic rats coincident with reduced K+ currents and these changes were linked to enhanced C-fiber excitability and hyperalgesia[382]. Most recently, voltage gated K_v7 (KCNQ) channels, which produce a slow non-inactivating outward K^+ current also called the M current due to its modulation by muscarinic antagonists[392], have been examined. There was decreased mRNA and protein for the $K_v7.2$, $K_v7.3$ and $K_v7.5$ channels in the DRG of STZ-diabetic rats accompanied by reduced M current density and increased neuronal excitability[406]. A K_v7 channel activator reduced neuronal excitability and alleviated allodynia to von Frey filaments and thermal hyperalgesia

Hyperpolarization-activated and cyclic nucleotide-gated channels (HCN1–4) are a distinct category of voltage-gated ion channels whose threshold potentials are regulated by cyclic nucleotides and that have been implicated in neuropathic pain states[361]. Inhibition of

HCN's1–4 or ablation of HCN2 alleviated allodynia to von Frey filaments but not thermal hypoalgesia in diabetic mice[360]. Expression of HCN1–4 protein was not altered in the peripheral nerve of diabetic mice and it was speculated that a measured increased in intracellular cAMP might activate HCN2 and thus increase primary afferent firing.

5.10. Voltage gated sodium channels: Voltage-gated sodium channels (VGSC: $Na_V1.1$–1.9) are critical regulators of neuronal excitability and the discovery of gain of function mutations to $Na_v1.7$, $NA_v1.8$ and $Na_v1.9$ in human small fiber "channelopathy" pain states [333] has focused interest on the potential role of VGSC in painful diabetic neuropathy. Diabetes alters currents and protein expression of a variety of VGSC: $Na_v1.8$ protein expression is consistently reported as being decreased [73; 146; 257] with a parallel increased phosphorylation or post-translational modification by methylglyoxal (see above) considered indicative of activation[25; 147]. Others, such as Na_v's 1.1, 1.2, 1.3, 1.7 and 1.9 show increased protein expression[73; 146; 147; 328], while there is disagreement over the fate of $Na_v1.6$ [73; 146; 286]. Interestingly, around 10% of a cohort of patients with painful diabetic neuropathy expressed rare $Na_v1.7$ variants, some of which were gain of function variants[29]. These patients tended to report more severe burning pain and increased pressure sensitivity. A gain of function variant to the β sub-unit of VGSC has also been identified in a patient with painful diabetic neuropathy[11] while a recent genome wide association study of type 2 diabetics with or without pain has drawn attention to $Na_v1,2$ ([347]).

There have been a number of studies that have manipulated VGSC activity. Antagonists of overexpressed VGSC have been studied for their ability to block indices of neuropathic pain in both preclinical and clinical studies[353]. In diabetic rodents indices of neuropathic pain have been reduced by the non-selective VGSC blockers lidocaine[41] and mexiletine [400], by selective knockdown of $NA_v1.3$,[346], by induction of miR-96 to reduce $Na_v1.3$ expression[5] and by blockers of $Na_v1.7$[385] and $Na_v1.8$[367]. Topical lidocaine has shown efficacy against painful diabetic neuropathy [393] and is used off-label[9]. A clinical trial of a $Na_v1.7$ blocker in subjects with painful diabetic neuropathy showed only minor effects[228], perhaps reflecting the cohort of subjects in whom pain could be due to a variety of diabetes-related mechanisms. While the pathogenesis of altered expression and/or function of VGSC is not clear, other than relatively rare gain of function mutations and a link to hyperglycemia via increased glycolysis and methlyglyoxal for modification of $Na_v1.8$ activity[25], there is an interesting suggestion that mutations in $Na_V1.7$ may be a primary cause of both painful diabetic neuropathy and diabetes itself due to the location of this channel on both primary sensory neurons and pancreatic β cells[144].

5.11. Neurotransmitters and receptors: Purinergic P2X receptors are ligand (ATP)-gated non-selective cation channels location on neurons, Schwann cells and microglia[36]. There is increased P2X2R and P2X3R expression and current density in DRG of STZ-diabetic rats and mice and increased P2X4R expression by satellite glial cells[348]. Increased gene expression of P2X3R in diabetic rats has been linked to demethylation of the *p2x3r* gene[408]. Involvement of P2XR in pain is suggested by reports that peripheral and intrathecal delivery of antagonists alleviated tactile and thermal hyperalgesia in diabetic

animals[234; 348; 395; 408]. Increased activity of receptors located at synapses and on adjacent microglia has the potential to enhance primary afferent input and spinal sensitization of sensory processing.

The spinal cord of diabetic rodents shows increased glutamate and substance P ligand binding [179; 208] and increased mRNA for subunits of glutamatergic NMDA and AMPA receptors [355]. The NMDA NR1 and NR2B subunits also show and increased phosphorylation (activation) [80; 155] secondary to elevated protein tyrosine phosphatase activity[342]. NR2B expression is also increased in a model of pre-diabetes[342]. These findings are consistent with efficacy of spinally delivered NK-1 and NMDA antagonists against allodynia and hyperalgesia in diabetic rodents [39; 71; 79; 298]. Unfortunately, side-effect free targeting of spinal excitatory receptors as a strategy to treat painful diabetic neuropathy has been largely unsuccessful to date.

Of the spinal inhibitory receptors, $GABA_A$ expression is unchanged by diabetes[169] but inhibitory function is diminished secondary to reduced KCC2 activity (see above), while $GABA_B$ expression is reduced[383]. Both basal and stimulus-evoked spinal GABA levels are increased in diabetic rats[225] and may contribute to pain via dysfunctional $GABA_A$ receptors, as $GABA_A$ antagonists alleviate allodynia and hyperalgesia[169] whereas activation of $GABA_B$ receptors shows the expected inhibitory effects[213]. Multiple serotoninergic receptor agonists have been shown to alleviate indices of pain in animal models of diabetes, including agonists or indirect activators of $5\text{-}HT_{1A}$,[163] $5HT_{2A/C}$[236] and $5HT_7$[364] receptors. While spinal expression of $5HT_{2A}$ receptors is unchanged by diabetes[267], efficacy of duloxetine, a selective serotonin reuptake inhibitor approved for use against pain in diabetic patients[9], is via activation of these receptors in the spinal cord of diabetic rats[236]. Muscarinic M_2 receptors are increased in spinal cord of diabetic rats[55] and facilitate the antinociceptive actions of cholinergic agonists operating via $GABA_B$ receptors[54].

While increased expression and/or activity of ion channels and receptors may lead to hypersensitive or destabilized primary afferents and inappropriate electrical activity, the contribution of peripherally drive to pain in diabetes may be offset by progression to a degenerative neuropathy phenotype. No matter how electrically active a primary afferent becomes, it is effectively silent if it cannot release adequate neurotransmitter at the spinal dorsal horn. For example, in diabetic rats there is an early reduction in the synthesis[89], transport[356] and stimulus-evoked spinal release of both neuropeptide[44; 119] and amino acid[225] excitatory neurotransmitters that is concurrent with enhanced pain-associated behavior in the same animals. There is also a progression from increased, to loss of, synaptic markers in the spinal cord of diabetic rats[166; 211]. Pain generator sites may evolve over time, with initial pain driven by a hypersensitive or hyperactive periphery but progressing to spinal and CNS generator/maintenance sites as primary afferent input fades with first neurochemical, then physical, degeneration. Longitudinal clinical studies in subjects with diabetic neuropathy, using such techniques as microneurography[317], RDD[226] and MRI[314] to track activity of generator sites over time may be of value.

6. SUMMARY

A PubMed search at 7pm PST on 14th February 2020 using the search phrase “diabetic neuropathy treatment” returned 17,238 hits – a lot of words for a condition with no approved therapy. It is challenging to reconcile the plethora of biochemical and molecular changes in the nervous system of diabetic rodents described above with their mildly dysfunctional neuropathy phenotype and limited nerve pathology. It is also remarkable that so many highly selective interventions against specific pathways are completely effective in preventing or reversing indices of neuropathy and pain, despite presumably continued operation of multiple other documented pathways. The sheer volume of effective interventions must raise concerns about the relevance of preclinical models and assays to the clinical condition. Experimental models of diabetic neuropathy are perhaps best viewed as hypothesis-generating tools that offer a veritable cornucopia of potential pathogenic events and plausible targets for therapeutic intervention against neurodegeneration and pain (Figure 4). Relatively few of the biochemical and molecular changes described above have been confirmed in humans and, when they are, it is not easy to determine whether altered protein expression and/or activity has physiological and pathological consequences or is itself a consequence of neuropathy.

The challenge before us remains the same as it was over half a century ago following the advent of aldose reductase inhibitors[190] - namely translating mechanisms and interventions identified in preclinical models of diabetes into viable therapies to prevent and reverse diabetic neuropathy and neuropathic pain. Agents that appear promising in preclinical studies have consistently failed in clinical trials against degenerative diabetic neuropathy and there has been plenty of subsequent finger pointing, from allegations of poor drug design and unrepresentative animal models to flawed clinical trial designs and outcome measures[107; 222]. Encouragingly, recognition and analysis of prior failings [222] has prompted development of focused in vitro models to aid mechanistic and drug screening studies[118], animal models that more closely resemble the human diabetic condition [404], refinement of clinical protocols [32] and introduction of outcome measures such as nerve fiber density in the skin and cornea that highlight small fiber neuropathy[222; 276]. In contrast to degenerative neuropathy, there are a number of therapies approved by regulatory agencies to alleviate pain in diabetes, and others that are used off-label [9; 18]. However, it is notable that none were developed to target diabetes-specific mechanisms while efficacy is both unpredictable and restricted to small sub-sets of patients (NNT>5–10) [113]. Refinement of models of neuropathic pain and of assays towards those that incorporate more complex cognitive functions may improve the predictive value of preclinical studies[88] and have begun to be used in models of diabetes[378]. There is also a growing appreciation that pain in diabetic patients falls into distinct sub-types [20], potentially reflecting different dominant pathogenic mechanisms and thus responsiveness to targeted therapeutic interventions. Drugs not statistically effective against pain in an unrefined cohort have been shown to be effective in a sub-group defined by pain mechanism[86], and clinical trial designs are beginning to incorporate patient stratification based on the likely mechanism of both pain generation and the agent under investigation[317]. Together, these advances may allow the identification and development of translatable therapies that are tested against the

mechanistically-appropriate population and open an encouraging gateway into the world of personalized medicine.

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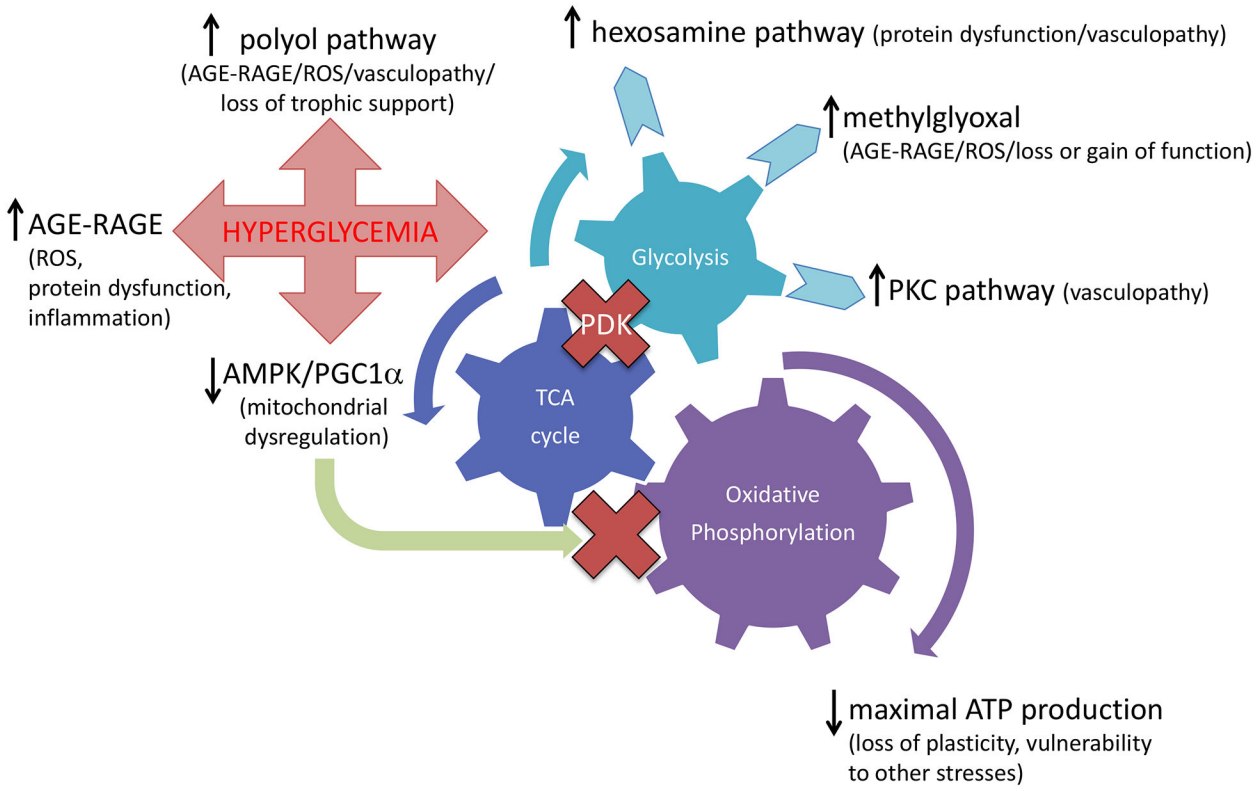

Figure 1: Mechanisms of glucotoxicity in diabetic neuropathy.

Hyperglycemia has been considered central to the pathogenesis of diabetic neuropathy and multiple mechanisms have been proposed from both preclinical studies and clinical observations (see text for details).

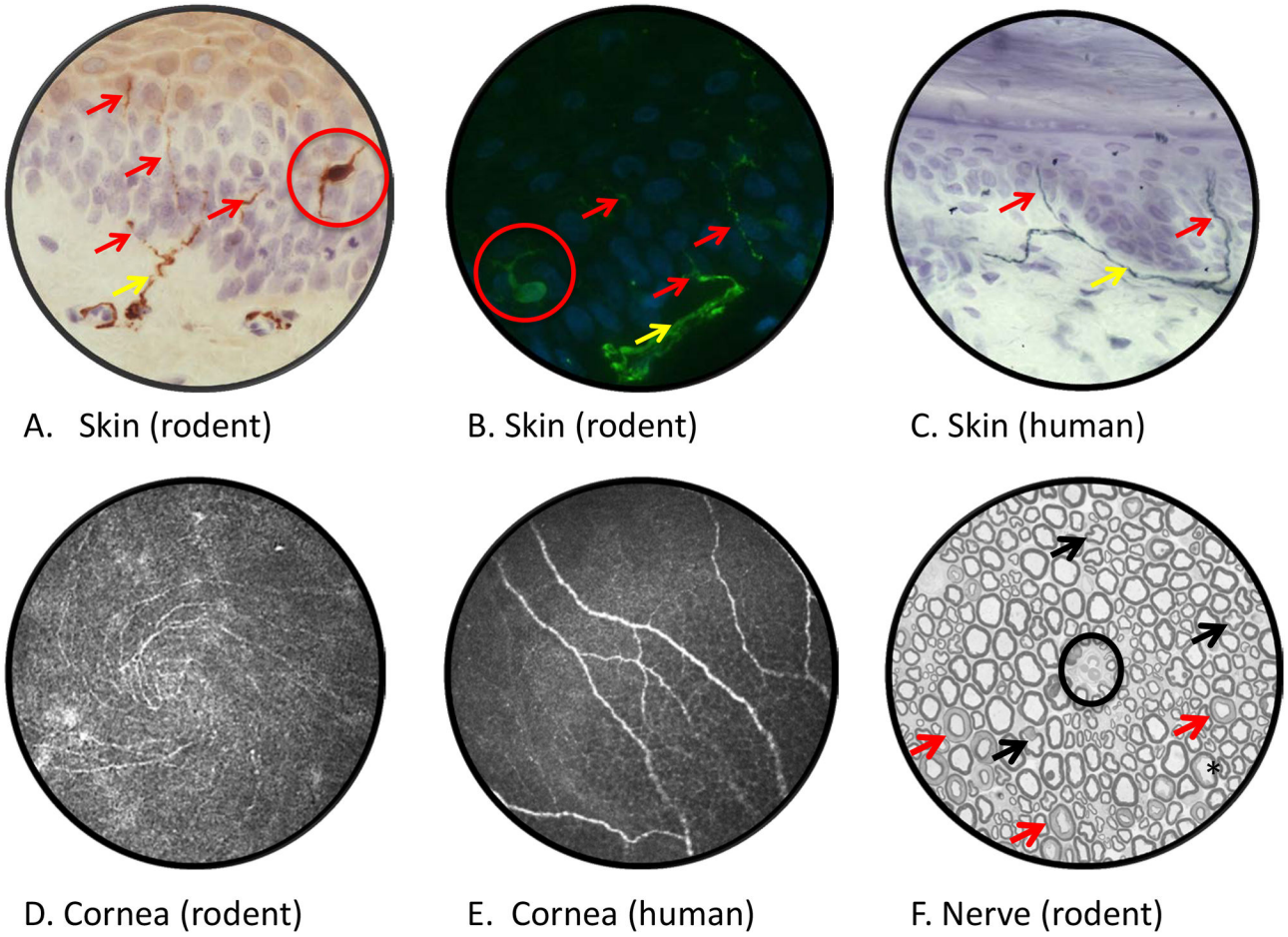

Figure 2: Imaging diabetic neuropathy.

Rat plantar skin stained with antibody to PGP9.5 and viewed by bright field (panel A) or fluorescence (panel B) microscopy reveals dermal nerves (yellow arrows) projecting across the dermal:epidermal junction and into the epidermis (purple/blue counterstained nuclei) where they form profiles of intra-epidermal nerve fibers (red arrows). Note that PGP9.5 also stains epidermal Langerhans cells (red circles). Diabetic rodents and humans (panel C) show early reductions in IENF density that are associated with both sensory loss and pain [23, 276]. Confocal images of the corneal sub-basal nerve plexus of a live mouse (panel D, showing inferior whorl) and human (panel E]. Reduced corneal nerve morphometric parameters are detected within weeks of onset of diabetes in rodents [52] and in early stages of clinical diabetic neuropathy [276]. A cross section of sciatic nerve from a STZ-diabetic rat (panel F), with an endoneurial blood vessel at the centre of field (black circle), lacks overt evidence of the axonal degeneration or demyelination common in nerve biopsies from diabetic patients. Apparently mis-shapen axons (black arrows) represent normal paranodal regions of the nerve fiber while multiple myelin profiles illustrate normal Schmidt-Lanterman incisures (red arrows). Mild axonal fixation artifact is illustrated by the black star. Morphometric analysis identifies reduced mean axonal diameter in the absence of significant fiber loss, indicative of axonal atrophy or impaired maturation. Technical details of procedures used to generate these images and representative data showing the effects of

diabetes are published [168]. Images by Ms. Katie Frizzi, Ms. Lucie Guernsey and Ms. Alex Marquez.

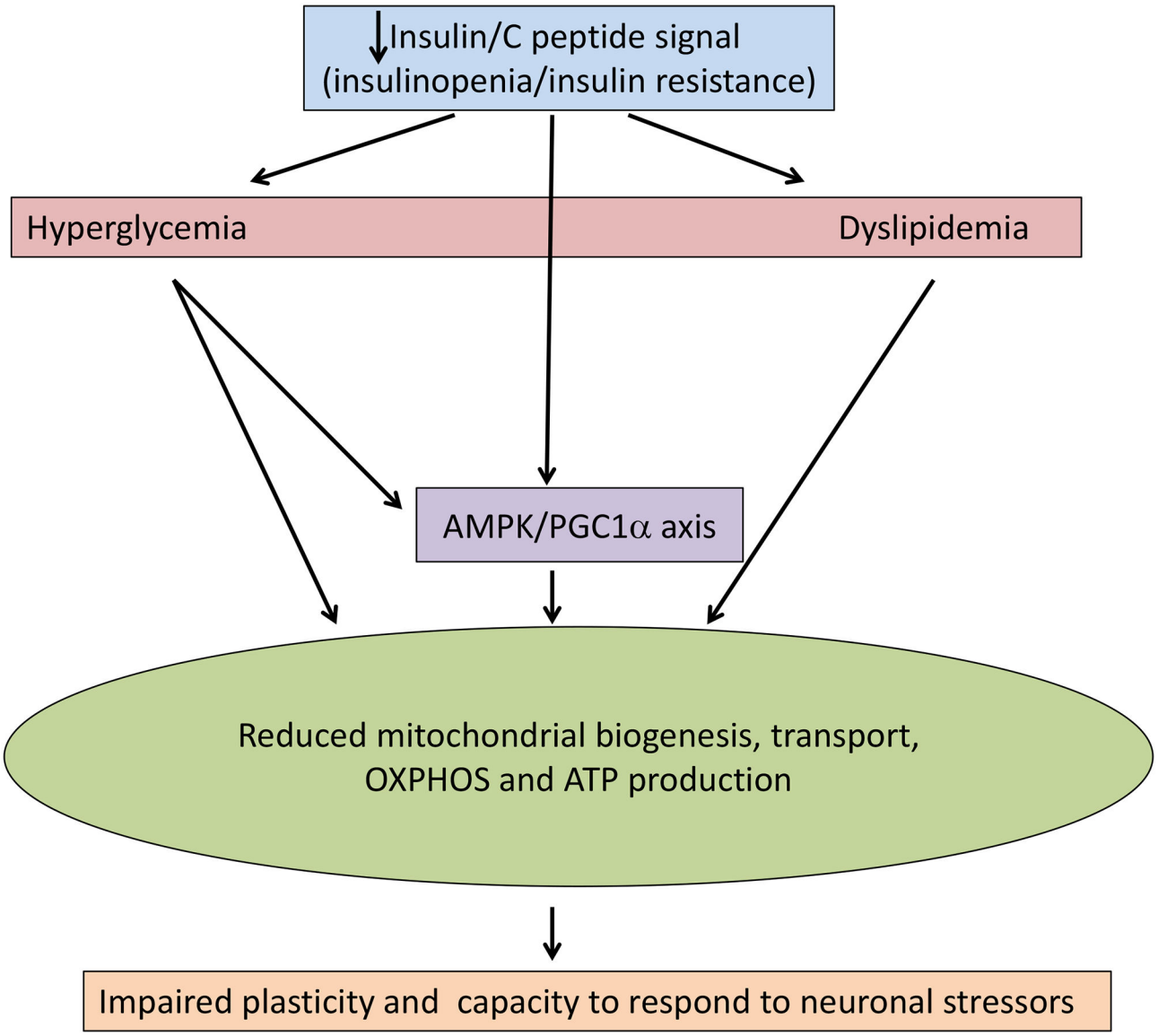

Figure 3: A convergence of pathogenic mechanisms?

There is accumulating evidence that the primary initiators of pathogenic cascades leading to diabetic neuropathy, impaired insulin signaling, hyperglycemia and dyslipidemia share a common pathway through disruption of mitochondrial bioenergetics.

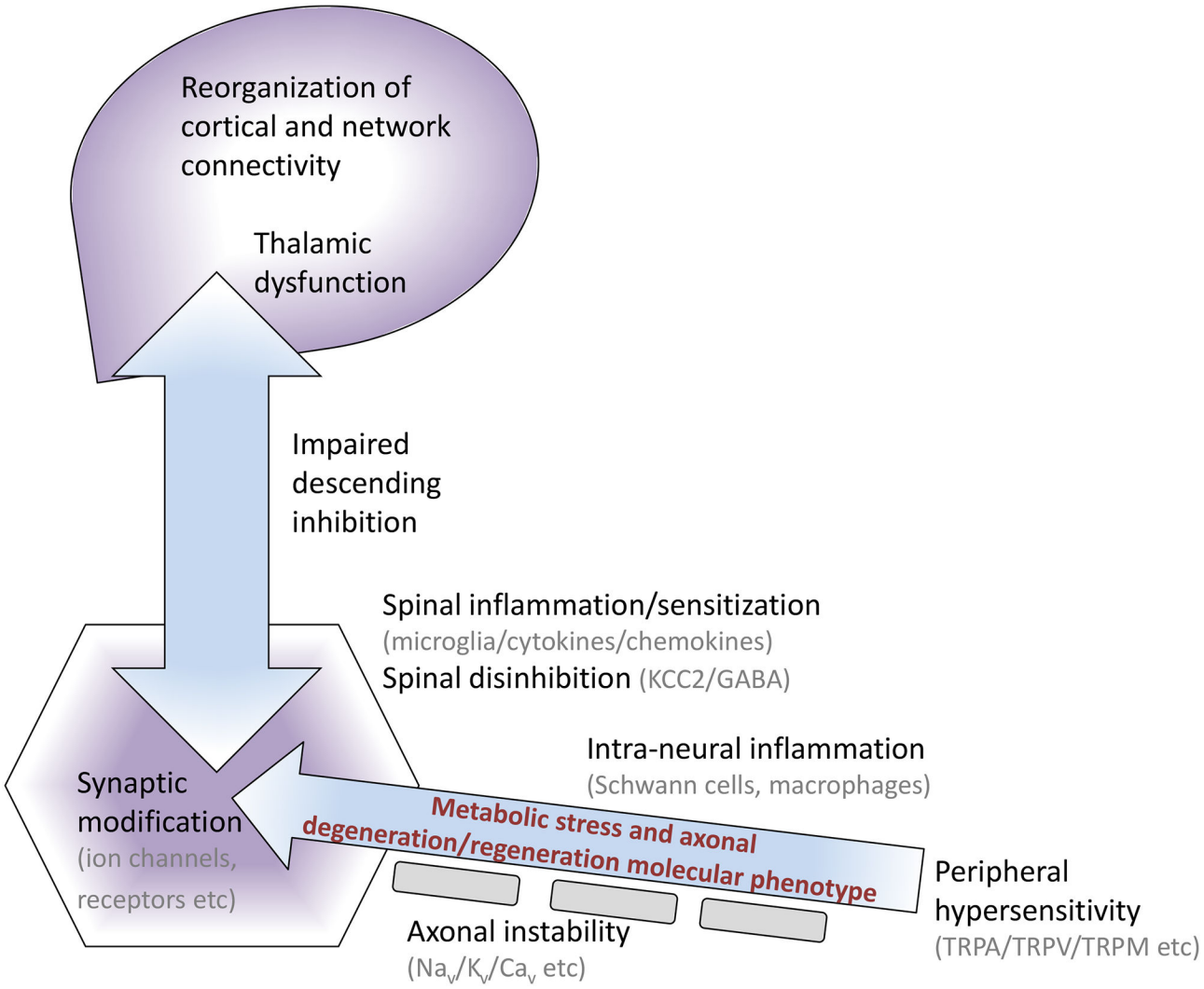

Figure 4: A plethora of potential pain precipitating pathways?

Animal models of diabetic neuropathy develop molecular and functional disorders throughout the neuraxis that have the potential to generate or amplify pain and thus serve as targets for therapeutic intervention. The majority of these disorders have yet to be validated in the human condition.

TABLE 1.

Potential biomarkers for painful vs painless diabetic neuropathy.

Studies where no change was detected are shown in italics.

Type	Tissue	Biomarker for painful neuropathy	Representative Publications
STRUCTURAL (PNS)	Nerve biopsy	Small fiber damage and regeneration	[34,216,224]
	Skin biopsy	Increased regeneration and/or axonal swellings	[30,58,59,114]
	Cornea	Increased corneal nerve loss	[177,178,226,276]
		Increased corneal nerve branching	[274]
STRUCTURAL (CNS)	Cortex	Atrophy of somatosensory cortex	[314]
FUNCTIONAL (PNS)	Nerve	Increased epineurial blood flow	[99]
	Skin	Impaired stimulus-evoked blood flow	[275]
	Skin	Increased LDI flare (small fiber function)	[196]
	Sensory systems	Severe hypoalgesia	[285,350]
FUNCTIONAL (CNS)	Spinal cord	Impaired rate dependent depression of H wave	[226]
	PAG	Dysfunction of descending inhibitory systems	[312]
	Thalamus	Hyperperfusion	[315]
	Anterior cingulate cortex	Hyperperfusion	[386]
	Limbic/striatal structures	Increased responses to stimuli	[362]
OTHER	Blood	Increased CRP and slCAM-1	[91]
		Increased TNFα,	[242,273]
		Increased iNOS	[273]
		Reduced vitamin D	[320]
		Reduced Glo-1	[329]
	Physiology	Sex (female)	[140,359]
		Increased BMI	[416]
		Autonomic dysfunction	[76,115,335,343]

TABLE 2:

miRNA implicated in the pathogenesis of diabetic neuropathy

miRNA species	Impact of diabetes	Model (tissue)	Effective therapeutic manipulations	Representative publications
multiple	Multiple upregulated Multiple downregulated	STZ-mouse (DRG)	Mimics/KO impact multiple indices of degenerative and painful neuropathy	[57]
multiple	Multiple upregulated Multiple downregulated	STZ-rat (DRG)	Not done	[132]
multiple	Multiple upregulated Multiple downregulated	STZ-rat (nerve)	Some expression changes normalized by taurine	[319]
miR-25	downregulated	db/db-mouse (nerve)	Precursor reduced inflammation markers	[412]
miR-29c	upregulated	db/db mouse (DRG, nerve)	KO improved neurite growth in vitro	[164]
miR-34c	upregulated	STZ-mouse (trigeminal)	Antagomir improved corneal nerve growth	[148]
miR-96	downregulated	HFD/STZ-rat (nerve)	Exercise increased miR, reduced $Na_v1.3$ and thermal pain	[5]
miR-106a	downregulated	STZ-mouse (DRG)	Not done	[394]
miR-146a	upregulated	STZ-rat (nerve)	Not done	[405]
		db/db-mouse (nerve)	Mimics improved neuropathy/pain	[215]
	downregulated	STZ-rat (nerve)	Not done	[105]
		db/db-mouse (nerve)	Inducer improved neuropathy/pain	[381]
miR-155	downregulated	STZ-rat (nerve)	Not done	[185]
	upregulated	STZ-rat (nerve	Antagomir improved neuropathy	[53]
miR-181a	upregulated	STZ-mouse (trigeminal)	Antagomir improved corneal nerve growth	[149]
miR-182	downregulated	STZ-mouse (trigeminal)	Agomir increased corneal nerve density	[384]