A METABOLIC MECHANISM FOR DIABETIC NEUROPATHY

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Abstract: *Elevated blood glucose alone cannot explain the development and progression of diabetic neuropathy (DN) and the lowering of blood glucose is insufficient in preventing and/or reversing neuropathy in patients with type 2 diabetes. Dicarbonyls, such as methylglyoxal (MG), are endogenous by-products of glycolysis, which are elevated in diabetic patients. Reactive metabolite such as MG can modify DNA as well as extra- and intracellular proteins, leading to the formation of advanced glycation endproducts (AGEs). MG can contribute to the development of DN via post-translational modification of neuronal ion channels involved in chemosensing and action potential generation in nociceptive nerve endings. Increased formation of AGEs leads to increased cellular stress, dysfunction and ultimately cell death. The interaction of AGE-modified proteins through cell surface receptors, such as RAGE, can lead to increased cellular activation and sustained inflammatory responses. An inflammatory immune response is associated with later, degenerative, stages of DN. The direct and indirect effects of dicarbonyls on nerves provides a unifying mechanism for the development and progression of DN. Preventing the accumulation of MG during diabetes and/or inhibiting of RAGE signalling may therefore provide new, more effective, therapeutic approaches for the treatment of DN.*

Cuvinte cheie: *neuropatie diabetică, mecanism, metabolism*

Rezumat: *Doar valorile crescute ale glucozei în sânge nu pot explica dezvoltarea şi avansarea neuropatiei diabetice, iar scăderea valorilor glucozei în sânge nu este suficientă pentru a preveni neuropatia la pacienţii cu diabet zaharat de tip 2. Dicarboxili cum ar fi metilglioxalul sunt produşi endogeni secundari glicolizei, înregistrând valori crescute la pacienţii diabetici. Metabolitul reactiv, de exemplu metilglioxalul poate modifica ADN-ul, precum şi proteinele extracelulare şi intracelulare, conducând la formarea de produşi finali de glicozilare avansată. Metilglioxalul poate contribui la dezvoltarea neuropatiei diabetice prin modificarea post - translaţională a canalelor ionice neuronale implicate în chemosensibilitate și generarea de acțiune potențială în terminațiile nervoase nociceptive. Formarea crescută de produşi finali de glicozilare avansată duce la creşterea stresului celular, disfuncție și în cele din urmă la moartea celulei. Interacțiunea proteinelor modificate ca urmare a produşilor finali de glicozilare avansată prin receptori celulari de suprafață, cum ar fi receptorii pentru produşi finali de glicozilare avansată, poate duce la creșterea activării celulare și la răspunsuri inflamatorii susținute. Un răspuns imun inflamator este asociat cu etapele ulterioare, degenerative ale neuropatiei diabetice. Efectele directe și indirecte ale dicarbonililor asupra nervilor oferă un mecanism unificator pentru dezvoltarea si avansarea neuropatiei diabetice. Prevenirea acumulării de metilglioxal în caz de diabet și / sau inhibarea semnalizării receptorilor pentru produşi finali de glicozilare avansată (RAGE) poate astfel oferi abordări terapeutice noi, mai eficiente privind tratamentul neuropatiei diabetice.*

Diabetes is a disease posing considerable economic burden on global health services. Approximately 50% of the diabetic patients develop diabetic neuropathy (DN) as a late complication.(1) DN is well characterized in the peripheral nervous system and has a distal predominance. Patients with DN display altered pain sensitivities such as increased pain sensitivity (*hyperalgesia*) as well as hyper-responsiveness to normally innocuous stimuli (*allodynia*) during the early stages of the diseases in the initial stages. Symptoms of sensory loss may be present throughout the course of the disease, but predominate in the later stages as a result of the degeneration of neurons and their myelin sheaths.(2) Since hyperglycemia characterizes diabetes, tight control of blood glucose continues to be the primary treatment option. However, the drawback of intensive glycemic control is increased occurrence of hypoglycaemic episodes with a risk of brain injury and death. Moreover, normalizing blood glucose does not significantly reduce the incidence of neuropathic symptoms in type II diabetic patients and can only marginally restore the abnormal nerve functions in type I diabetic patients.(3–8) These studies indicate that the pathways in which the metabolic flux is directed or redirected are more important than the increased level of glucose itself when considering a treatment strategy for DN. This conclusion is supported by a study in which it was shown that diabetic patients are more prone to accumulate triose phosphates (glycolytic intermediate) than healthy controls, even after normalization to individual glucose concentrations.(9) In diabetic patients, the concentration of triose phosphates correlated positively with the concentration of the reactive metabolite methylglyoxal (MG), formed by non-enzymatic dephosphorylation of these intermediates. This study showed that even at normal glucose levels, diabetic patients have

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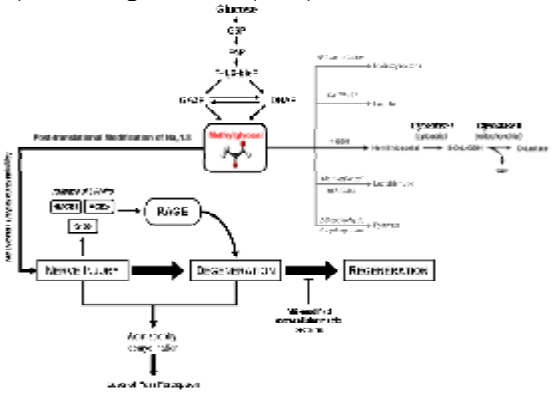
dramatically increased concentrations of glucose-derived reactive metabolites.

MG-induced hyperexcitability: a mechanism for hyperalgesia in the early stages of DN.

Hyperglycemia will lead to an increased flux through glycolysis and increased production of MG through the accumulation of triose phosphates.(10) (figure no. 1). Neuronal tissue has high energy demands and absorbs large amounts of glucose, independent of insulin even under normoglycemic conditions, and as such, is at higher risk for the accumulation of MG. MG can be metabolized by (*i*) MG reductase to lactaldehyde (11); (*ii*) aldose reductase isozymes, such as Akr1b1, which the NADPH-dependent reduction of MG to hydroxyacetone (12); (*iii*) betaine aldehyde dehydrogenase, also known as Aldh7a1, which catalyzes the oxidation of MG to pyruvate (13) and (*iv*) 2-oxoaldehyde dehydrogenase which can also catalyze the oxidation of MG to pyruvate.(13)

Figure no. 1. The Production & Detoxification of Methylglyoxal and its role in the Diabetic Neuropathy. Glucose-6-phosphate (G6P), Fructose-1, 6-bisphosphate (F-1, 6-biP), Glyceraldehyde-3-phosphate (GA3P), Dihydroxyacetone phosphate (DHAP), Ribose-5-phosphate (R5P), reduced glutathione (GSH)



Recent research has identified that DJ1/Park7 can function to metabolize MG directly to lactic acid, independent of glutathione.(14) However, the majority of the MG produced during glycolysis is metabolized to the stable end product, D-lactate by glyoxalase 1 (Glo1) and glyoxalase 2 (Glo2) along with catalytic amounts of reduced glutathione (GSH).(15) It has been shown that within the context of diabetic neuropathy, sciatic nerves are more susceptible to MG due to a reduction in the transcription, expression and activity of Glo1, although the mechanism for this down regulation remains uncertain. Mice with peritoneal damage represent a good model to study Glo1 activity.(16) Reduction in the amount of Glo1 in peripheral nerves of diabetic mice has been correlated with increased sensitivity to mechanical pain.(17) Mouse-strains harboring multiple copies of the Glo1 gene are less prone to developing diabetic hyperalgesia and reduced of nerve fiber density, as compared to mice with a single copy of the gene.(18) However, to interpret pain measurements from genetically modified mice induced with diabetes, it is important to critically evaluate the mouse model to allow conclusions relevant for human DN.(19)

The association between reduced Glo1 activity and painful DN has also been shown in clinical studies performed on diabetic patients (20). Furthermore, it has been demonstrated that knock-down of Glo1 in *C.elegans*, a well characterized model for studying mechanisms of neuropathy, suitable because of its easily accessible nervous system, resulted in accelerated neuronal degeneration associated with aging.(21,22) Thus, importance of has not only been implicated in maintenance of nerve function, but also neuronal integrity. MG, accumulated in the neuronal tissue during diabetes, can react irreversibly with the free amino groups of the lysine and arginine to generate advanced glycation endproducts (AGEs).(10,23) Numerous studies have been published showing increased glycation of neuronal tissue in diabetes.(24–31) Elevated MG and AGEs have been shown to modulate pain perception by modifying ion channels present in the peripheral nerves. Bierhaus et al showed that MG at concentrations found in the plasma of diabetic patients can rapidly modify arginine residues within the voltage-gated sodium channel $Na_V1.8$, a channel protein playing an essential role in acute and chronic pain.(32) odification of $Na_V1.8$ by MG is associated with increased electrical excitability and facilitated firing of nociceptive neurons. MG treatment likewise causes a depolarizing shift in the resting membrane potential of cultured DRG neurons and reduces current threshold for activation of action potentials. The reduction in depolarization required to reach the voltage threshold, observed in the presence of MG, is independent of the $Na_V1.8$ MG-modification. The MG-induced depolarization could contribute to increased neuronal excitability by facilitating the activation of $Na_V1.8$ that normally has a relative high voltage threshold. Comprehensive findings have also been reported for the transient receptor potential channel subfamily A, member 1 which serves as a almost universal chemosensor in nociceptors (TRPA1).(33,34) Thus, a metabolic change resulting in excessive accumulation and reduced detoxification of MG can explain nerve dysfunction during early diabetes. However, the effect of MG and the consequences of MG-induced hyperexcitability may also provide the conditions by which the characteristic symptoms of the late stage of DN, through induction of neuronal damage via activation of an immune response.

Does MG-induced hyperexcitability induce inflammation-driven neuronal injury?

Continued metabolic insults during diabetes provoke an inflammatory response in the neuronal tissue.(35–38) In the peripheral nerves, endoneurial resident macrophages and Schwann cells, which are the nerve-resident phagocytic cells, can produce proinflammatory cytokines such as IL-1β, IL-6 and TNF-α upon activation (39,37,40). The inflammatory response is exacerbated by macrophages and lymphocytes infiltrating into the peripheral nerve tissue.(41–43) Proinflammatory mileu in central nervous system is mediated by microglial cells during diabetes.(44–46) AGEs formed during diabetes bind to RAGE (Receptor for Advanced Glycation End Products) and trigger of signalling pathways that result in sustained activation of the proinflammatory transcription factor NF-κB.(37,47,48) Expression of RAGE on hematopoietic cells has recently been shown to be sufficient for preventing regeneration after injury during diabetes (49). Using mouse models of neuropathic pain, several studies have linked the proinflammatory cytokines to hyperalgesia.(50) The nervous tissue is subject to ischemic injury during diabetes. Schwann cells and macrophages initiate nerve fibre loss distal to the site of injury. This process is termed Wallerian degeneration. Schwann cells also begin demyelination of the long axons of the peripheral nerves.(51–53) Under hyperglycaemic conditions, Schwann cells have been reported to undergo apoptosis.(54) MG-induced activation of p38 MAPK pathway has shown to be responsible for Schwann cell death.(55) Under normal conditions, the immune response involves an anti-inflammatory phase follows the proinflammatory phase, wherein the regeneration of the damaged nerve occurs. The transparent embryos zebrafish can be used to study nerve regeneration during diabetes, permitting neurite growth to be imaged.(56) In diabetes, the nerve

regeneration process, which is orchestrated by Schwann cells, is greatly impaired. Hyperglycemia suppresses Schwann cell proliferation, which is prerequisite for nerve regeneration and also diminishes neurite regeneration length. MG modification has been implicated in failure of nerve regeneration and collateral sprouting.(57,58) Thus, in later stages of diabetes, progressive loss of neuronal integrity, myelination in combination with compromised nerve regeneration accounts for loss of sensory perception.

Conclusion:

An imbalance between production and detoxification of reactive metabolites provides a unifying mechanism for the development and progression of DN. The early symptoms of the disease are mediated by structural and functional modifications of membrane-bound ion channel proteins, whilst the later stages are mediated by either direct actions of MG on intracellular targets or, indirectly, through modulation of the immune response by RAGE activation. Whether the altered metabolism in the nerves induces and shapes a local inflammation during DN, or if systemic metabolic effects of diabetes on the immune system determines the inflammation in the nerve remains a question.

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