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POTENTIAL ROLE OF AUTOPHAGY MODULATORS IN THE PROGRESSION OF DIABETIC NEUROPATHY

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ABSTRACT

Diabetic peripheral neuropathy (DPN) is a prevalent consequence of diabetes, affecting 50- 60% of diabetic individuals and substantially influencing global amputation rates. The pathogenesis of diabetic peripheral neuropathy (DPN) encompasses many pathways, including the buildup of extracellular matrix proteins, neuroinflammation, axonal degeneration, and the loss of unmyelinated fibers, resulting in sensory conduction delays and nerve injury. Hyperglycemia significantly contributes to this illness by its impact on oxidative-nitrosative stress, mitochondrial dysfunction, and demyelination. Current FDA-approved therapies for neuropathic pain in diabetic peripheral neuropathy (DPN), such as duloxetine and pregabalin, largely focus on neurotransmitter pathways but exhibit limited effectiveness due to the disease's multifactorial characteristics. This research investigates the possibility of autophagy regulation as a treatment approach for diabetic peripheral neuropathy (DPN), emphasizing its function in cellular quality control and the reclamation of damaged components. The processes of autophagy, encompassing macroautophagy, chaperone-mediated autophagy, and microautophagy, are examined concerning their relevance in the etiology of diabetic neuropathy. The research analyses the correlation between protein misfolding, oxidative stress, and endoplasmic reticulum dysfunction in diabetes, highlighting the potential of augmenting autophagic mechanisms to alleviate these impacts. The function of the ubiquitin-proteasome system in protein breakdown and cellular homeostasis is also examined. The findings indicate that targeting autophagy and associated pathways may provide novel strategies for managing diabetic peripheral neuropathy, necessitating additional exploration of pharmacological

compounds capable of successfully modulating these processes.

KEYWORDS: Hyperglycemia, macroautophagy, neuroinflammation.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a prevalent consequence of diabetes, affecting around 50–60% of diabetic individuals, and is the primary cause of amputations globally.[1,2] Initial alterations in individuals with diabetic peripheral neuropathy (DPN) encompass the buildup of extracellular matrix proteins, inflammation, axonal degeneration, and the loss of unmyelinated fibers, resulting in sensory conduction delays and permanent nerve damage. Hyperglycemia is well recognized as a primary factor in diabetic peripheral neuropathy (DPN).[3-7] regarding alterations in oxidative–nitrosative stress, neuroinflammation, mitochondrial malfunction, bioenergetic crisis, and demyelination.[7]

Diabetes, a chronic metabolic condition marked by hyperglycemia, is a significant contributor to morbidity and death globally.[8] Diabetic neuropathy (DN) is a severe microvascular consequence linked to prolonged diabetes, characterized by tingling in the extremities, scorching pain, allodynia, and hyperalgesia.[9] The incidence of diabetic nephropathy may reach 50–60% in persons with both forms of diabetes.[10] Duloxetine and pregabalin are the sole FDA-approved medications for the management of neuropathic pain, the primary therapeutic outcome in patients with diabetic neuropathy (DN). Owing to their influence on neurotransmitter activity, they may impact pain processing pathways and hence are more effective in alleviating symptoms related to diabetic neuropathy.[11] Various pathogenic ideas, including oxidative-nitrosative stress, neuroinflammation, mitochondrial failure, bioenergetic crisis, axon-glia interactions, and demyelination, have been recognized in the etiology of diabetic neuropathy (DN).[12,13] Nevertheless, several pharmaceuticals aimed at these pathways have shown restricted therapeutic efficacy in extensive randomized controlled studies.[14] The ineffectiveness of these medications may stem from the intricate interrelated pathomechanisms and the stage-specific preponderance of particular pathways. Consequently, pharmaceuticals targeting many routes may be more effective than those focused on one pathway. Alternatively, medications exhibiting pleiotropic effects on molecular signaling pathways via their influence on cellular quality control mechanisms may represent a potential route shortly.[15]

Autophagy is a cellular catabolic mechanism that recycles damaged cellular components via lysosomal degradation.[16] The deregulation of autophagy is implicated in the development of

several malignancies and neurological diseases.[17,18] A variety of data suggests that peripheral neuropathies associated with neurodegeneration share significant similarities with the primary alterations observed in neurodegenerative illnesses.[19] Therefore, targeting autophagic modulation may be pertinent as a therapeutic approach in the treatment of peripheral neuropathies, particularly diabetic neuropathy. This article examines the theoretical dimensions of stimulating autophagic flow to avert the buildup of harmful substances in hyperglycaemic neuronal and Schwann cells. The subsequent sections cover several methods for therapeutically manipulating autophagic pathways.

BASIC MACHINERY OF AUTOPHAGY

Autophagy is categorized into three subgroups according to the transport of cellular cargo to lysosomes.[16] Macroautophagy, now termed autophagy, transpires via the creation of double-membrane vesicles known as autophagosomes, which then merge with lysosomes to generate autolysosomes.[20] Autophagy is a multi-faceted cellular quality control mechanism facilitated by an evolutionarily conserved array of proteins known as autophagy-related proteins (Atg).[21] Autophagy commences with the creation of a phagophore around cellular cargo, a process referred to as nucleation. The phagophore may originate from the Golgi apparatus or the endoplasmic reticulum. It is constituted by the collaboration of Atg 13 and Atg 17 (FIP200) facilitated by Atg1 (Ulk 1 in mammals).[22] This process is regulated by the mammalian target of rapamycin (mTOR) kinase, rendering autophagy dependent on nutrition supply and stress signals. mTOR induces the phosphorylation of Atg13, obstructing its interaction with Atg1, hence inhibiting autophagy in nutrient-abundant environments.[23] The subsequent activity of class III PI3K enzyme, vesicular protein sorting (Vps34), catalyzes the conversion of phosphatidyl inositol (PI) to phosphatidyl inositol triphosphate (PI3P) with the assistance of Beclin1 (the mammalian analog of Atg6), facilitating the recruitment of more Atg proteins to the expanding phagophore membrane.[22] The expansion of the phagophore and its development into an autophagosome entails the function of two ubiquitin-like mechanisms.[24] In the Atg5-Atg12 complex, Atg7 and Atg10 function as E1 and E2 ligases, respectively, facilitating the attachment of this complex to the autophagosome via Atg16L. The intricate Atg5-Atg12-Atg16L complex facilitates the recruitment of LC3B-II into the autophagosome and causes its curvature.[22]

Microtubule-associated protein light chain (LC3B), the mammalian homolog of Atg8, undergoes cleavage by Atg4 and is then modified by Atg7 and Atg3, the E1 and E2 ligases, to

produce LC3B-II, which is LC3B conjugated to phosphatidyl ethanolamine.[24] The mature autophagosome subsequently recruits cargo, either selectively or non-selectively, for sequestration and transports it to lysosomes via endosomal trafficking. Autophagosome trafficking entails the activity of Rab7 GTPases and cytoskeletal motor proteins.[25] The lysosomal hydrolases subsequently degrade the internalized cellular material and transport the fundamental subunits to the cytoplasm via permeases for recycling. Chaperone-mediated autophagy (CMA) facilitates the direct translocation of aggregated proteins across the lysosomal membrane via a receptor (LAMP-2A).[26] For a protein to undergo lysosomal breakdown by CMA, it must include a pentapeptide motif biochemically analogous to KFERQ within its amino acid sequence.[27] This motif is identified by the cytosolic chaperone, a heat shock cognate protein of 70 kDa (Hsc 70), which, in conjunction with its regulatory co-chaperones, transports the substrate protein to the lysosomal surface. The substrate protein–chaperone complex then associates with LAMP-2A, serving as a receptor for this autophagic pathway, unfolds the substrate, and facilitates its internalization.[28] LAMP2A, upon interacting with the protein-chaperone complex, experiences conformational alterations that result in multimerization. The presence of a lysosome-specific form of Hsp90 on the luminal side of the lysosomal membrane is essential to preserve the stability of LAMP2A receptors which undergo continuous cycles of assembly and disassembly.[29] Microautophagy is the third subtype of autophagy wherein the lysosome directly creates invaginations around cellular cargo and internalizes it.[30]

PROTEIN AGGREGATION AND ER STRESS IN DN

Schwann cells surrounding peripheral nerve axons primarily participate in myelination, essential for action potential conduction and axonal integrity preservation.[31] These cells synthesize myelin, which consists of proteins, cholesterol, and lipids, for myelination. These cells are particularly vulnerable to toxic assaults, including DNA damage, oxidative stress, disrupted homeostasis, and the buildup of damaged proteins.[32] Protein synthesis is affected by several variables including heredity, age, and cellular environmental circumstances, such as changes in the endoplasmic reticulum (ER). One of the primary functions of the endoplasmic reticulum is the synthesis and folding of proteins, in addition to calcium homeostasis and the production of proteins and lipids. Multiple mechanisms influencing ER function encompass disrupted redox status, modified glycosylation, and changed protein synthesis rates, which hinder oxidative protein folding and culminate in the accumulation of misfolded or unfolded proteins, hence inducing ER stress.[33]

The pathophysiology of diabetic nephropathy (DN) centers on a unifying mechanism, namely reactive oxygen species (ROS), which leads to oxidative stress and a tendency for protein misfolding and aggregation. Proteins are very vulnerable to changes by reactive oxygen species (ROS).[34] ROS-induced protein changes may be reversible, including S-glutathionylation and S-nitrosation.[35] Irreversible protein changes, such as carbonylation, lead to protein misfolding and aggregation, contingent upon the extent of carbonylation. Both the endoplasmic reticulum (ER) and the ubiquitin-proteasome system (UPS) function as quality control mechanisms for proteins dysregulated in hyperglycaemic situations.[36] The endoplasmic reticulum necessitates a diminished environment for the oxidative folding of proteins. The decreased environment is sustained by antioxidants, including reduced glutathione, among others. Nonetheless, the concentrations of reduced glutathione produced from reduced Nicotinamide adenine dinucleotide phosphate (NADPH) diminish in diabetic nephropathy due to the suppression of the pentose phosphate pathway.[37] The carbonylation of endoplasmic reticulum chaperone proteins may interfere with the protein folding process in the lumen, leading to the production of misfolded proteins and aggregates.[38] It can then activate the unfolded protein response (UPR) that either fixes or destroys misfolded proteins based on severity.[39]

While oxidative stress activates the ubiquitin-proteasome system, persistent hyperglycemia hinders its efficacy. Methylglyoxal, an enhanced consequence resulting from increased glycolysis, contributes to the production of advanced glycation end-products (AGEs) and modifies the 20S proteasome subunit, ultimately leading to the buildup of polyubiquitinated proteins.[40] Heat shock proteins (HSPs) are molecular chaperones that facilitate the correct folding of proteins and inhibit the development of unfolded or misfolded proteins. These are generated by the activation of heat shock transcription factor 1 (HSF-1). Under cellular stress conditions, including oxidation and protein unfolding, HSF-1 is activated, leading to the transcriptional upregulation of HSPs.[41] However, in diabetes settings, the activation of HSF-1 is impaired, leading to heightened protein misfolding and aggregation.[42]

Protein misfolding and aggregation in diabetic neuropathy (DN) is evidenced by the aggregation of PMP22, a key component of myelin. The carbonylation of PMP22 at the leucine 19 residue alters its shape from a helix to a β-sheet, leading to aggregation. In typical neurons, the predominant portion of freshly synthesized PMP22 (80%) undergoes degradation. The breakdown of PMP22 is impaired in DN, leading to aggregation and buildup owing to a reduction in autophagy and lysosomal processes. The aggregation of PMP22 and modifications

in protein degradation pathways may also play a role in the etiology of diabetic neuropathy (DN).[43]

OXIDATIVE STRESS AND CYTOTOXICITY IN DN

Oxidative stress is recognized as critically significant in the development of several illnesses, including cancer, diabetes, and cardiovascular disorders. It is also implicated in the pathophysiology of diabetic microvascular problems, including neuropathy.[44] The primary cellular generator of reactive oxygen species, the mitochondrion, is seen to be malfunctioning in both neuronal and non-neuronal cells of individuals with diabetes. Chronic hyperglycemia leads to the buildup of depolarised mitochondria in dorsal root ganglion (DRG) neurons, resulting in death.[45] A diminished amount of Bcl2 in diabetes is implicated in the compromise of mitochondrial membrane integrity. Fernyhough et al. showed that diminished mitochondrial activity in peripheral neurons is associated with decreased insulin/neurotrophic support. Insulin is hypothesized to support mitochondrial membrane integrity and maintenance by regulating the PI3K/Akt/CREB pathway.[46] Knock-out experiments in animals demonstrate that mitochondrial activity in Schwann cells is crucial for preserving axonal caliber and myelination in large peripheral myelinated nerves.[47] Mitochondrial dysfunction mostly arises from the production of impaired electron transport chain (ETC) components or increased reactive oxygen species (ROS) formation by the ETC.[41] The subsequent event arises from an increased supply of NADH to the electron transport chain, resulting in the partial reduction of molecular oxygen to superoxide in a hyperglycaemic condition. Studies on diabetic rats conclusively showed that hyperglycemia impaired the operation of electron transport chain enzyme complexes and some enzymes of the tricarboxylic acid (TCA) cycle.[49] The breakdown of mitochondrial function and metabolism results in diminished ATP production, leading to a bioenergetic crisis and subsequent necrosis. A sufficient supply of ATP is crucial for neurons to sustain electrochemical gradients, neurotransmission, and synaptic plasticity.[50] Impaired mitochondrial function is linked to the dissipation of membrane potential across the inner mitochondrial membrane, resulting in the release of apoptotic factors, including cytochrome c, from the mitochondrial matrix into the cytosol. The release of cytochrome c, followed by the activation of caspases, ultimately leads to apoptosis.[51]

Mitochondrial dysfunction in hyperglycemia is linked to Ca2+ dyshomeostasis. Increased intramitochondrial Ca2+ concentrations accelerate mitochondrial function by activating TCA cycle enzymes, hence further augmenting ROS production.[52] All the previously indicated

cycles of events recur, leading to ineffective mitochondrial function (diminished ATP, elevated ROS).

MODULATION OF AUTOPHAGY IN PERIPHERAL NEUROPATHIES

Despite efforts to investigate the role of autophagy in experimental diabetic nephropathy (DN), these endeavors have failed to yield a definitive and coherent understanding of autophagic processes in the context of in vivo DN. R Towns et al. revealed that sera from individuals with type 2 diabetic neuropathy when exposed to neuroblastoma cells, results in the production of autophagosomes, as shown by elevated LC3-II antibody.[53] While they proposed the stimulation of autophagosome formation with internalized mitochondria under diabetic circumstances, they have not demonstrated increased autophagic flux, a critical metric for quantifying the dynamics of autophagy.[54] A decreased mitophagic flux and associated mitochondrial abnormalities were seen in cerebellar Purkinje neurons under diabetes circumstances in 24-week STZ-induced diabetic mice.[55] The experimental evidence of compromised autophagy in diabetes circumstances, along with the pharmacological potential of autophagy inducers in animal models of neuropathy, provides a compelling reason for the evaluation of the current concept.[56,57]

Enhancing autophagic flux has been shown to have a positive impact on numerous animal models of peripheral neuropathy, including Bortezomib-induced sensory neuropathy, spinal nerve ligation-induced neuropathic pain, and chronic constriction injury (CCI)-induced neuropathy.[58-60] The degree of therapeutic advantage from autophagy regulation is contingent upon the particular type of autophagy engaged and the subsequent processes, which exhibit varying predominance in the pathogenesis of various peripheral neuropathies.[61,62] The CMA regulates the recycling of several proteins containing the KFERQ motif.

This motif is also found in IjB protein, a cytosolic inhibitor of NF-kB. Consequently, the activation of CMA correlates with increased NF-kB signaling, a crucial element of immunological and inflammatory responses.[63] This contradicts our traditional comprehension of the neuroinflammatory concept of neuropathies. Regardless of the neuropathy type, increased mitophagy is anticipated to yield therapeutic benefits, as mitochondria are principal sources of oxidative stress, a fundamental pathogenic mechanism in many peripheral neuropathies.

ALTERNATIVES TO AUTOPHAGY: THERAPEUTIC RELEVANCE TO DN

The Ubiquitin Proteasome System

Hyperglycemia linked to diabetes disrupts cellular homeostasis due to the inadequacy of quality control systems. In conjunction with autophagy, ATPases linked with various cellular functions (AAA+ proteases) are recognized for their significant involvement in cellular proteostasis.[64] Among the several AAA+ proteases, the ubiquitin-proteasome system (UPS) is crucial for the degradation of transient cytosolic protein aggregates.[65] UPS is a significant cellular mediator activated in response to UPR induced by ER stress. Significant doubt persists regarding the involvement of UPS in diabetic situations, as previous reports yield contradicting results.[40] Pharmacological enhancement of proteasome activity can improve protein recycling in diabetic circumstances via inhibitors of deubiquitinating (DUB) enzymes and proteolysis-targeting chimeras (PROTACs).[66] Proteasome inhibition demonstrates efficacy in several experimental types of diabetes complications. These medicines require meticulous therapeutic evaluation in experimental models of diabetic nephropathy to identify any off-target effects alongside their pharmacological impact. Nevertheless, careful consideration must be undertaken before targeting the proteasomal system as a therapeutic approach in diabetic nephropathy, given its multifaceted roles in protein turnover inside neurons.

MANAGEMENT ALTERNATIVES IN DPN

An unequivocal cure for DPN or any other problems of DM has yet to be established, however certain drugs are traditionally beneficial. It is noteworthy to examine the pathophysiological connections between hyperglycemia and oxidative stress. The enhanced adjuvant action of antioxidants and free radical scavengers remains crucial in the prevention of diabetic peripheral neuropathy in diabetic patients.[67]

DISCUSSION

Diabetic peripheral neuropathy (DPN) is a significant complication of diabetes, substantially impairing the quality of life for individuals impacted. The aetiology of diabetic peripheral neuropathy (DPN) is complex, encompassing basic mechanisms such as oxidative stress generated by hyperglycemia, neuroinflammation, mitochondrial dysfunction, and compromised cellular quality control. While pharmacological therapies like as duloxetine and pregabalin provide symptomatic relief, their limitations highlight the need for more effective therapeutic strategies. Regulating autophagy may serve as a way to alleviate cellular

dysfunctions associated with DPN.

Autophagy has a crucial function in preserving cellular homeostasis, especially in neurones and Schwann cells, which are pivotal to diabetic peripheral neuropathy disease. Autophagy facilitates the removal of impaired proteins and organelles, including mitochondria, that accumulate as a result of oxidative stress and neuroinflammation in diabetic peripheral neuropathy (DPN). Dysregulated autophagy in diabetes results in the accumulation of harmful cellular constituents, exacerbating brain injury. Nonetheless, although experimental models have shown the potential of autophagy regulation in alleviating neuropathy symptoms, the practical applicability remains ambiguous, partially due to contradictory findings in animal research. Certain studies indicate that augmenting autophagic flux, particularly mitophagy, may mitigate oxidative stress and enhance neuronal function in diabetic peripheral neuropathy (DPN). The intricacy of autophagy and its context-dependent effects require more investigation to pinpoint particular pathways for potential therapeutic targeting. The paper indicates that autophagy-related mechanisms, including macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy, are essential for maintaining cellular quality control during stress situations. CMA, which entails the direct transport of proteins to lysosomes for destruction, may be particularly pertinent for mitigating the protein misfolding and aggregation reported in DPN. Nonetheless, the activation of CMA in DPN may paradoxically enhance neuroinflammation via NF-kB signalling, suggesting that treatment approaches aimed at autophagy must be meticulously calibrated to prevent aggravating the inflammatory response.

In conjunction with autophagy, the ubiquitin-proteasome system (UPS) functions as an essential quality control mechanism for the destruction of damaged or misfolded proteins. Oxidative stress in diabetes impairs UPS function; nevertheless, recent studies indicate that increasing proteasomal activity may improve protein turnover and mitigate cellular damage. However, the therapeutic promise of targeting the UPS in DPN requires caution, since proteasomal inhibition may yield unforeseen effects on cellular proteostasis. Additional thorough research are necessary to evaluate the safety and efficacy of UPS-targeted therapies.

The therapy landscape for DPN is complex due to the complicated interplay of several disease mechanisms. The article states that while current treatments may alleviate symptoms, they fail to rectify the underlying cellular dysfunctions, highlighting the need for novel therapies that target the root causes of the disease. Given the growing evidence of autophagy's

involvement in peripheral neuropathy, therapeutic strategies that modulate autophagic mechanisms, particularly in neurones and Schwann cells, may offer a more comprehensive approach. Moreover, the integration of autophagy control with treatments aimed at oxidative stress and neuroinflammation may have synergistic benefits, hence enhancing the overall efficacy of diabetic peripheral neuropathy treatment.

CONCLUSION

Modulating autophagic pathways may serve as a therapeutic method for diabetic peripheral neuropathy. Despite the challenges in translating preclinical findings to clinical applications, continued research into the precise regulation of autophagy and other cellular quality control mechanisms may provide more effective treatments for DPN in the future. Furthermore, analysing the complex interplay between oxidative stress, inflammation, and autophagy will be essential in developing therapies that not only alleviate symptoms but also restore cellular function and prevent disease development.

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