



HYPERGLYCEMIA-INDUCED NEURONAL DAMAGE: MOLECULAR MECHANISMS AND POTENTIAL THERAPEUTIC STRATEGIES

¹Abinaya G*, ²Vimalya S, ³Bhavani N, ⁴Muneeshwaran G, ⁵Arokiya R

¹M. Pharm, Department of Pharmacology, Sri Vijay Vidyalaya College of Pharmacy, Dharmapuri-636807, Tamil Nadu, India.

²M. Pharm, Department of Pharmacology, Sri Vijay Vidyalaya College of Pharmacy, Dharmapuri-636807, Tamil Nadu, India.

³M. Pharm, Department of Pharmaceutics, College of Pharmacy Madurai -625020, Tamil Nadu, India.

⁴M. Pharm, Department of Pharmaceutics, College of Pharmacy, Madurai-625020, Tamil Nadu, India.

⁵M. Pharm, Department of Pharmacognosy, College of Pharmacy, Madurai-625020, Tamil Nadu, India.

Affiliated to Tamil Nadu Dr.M.G.R Medical University, Guindy, Chennai-600 032, Tamil Nadu, India.

Corresponding Author*- Abinaya G, M. Pharm, Department of Pharmacology, Sri Vijay Vidyalaya College of Pharmacy, Dharmapuri-636701, Tamil Nadu, India.

ABSTRACT:

Hyperglycaemia-induced neuronal damage is an important complication of diabetes mellitus and is associated with progressive alterations in neuronal function and structure. Persistent elevation of blood glucose can initiate multiple molecular and cellular mechanisms, including oxidative stress, mitochondrial dysfunction, advanced glycation end-product formation, neuroinflammation, impaired insulin signalling, and activation of apoptotic pathways. These interconnected mechanisms contribute to neuronal injury and may subsequently affect cognitive, sensory, and motor functions. Understanding the molecular basis of hyperglycaemia-induced neuronal damage is therefore essential for identifying potential therapeutic approaches.

This review focuses on the major molecular mechanisms involved in hyperglycaemias-induced neuronal damage and discusses potential therapeutic strategies for preventing or attenuating neuronal injury. Particular emphasis is given to oxidative stress, reactive oxygen species generation, mitochondrial dysfunction, neuroinflammatory signalling, apoptosis, advanced glycation, and disruption of neuronal survival pathways. The review also discusses emerging therapeutic approaches, including conventional antidiabetic agents, antioxidants, anti-inflammatory strategies, neuroprotective agents, and plant-derived bioactive compounds. In addition, the potential role of combination and synergistic therapeutic approaches in targeting multiple pathological pathways is highlighted. A better understanding of these mechanisms may support the development of effective strategies for reducing diabetes-associated neuronal complications and improving neurological outcomes.

Keywords: Hyperglycaemia; Neuronal damage; Diabetes mellitus; Oxidative stress; Neuroinflammation; Mitochondrial dysfunction; Apoptosis; Neuroprotection; Therapeutic strategies; Plant-derived bioactive compounds.

INTRODUCTION:

One of the main causes of diabetes -related neuronal damage is persistent hyperglycaemia. Prolonged exposure to elevated glucose levels produces metabolic disturbances in neuronal and supporting cells, eventually affecting neuronal function and survival. The polyol, hexosamine, protein kinase C (PKC), and advanced glycation end-product (AGE) pathways are among the linked pathways that are triggered by hyperglycaemia. These metabolic changes contribute to oxidative stress, mitochondrial dysfunction and abnormalities in cellular signalling.

Excessive glucose metabolism can increase the formation of reactive oxygen species (ROS), which may damage neuronal membrane lipids, proteins and DNA. Mitochondrial dysfunction further increases ROS production and may reduce cellular energy availability. In addition, AGE accumulation and AGE-RAGE signalling can promote oxidative and inflammatory responses. Persistent neuroinflammation, together with oxidative and metabolic stress, can contribute to axonal degeneration, demyelination and impaired neuronal function.

Recent evidence indicates that oxidative stress and inflammation interact closely during diabetic neuronal injury. Hyperglycaemia-induced mitochondrial dysfunction can activate inflammatory pathways such as NF- κ B, JAK/STAT and NLRP3, thereby increasing inflammatory signalling and neuronal sensitisation. It might not be enough to totally stop neuronal damage by focusing simply on blood glucose.

Therefore, potential therapeutic strategies are increasingly focused on multitarget neuroprotection, including reduction of oxidative stress, suppression of neuroinflammation, preservation of mitochondrial function and prevention of neuronal apoptosis. When combined with proven antidiabetic medications,

natural ingredients with anti-inflammatory and antioxidant qualities may offer further neuroprotective advantages and represent an important area for further investigation.

OXIDATIVE STRESS AND NEUROINFLAMMATION IN HYPERGLYCEMIA-INDUCED NEURONAL DAMAGE

One of the mechanisms of neuronal damage brought on by hyperglycaemia is oxidative stress. Persistent elevation of glucose increases the generation of reactive oxygen species (ROS), particularly through mitochondrial metabolic disturbances. When ROS production exceeds the capacity of endogenous antioxidant systems, oxidative damage occurs in neuronal lipids, proteins and DNA. This imbalance can impair neuronal function and contribute to axonal and cellular degeneration.

Hyperglycaemia-induced oxidative stress is closely associated with neuroinflammation. Overproduction of ROS can trigger inflammatory signalling pathways like MAPK and NF- κ B. Resulting in increased production of inflammatory mediators including TNF- α , IL-1 β and IL-6. Activation of these pathways can further enhance oxidative stress and create a continuous cycle of inflammation and neuronal injury.

Mitochondrial dysfunction also contributes to this process by increasing ROS generation and disturbing neuronal energy metabolism. Recent evidence considers oxidative stress as an important link between metabolic abnormalities, mitochondrial dysfunction, inflammation and progressive neural damage. Therefore, targeting ROS generation, mitochondrial dysfunction, NF- κ B-mediated inflammation and antioxidant defence systems may provide potential approaches for neuroprotection. Antioxidant and anti-inflammatory strategies are being investigated to reduce neuronal injury and preserve nerve function in diabetes.

NATURAL PRODUCTS AND ANTIDIABETIC DRUGS AS EMERGING NEUROPROTECTIVE STRATEGIES IN DIABETES

Natural products are increasingly studied for their potential to protect neural tissues from diabetes-associated damage. Many plant-derived compounds possess antioxidant, anti-inflammatory and glucose-lowering properties, which may help reduce the mechanisms involved in neuronal injury. Bioactive components found in fenugreek include trigonelline, saponins, and 4-hydroxyisoleucine and studies have reported antidiabetic and antioxidant effects.

Antidiabetic drugs may also provide benefits beyond glucose control. Metformin, for example, has been investigated for effects involving oxidative stress, inflammation and cellular energy pathways. Combining conventional antidiabetic therapy with bioactive natural products may therefore provide a broader approach to controlling metabolic abnormalities and protecting neurons.

Fenugreek supplementation has shown beneficial effects on glycaemic parameters in clinical studies, while its antioxidant and neuroprotective properties provide a rationale for further investigation in diabetes-associated neuronal damage.

HERB-DRUG SYNERGY IN DIABETES-ASSOCIATED NEUROLOGICAL COMPLICATIONS

Combining herbal products with conventional antidiabetic drugs is being investigated as a potential multitarget approach to diabetes management. Fenugreek contains bioactive constituents with hypoglycaemic and antioxidant properties, while metformin improves glucose regulation through metabolic pathways. Preclinical evidence has reported greater glucose-lowering effects when fenugreek was combined with metformin than with either treatment alone.

Fenugreek supplementation has also been studied as an add-on to metformin therapy, with improvements in glycaemic parameters reported in clinical studies. However, direct evidence for a synergistic neuroprotective effect of fenugreek plus metformin is still limited. Therefore, investigating their combined effects on oxidative stress, inflammation and neuronal damage may provide a useful basis for evaluating their potential neuroprotective synergy.

ROLE OF FENUGREEK IN NEUROPROTECTION

Fenugreek (*Trigonella foenum-graecum*) contains bioactive constituents such as trigonelline, saponins and polyphenols, which have been associated with antidiabetic and antioxidant activities. These properties may help reduce oxidative and metabolic stress associated with diabetes. Trigonelline has also shown potential neuroprotective actions through modulation of oxidative stress and cellular signalling.

Experimental evidence suggests that fenugreek extract may have anti-neuropathic effects, including improvement of nerve function and recovery of nerve fibres in animal models. Therefore, its antioxidant, antidiabetic and potential neuroprotective properties provide a rationale for investigating fenugreek against diabetes-associated neuronal damage.

ROLE OF METFORMIN IN NEUROPROTECTION

Metformin is a widely used antidiabetic drug that may have beneficial effects on neuronal health in addition to its glucose-lowering action. Experimental studies suggest that metformin can reduce oxidative stress and inflammation, which are important contributors to diabetes-associated neuronal damage. Additionally, metformin may improve mitochondrial function by influencing cellular energy consumption and AMPK signalling and neuronal survival. These properties suggest that metformin could provide additional protection against neuronal injury associated with chronic hyperglycaemia. However, further experimental studies are required to establish its direct neuroprotective effects.

NEUROINFLAMMATION IN DIABETES-INDUCED NEURONAL DAMAGE

Chronic hyperglycaemia can trigger inflammatory responses in nervous tissues and contribute to neuronal injury. Increased oxidative stress may activate microglial cells and inflammatory signalling pathways, resulting in the release of cytokines such as TNF- α , IL-1 β and IL-6. Persistent inflammation can disturb neuronal function and increase cellular damage.

Neuroinflammation also interacts with oxidative stress and mitochondrial dysfunction, creating a cycle that promotes progressive neuronal and axonal injury. Therefore, reducing inflammatory responses may be an important approach for preventing or limiting diabetes-associated neuronal damage.

POTENTIAL SYNERGISTIC NEUROPROTECTIVE EFFECT OF FENUGREEK AND METFORMIN

Fenugreek and metformin may provide complementary effects against diabetes-associated neuronal damage. Fenugreek contains antioxidant and antidiabetic compounds, while metformin helps control blood glucose and may reduce oxidative stress and inflammation. Their combined actions may potentially reduce hyperglycemia-related metabolic and neuronal stress more effectively than either treatment alone.

Combination may act through multiple pathways involving glucose regulation, oxidative stress and inflammatory responses. However, direct evidence for a synergistic neuroprotective effect of fenugreek and metformin on neuronal damage is currently limited. Therefore, further experimental studies are needed to determine whether their combination can provide enhanced neuronal protection in diabetes.

MITOCHONDRIAL DYSFUNCTION AND NEURONAL INJURY

Mitochondria are essential for energy production and normal neuronal function. Persistent hyperglycaemia increases mitochondrial stress and excessive production of reactive oxygen species. This can reduce ATP production and disturb normal neuronal activity. Continued mitochondrial dysfunction increases oxidative stress and may activate apoptotic pathways, resulting in neuronal injury and cell death. Therefore, maintaining mitochondrial function may help protect neurons against diabetes-induced damage.

AGE-RAGE PATHWAY AND NEURONAL DAMAGE

Chronic hyperglycaemia promotes the formation of advanced glycation end products (AGEs), which can accumulate in neuronal tissues. AGEs interact with their receptor, RAGE, and activate oxidative and inflammatory signalling pathways. This increases reactive oxygen species production and promotes neuronal stress.

Continuous AGE-RAGE activation can contribute to mitochondrial dysfunction, neuroinflammation and neuronal apoptosis. These changes may impair neuronal function and increase the progression of diabetes-associated neuronal damage. Therefore, inhibition of AGE formation or AGE-RAGE signalling may represent a potential neuroprotective strategy.

POLYOL PATHWAY AND NEURONAL INJURY

Through the polyol pathway, persistent hyperglycaemia enhances the conversion of glucose to sorbitol. This process consumes NADPH and can reduce the availability of cellular antioxidant protection. Accumulation of sorbitol may also disturb cellular osmotic balance and contribute to neuronal stress. Increased polyol pathway activity promotes oxidative stress and can affect neuronal and Schwann cell function. These changes may contribute to axonal dysfunction and progression of diabetes-associated neuronal injury. Therefore, inhibition of excessive polyol pathway activity may help reduce hyperglycaemia-related nerve damage.

NEURONAL APOPTOSIS AND CELL DEATH

Persistent hyperglycaemia can activate apoptotic pathways in neuronal cells through oxidative stress, mitochondrial dysfunction and inflammatory signalling. Increased oxidative damage may disturb the balance between pro-apoptotic and anti-apoptotic proteins, leading to activation of caspases and neuronal cell death.

Loss of neuronal cells can contribute to impaired nerve function and progression of diabetes-associated neurological complications. Therefore, reducing oxidative stress and preventing excessive activation of apoptotic pathways may help preserve neuronal survival and function.

AXONAL DEGENERATION AND DEMYELINATION

Chronic hyperglycaemia can harm neuronal axons by impairing mitochondrial activity, oxidative damage, and metabolic stress. Axonal transport can be disrupted and nerve fibre maintenance impacted by reduced energy availability. Progressive axonal damage can lead to impaired nerve conduction and loss of normal neuronal function.

Diabetes can also affect Schwann cells and myelin integrity, contributing to demyelination and further impairment of nerve transmission. The combined effects of axonal degeneration and myelin damage can contribute to the progression of diabetes-associated neurological complications.

HISTOPATHOLOGICAL CHANGES IN DIABETES-INDUCED NEURONAL DAMAGE

Nervous tissues may undergo structural alterations as a result of diabetes-related neuronal injury. Prolonged hyperglycaemia, oxidative stress and inflammation may cause neuronal degeneration, cellular shrinkage and alterations in the normal organization of neural tissue. These changes can be observed through histopathological examination.

In experimental diabetic models, microscopic evaluation may reveal neuronal loss, vascular changes, inflammatory alterations and degeneration of neural cells. Histopathological assessment therefore provides useful structural evidence to support biochemical and behavioural findings and to evaluate the protective effects of potential neuroprotective treatments.

RESEARCH GAP AND FUTURE PERSPECTIVES

Diabetes-induced neuronal damage involves several interconnected mechanisms, including oxidative stress, apoptosis, neuroinflammation, and malfunctioning mitochondria. Although different antidiabetic and natural agents have shown protective effects individually, evidence regarding their combined neuroprotective activity is still limited.

Fenugreek possesses antidiabetic and antioxidant properties, while metformin provides effective glucose control and may influence cellular stress pathways. However, the potential synergistic effect of fenugreek and metformin on diabetes-induced neuronal damage requires further experimental investigation. Therefore, evaluating their combined neuroprotective effects in diabetic animal models may provide useful evidence for developing complementary strategies against diabetes-associated neuronal injury.

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