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Review

Molecular pathways of diabetic neuropathy: mechanistic insights and advances in experimental models

Nikhat Warsi [1], Vaishali Chadha [1], Ashok Kumar Gupta [1] *, Ambika Nand Jha [1]

[1] School of Pharmacy, Sharda University, Knowledge Park III, Greater Noida, Uttar Pradesh, India

* Correspondence to: Ashok Kumar Gupta, School of Pharmacy, Sharda University, Knowledge Park III, Greater Noida, Uttar Pradesh, 201306, India. Phone: +91-7004278836; E-mail: ashokg195@gmail.com

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Abstract

Diabetes Mellitus (DM) is known as chronic metabolic illness characterized by hyperglycemia. Nephropathy, retinopathy, neuropathy, osteopathy, and various other consequences are caused by chronic hyperglycaemia. Among all diabetic complications, diabetic neuropathy is enervating complication which may leads to numbness, pain, fatigue, muscle weakness and foot ulcers. This review article focusses on detailed overview on pathophysiology of Diabetic Neuropathy (DN). Animal models have long been indispensable for investigating and characterizing disease pathogenesis, identifying disease targets, and assessing novel therapeutic agents and treatments *in vivo*. This review gives a fundamental summary of diabetes, its causes, and its effects on animal models of diabetes induction, pathophysiology and use of animals in various approaches such as chemical, surgical, genetic, viral, hormonal etc. Additionally, this paper emphasises on pathways related to neuropathy and about various animal models for diabetes.

Keywords: animal models, diabetic complications, hyperglycemia, diabetes induction, diabetic neuropathy

Abbreviations: BB/Wor – Bio-Breeding/Worcester; BBDP – Bio-Breeding Diabetic Prone; BBDR – Bio-Breeding Diabetic Resistant; BTBR – Black and Tan Brachyury; CD-1 – Cluster of Differentiation-1; C57BL/6 – C57 Black 6; GFR – Glomerular Filtration Rate; GLUT2 – Glucose Transporter 2; ICR – Institute of Cancer Research; Iddm/kdp1 – Insulin-Dependent Diabetes Mellitus/Komeda Diabetic Prone 1; $Ins2^{+}$ – Insulin 2 Positive; KDP – Komeda Diabetic Prone; KND – Komeda Nondiabetic; LETL – Long-Evans Tokushima Lean; MHC – Major Histocompatibility Complex; NAD – Nicotinamide Adenine Dinucleotide; NIDDM – Non-Insulin-Dependent Diabetes Mellitus; NOD – Non-Obese Diabetic; STZ – Streptozotocin; ZDF – Zucker Diabetic Fatty.

Introduction

Diabetic Mellitus (DM) is the most considerable metabolic disorders world-wide with its increasing trends up-to 578 million by 2030 [1]. Over the years there has been increase in complications such as Nephropathy, retinopathy, neuropathy and erectile dysfunction. Considering Neuropathy, it is the damage caused in the nervous system of different region either individually or in combination [2]. It has various linked symptoms such as motor neurons disturbances, alterations in pain fibres and slower dysfunction of autonomic nervous system. There are several forms of neuropathy, including proximal, focal, autonomic, and peripheral neuropathy [3, 4]. Diabetic Neuropathy involves several reasons in the pathogenesis by disruption of glucose metabolism [5]. Peripheral Neuropathy among other neuropathy opts to have common affect in population having nerve damage in feet, legs or arms and hands. Diabetic Neuropathy is mainly linked type 2 Diabetes Mellitus, with painful nerve sensations Along with abnormal sensory symptoms at early stages

with respect to autonomic nervous system, motor and sensory neurons [6, 7]. The pathogenesis involves inflammation due to reactive oxygen species in the peripheral nerves which causes hyperexcitability in the central neurons, afferent nociceptors as well involves spontaneous production of impulses in the axons and ganglia roots [8]. Recent studies suggest that there is involvement of mitochondrial dysfunction, activation of Tumour necrosis factor (TNF-α) which also leads to oxidative stress in painful diabetic neuropathy [9]. However, there are other pathogenic factors such as Tumour necrosis factors (TNF-α) and activation of interleukin 1-Beta (IL-β) which ultimately leads to nerve damage and cell death [10]. From multiple studies it is concluded that type-2 diabetes is most common form among all DM, it is mainly lifestyle related and develops over time, and therefore it is also called as adult onset diabetes. Chronic pancreatitis or drugs like thiazide, diuretics, and diazoxide when administered for a long time can also cause diabetes; it is due to the resistance of insulin and accounts for more than 90% cases of the diabetes. Similarly, 4–5% people suffer diabetes caused due to placental hormones [11]. Animal models have always been used for the purpose of study and research for identifying and selecting the drugs for the treatment. Rodents such as mice, rats, and hamsters have been proven to be effective source for conducting research, particularly in uncovering the pathogenesis of diseases [12]. Most diabetes research relies on animal models due to the disease's complex ethology and multi-structural interactions.

Molecular mechanisms of nerve damage

To many extent several Pre clinical and clinical studies suggests that Neuropathy associated pain involves potential targets with associated mechanisms in multidirectional pathways, involving NADPH glucose metabolic runway, hexosamine pathway (Glycolysis and GFAT), protein kinase C pathway (calcium upregulation), Advance glycation end product, oxidative stress, mitogen activated protein kinases, poly ADP Ribose polymerase, Nuclear factor light chain kappa activated B cells, Hedgehog, Inflammatory cytokines (IL-1,4,6,8 & 10), cyclooxygenase, nerve growth factor, autophagy, Glycogen synthase kinase 3, Pyruvate dehydrogenase kinases, Satellite glial cells and Long non-protein coding RNA [13]. DM is a complex disorder with several complications of which one is its inductions like being exposed to chemicals and toxins, among animals' models streptozotocin are efficient in the prevalence of diabetes mellitus related complications [14, 15].

Polyol pathway

Polyol pathway includes the enzymes sorbitol dehydrogenase and aldose reductase (AR), which results in increased glucose absorption. When NADPH, a cofactor of sorbitol is present, AR is responsible for converting glucose; when NAD+ is present, it is further transformed into fructose. This route is used to digest low concentrations of glucose but when on higher side of glucose is consumed it increases the NADPH levels and reductive stress [16, 17].

Hexosamine pathway

The fructose-6-phosphate amidotransferase (GFAT) enzyme transforms the glucosesamine-6-phosphate produced during glycolysis into glucosamine-6-phosphate, a process associated with neuropathic alterations via the production of UDP-N-acetylglucosamine [18]. Increased GFAT activity is linked to hyperinsulinemia and decreased insulin sensitivity in type 2 diabetes [18, 19]. The transcription factor Sp1 is activated by UDP-N-acetylglucosamine build-up, and this in turn causes the production of Plasminogen Activator Inhibitor-1 (PAI-1) and Transforming Growth Factor-β (TGF-β) [20]. These molecular changes induce endothelial cell damage and drive smooth muscle cell growth, eventually worsening diabetic vascular problems. Furthermore, causes DNP which is responsible for damaging the vessels which supplies blood to the nerves [20, 21].

Protein kinase-C pathway

Protein Kinase C (PKC) is significantly associated with the onset of diabetic neuropathic pain, since increased concentrations of diacylglycerol and intracellular calcium facilitate the activation of various PKC isoforms [22]. Both traditional isoforms (α, βI, βII, and γ) and new isoforms (δ, ε, η, and θ) exhibit enhanced activity under these circumstances, leading to a series of signalling modifications that facilitate neuronal impairment and increased pain sensitivity [23, 24]. The PKC pathway obtained from Gylceraldehde-3-Phosphate from the glycolysis pathway which further gets converted into dihydroxyacetone and results into the formation of glycerol-2-phosphate and finally into DAG itself [24]. The DAG or advance glycation end product

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(AGEs) is responsible for the activation PKC and other attached signalling pathways such as Vascular Endothelial Growth Factor (VEGF), plasminogen activator inihibitor-1 (PAF-1), Nuclear Factor Kappa-B (NF-κB) and Transforming Growth Factor Beta-I (TGF-βI) which further is responsible for microvascular complications in the nerves [25]. Also, the down regulation of Na^+/K^+ ATPase causes severe sciatic nerve conduction velocity and blood flow in the nerves [25, 26].

Advance glycation end product (AGEs)

Such activation occurs when high glucose and related saccharides undergo non enzymatic reactions due to which alterations in the chemical structure is seen in lipids and proteins [27]. Such accumulation of AGE leads to attachment of methylglyoxal which is responsible for the vascular damage [27, 28]. In Type-1 DM, reduction of glyoxalase-1 occurs due to elevation of AGE & Receptor for AGE (RAGE) [29]. Increased cellular damage and inflammation are reflected in the NF-κB subunit's p65 activity. When AGE-RAGE signalling is seen in endothelium and Schwann cells, it indicates the onset of diabetic neuropathy [30]. This relationship increases NADPH oxidase activity, causes oxidative stress, and eventually causes apoptosis [31].

Oxidative stress

Oxidative stress occurs in cells when the production of free radicals surpasses their elimination or when essential enzyme routes for their neutralization are compromised [32]. This imbalance substantially leads to DNP, whereby an overabundance of reactive oxygen and nitrogen species—such as hydrogen peroxide, superoxide, and hydroxyl radicals induces cellular damage and impairs normal physiological functioning [32, 33]. Mostly studies suggest that nitrosative stress is caused by nitrotyrosine and peroxynitrite which leads to diabetes induced pain, these free radicals' generation shunts glucose to polyol pathways, PKC pathways, hexosamine pathways and AGE-RAGE inter relationships which leads to overconsumption of NADPH and cytotoxic metabolites [34]. Intracellular redox imbalance causes extensive lipid, protein, and DNA damage, which in turn causes mitochondrial malfunction and an overabundance of reactive oxygen species (ROS) [35]. In the end, this cascade leads to the degeneration of Schwann cells, myelinated axons, and sensory neurons in the dorsal root ganglia, which severely impairs the peripheral nervous system [35, 36].

Poly ADP-Ribose polymerase (PARPs)

The enzyme poly ADP-ribose polymerase (PARP) is essential for both DNA repair and apoptosis control. However, excessive PARP activation in diabetes mellitus leads to oxidative stress and single-strand DNA breaks, which worsen tissue damage by encouraging the production of reactive oxygen and nitrogen species [37]. The upregulation of PARP causes NAD+ depletion and further decelerates glucose metabolism and generation of energy. However, it also shows significant ribosylation of ADP that produces glyceraldehyde-3-phosphate dehydrogenase (GADPH) and eventually cause nerve damage to the blood vessels [38]. Some studies also suggest PARP activation is responsible for deficit in nerve conduction, sensory and motor nerves, gene expression, altered transcriptional regulation, energy failure and dysfunctional neurovascular system in animal models [39].

Mitogen-activated protein kinases (MAPK)

Subfamilies of mitogen-activated kinases include p38, extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK). These kinase groups are crucial for cellular signal transduction, controlling a variety of functions such as inflammatory pathways, proliferation, and stress reactions. ERK domains present 1 and 2 are responsible for the neuronal apoptosis whereas upregulation of these is directly linked to neuropathic pain and JNK upregulation causes phosphorylation of neurofilaments on the other side downregulation causes neuronal regeneration in the animal model [40, 41]. Emerging evidence indicates that long noncoding RNAs play a crucial regulatory role in pain modulation by influencing key signalling pathways such as ERK1/2 and p38 MAPK. Their activation of these pathways contributes to heightened thermal sensitivity and mechanical pain responses, suggesting that targeted inhibition of specific lncRNAs may help stabilize pain thresholds. This mechanism highlights the therapeutic potential of modulating lncRNA-mediated signalling to manage abnormal nociceptive sensitivity [42].

The activation of B cells by nuclear factor kappa light chain enhancer (NF-κB)

These are accountable for all immunological responses and apoptosis, since they are governed by NF-κB, with inflammation induced by analogous stimuli. It is found in sciatic and sural nerves although the

activity is significantly seen in schwann cells in the presence of high glucose levels. It is also associated with the p65 subunit of NF-κB, which induces inflammatory demyelination [43]. The oxidative-nitrosative stress is responsible for the nerve fibre damage and impaired blood supply in the vessels also they release some inflammatory markers like prostaglandins and bradykinins. Such stimulation leads to sensitivity to noxious sensation which leads to neuropathic pain [37].

Hedgehog (Hh)

The hormone, which is made up of proteins produced in the peripheral nervous system, oversees cell division, survival, and death. The process of degeneration and regeneration is started by injury to the peripheral nerves. Both desert and sonic hedgehogs are present throughout the trail. The sonic hedgehog protein facilitates neovascularization in the injured nerve, promoting healing in the animal model [44, 45].

Inflammatory cytokines

Cytokines are proteins including over 30 isoforms of interleukin, categorized as anti-inflammatory (*e.g.*, IL-4 and IL-10) and pro-inflammatory (*e.g.*, IL-1 beta, IL-6, and IL-8). One of the most common proinflammatory cytokine known as TNF- α gets activated through various other lymphocytes, natural killer cells, mast cells and macrophages [44]. It has been studied from pre-clinical and clinical data that IL-6 and TNF- α is seen in the animal model with STZ. Also, TNF- α is seen elevated in humans as well and the level of TNF- α is directly linked to pain threshold [45].

Cyclooxygenase (COX)

There are three types of cyclooxygenase enzymes (COX1, COX2 and COX3) and are involved in the haemostasis of the cell which remains usually normal but get activated due to high glucose level, activation of PKC, oxidative stress and inflammatory cytokines [45]. In the animal model it has been significantly seen that COX deficient rodents show less nerve damage, lesser conduction velocity, diminish levels in nerve fiber density and decreased blood flow in the myelin sheath [46].

Nerve growth factors (NGF)

NGF is substantially associated with nerve propagation and related factors such as glial cell-derived neurotrophic factor (NT-3, NT-4, and NT-5), brain-derived neurotrophic factor, and insulin-like growth factors I and II, which contribute to propagation, sensitization, angiogenesis, and cellular proliferation [45–47]. NGF is also accountable for the damage of tiny nerve fibre and sympathetic neurons [47]. NGF also affects the expression of substance P and calcitonin gene peptides, two neuropeptides, in sensory neurons. In the diabetic animal model, lower skin fibre and NGF levels are linked to the development of polyneuropathy [48, 49].

Autophagy

Autophagy is a metabolic process which is activate by oxidative stress in cytoplasmic molecules is sent to the lysosomes for degradation and re assumption of the other products and taken up the molecules which are important for the recycling pathways for the maintenance of homeostasis [48]. Then there few autophagosomes which are double membrane vesicles and are generated when a phagophore engulfs degraded material present in the cytoplasm [49].

Glycogen synthase kinase 3 (GSK3)

GSK3 is responsible for phosphorylating the threonine and serine amino acids, encoding GSK3-alpha and GSK3-beta. It is also involved in the migration, apoptosis, glucose regulation and cellular proliferation. It has been suggested from the pre-clinical studies that in animal model of diabetes peripheral as well as inflammatory responses are regulated by GSK3-beta, and the mRNA is upregulated as seen in endurance training of the rats [49, 50].

Pyruvate dehydrogenase kinases (PDKs)

Typically, metabolic status involves a balance between nutritional intake and expenditure, including two distinct pathways: glucose and fatty acid use prior to the TCA cycle. After converting Acyl-CoA in the cytosol, the fatty acid enters the mitochondria for further metabolism. In the mitochondria, fatty acid oxidation results in the conversion of Acetyl-CoA. Whereas glucose metabolism requires pyruvate from the glycolysis which inside mitochondria go through oxidative decarboxylation to give acetyl-CoA via mitochondrial gate keeping enzymes such as pyruvate dehydrogenase complex known as PDC. Acetyl-CoA is prevalent in both fatty acid and glucose metabolism, whereby the pyruvate dehydrogenase kinases (PDKs) phosphorylate

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the pyruvate dehydrogenase complex (PDC), inhibiting it, which then causes an accumulation of pyruvate and leads to lactic acid generation [45, 50].

Satellite glial cells (SGCs)

Satellite glial cells are in sensory, sympathetic, and parasympathetic ganglia, surrounding the neuronal cell bodies. It has been studied that from animal and human models of diabetes there is upregulation of P2X4R and P2X7R, of nociceptor, which leads to peripheral neuropath and related symptoms [49].

Long Nonprotein coding RNA

The long non-protein coding RNA (NONRATT021972) exhibits overexpression in the neurological system, particularly in diabetic rats. The currents stimulated by BzATP are marginally elevated compared to the control. and downregulation is evident in P2X7, glial fibrillary acidic protein (GFAP) and TNF-alpha also is associated with release of proinflammatory cytokines which are responsible for the complication in diabetic neuropathy in the elder patients [49, 51].

Neuropathy in diabetic cases involves several pathophysiological pathways shown in Figure 1.

Animal models for diabetes

Chemically induced models

Streptozotocin induced models

Streptozotocin (STZ) is a naturally occurring compound derived from the fungus Streptomyces achromogenes and is a glucosamine derivative of nitrosourea. N-(methylnitrosocarbamoyl)-α-D-glucosamine (NAD) is recognized for its antibacterial characteristics and its ability to trigger beta-cell death [52]. Beta-cell damage is mediated through processes such as methylation, free radical generation, and nitric oxide production [53]. Due to selective targeting on ß-cells, STZ is extensively used to cause diabetic mellitus (Figure 2). Its ability to target pancreatic beta cells specifically makes it the favoured option. It reaches these cells via the transmembrane carrier protein glucose transporter GLUT2, which causes necrosis and eventual cell death [54]. At higher doses, STZ exerts its effects through alkylating activity, while at lower doses, it stimulates immunological and inflammatory response due to glutamic acid decarboxylase release. Rats should get 60 mg/kg of diabetic medication (given intraperitoneally or intravenously), while mice should receive 170–200 mg/kg (provided either intraperitoneally or intravenously) (Patel *et al*. 2006). It has been shown that giving golden hamsters an intraperitoneal dosage of 50 mg/kg may cause diabetes [55]. NAD is provided 15 minutes before STZ (65 mg/kg, i.v.) resulting in moderate hyperglycaemia and preserving the pancreatic ß-cells because of NAD's (antioxidant properties [56]. The key advantages of using STZ include its high selectivity for beta cells, lower mortality rates, and prolonged diabetes induction. Due to this selectivity, STZ does not affect pancreatic alpha cells [57].

Alloxan induced model

A urea derivative called alloxan selectively necrotizes pancreatic beta cells. Chemically, it is a 2,4,6-trione of 5,5-dihydroxyl pyrimidine [58]. There are two ways that diabetes is brought on following the administration of alloxan, there is an abrupt elevation in insulin levels, which suppress the glucose activity [59]. Firstly, Pancreatic beta cells are destroyed by free radicals generated during the conversion of alloxan to dihydroalloxan (dilauric acid), followed by its subsequent reoxidation.. The second mechanism that cell death occurs due to the connection of alloxan with sulfhydryl (SH) groups [60]. Alloxan is most frequently delivered to rats at the dose of 150 mg/kg (i.v.), however the effective dose must be larger when given i.p. or s.c. [61]. The medication is administered in doses ranging from 90 to 200 mg/kg of body weight. The dose is significantly influenced by the route of administration [61]. The disadvantage is that it results in high death rate in rats, reversible diabetes, and animal ketosis [62].

Dithizone induced model

Dithizone is administered intravenously to induce diabetes. In the dithizone-induced diabetic model, blood levels of calcium and sodium decreased while those of iron, zinc, and potassium rose relative to the normal state. The levels of copper and magnesium were consistent [63]. Dithizone, a zinc chelating agent, has the capacity to penetrate membranes and combine zinc within liposomes with the release of protons, which can increase diabetogenicity. These complexing substances acidify the contents of lipid vesicles with entrapped zinc ions at pH 6 when they are introduced. Such proton release takes place within the pancreatic beta-cells' zinc-containing insulin storage granules; this causes the insulin to become soluble, which causes osmotic stress leading to the rupture of granule and hence diabetes is induced [63].

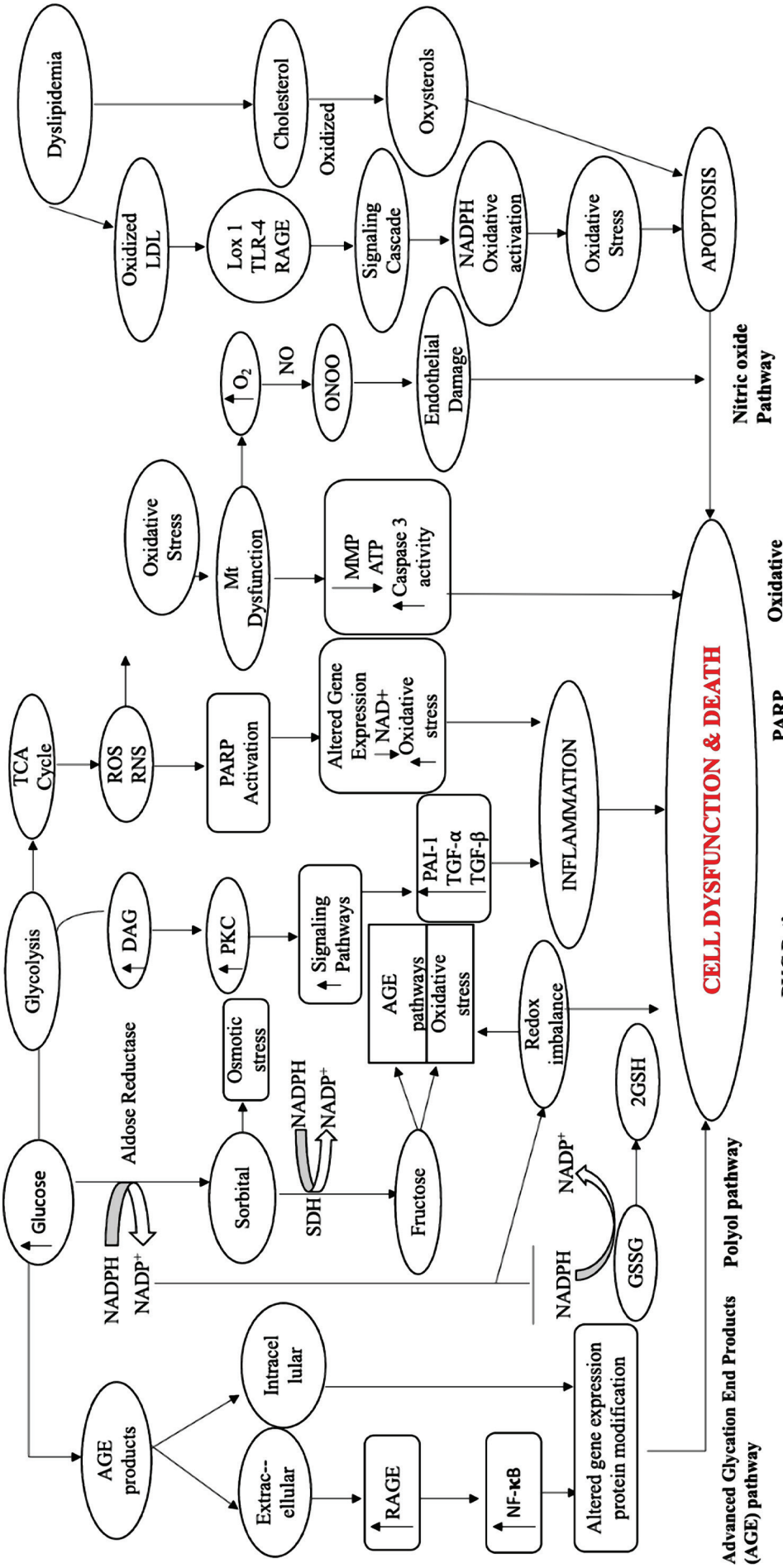

Figure 1: Diabetic neuropathy: Some important pathophysiological pathways.

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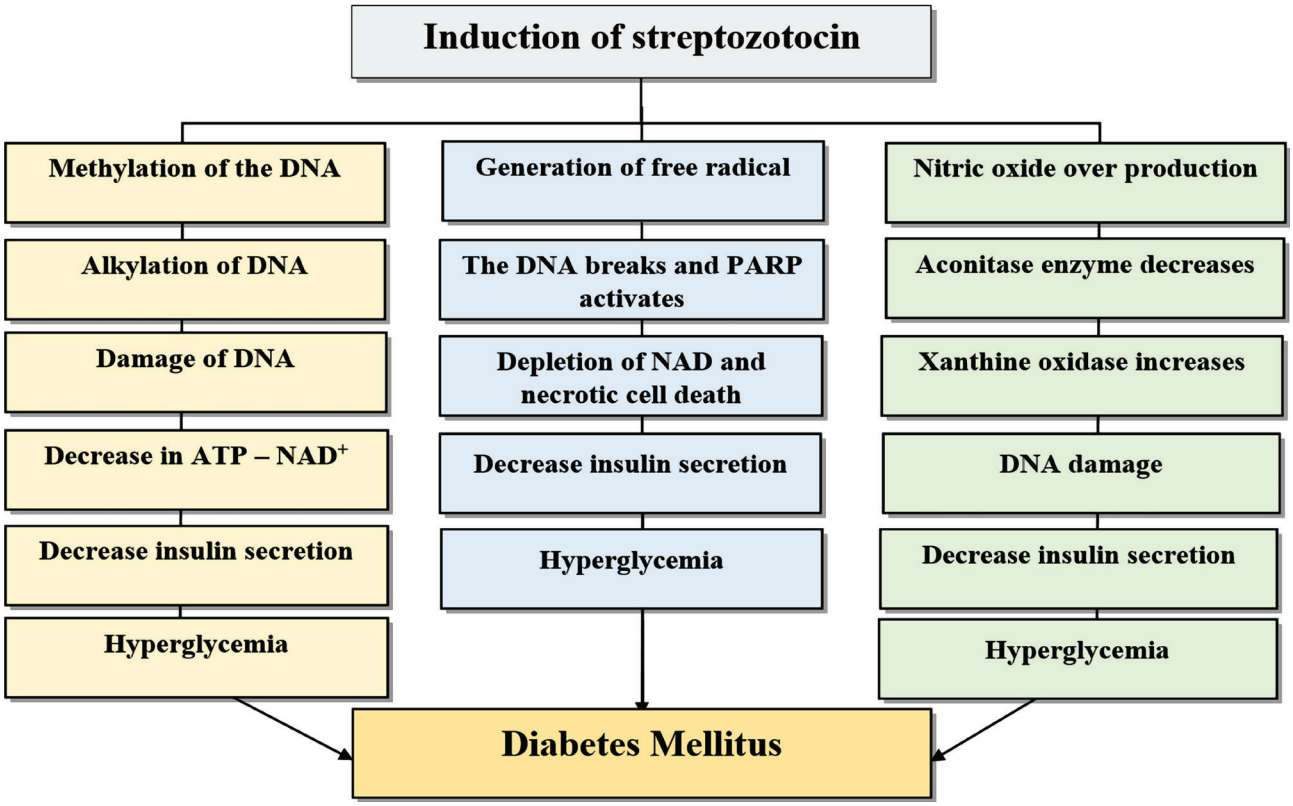

Figure 2: Mode of action of streptozotocin.

Many other compounds in rat model are also being used [64, 65] for inducing diabetes, as shown in Table 1.

Spontaneously induced model

Research indicates that several spontaneous models exist for both type of diabetes. The NOD (Non-Obese Diabetic) mouse is perhaps the most effective spontaneous model for Type 1 diabetes. It was created by breeding the progeny from the original cataract study. It shows human immunological characteristics [66, 67] Type 1 diabetes can be caused by several NOD mice genes.

In 1983, a spontaneously diabetic rat displaying polyuria, polyphagia, and polydipsia was observed within a colony of type of Rats known as outbred Long-Evans rats originated in and bought from Charles River Canada in 1982 [68]. The diabetic strain of LETL was bred from these rats. When diabetes first appears, there are no genetic variations in the frequency or intensity of the symptoms, which include weight loss, hyperglycaemia, polyphagia, quickly developing polyuria, lymphocyte migration into the islets, beta cell death, and lymphocyte discoloration.

Wistar rats are a specie of Rat that have been outbred to produce Type 1 Biobreeding rats (BB). It has been shown that a cell-mediated autoimmune process in these animals leads to the development of diabetes [69, 70]. It includes strains that are both bioavailable and resistant to diabetes [71]. It's been discovered that those with BBDP are more likely to develop retinopathy and neuropathy as secondary consequences of diabetes.

Table 1: Various chemical agents used for inducing diabetes.

Compound	Dose	Experimental model	Reference
Dehydroascorbic acid	200–300 mg/kg	Rat	[64, 65]
Dehydroisoascorbic acid	1.5 mg/kg	Rat	[64, 65]
Methylalloxan	53 mg/kg	Rat	[64, 65]
Ethylalloxan	50–130 mg/kg	Rat	[64, 65]

After puberty, BB rats are more likely to develop diabetes, which can cause hyperglycaemia, ketonuria, and hypoinsulinema [70].

As a result of inbreeding initiated in 1990, two sub-strains were developed: the Komeda Diabetes Prone (KDP) and the Komeda Nondiabetic (KND). These rats have moderate to severe levels of lymphocyte infiltration (insulitis), and they are linked to lymphocyte infiltration. A genetic study of diabetes type 1 in (KDP) rats revealed that the important susceptibility genes MHC and Iddm/kdp1 accounted for most of the genetic propensity to diabetes [72].

Genetically induced models

Akita mice are the best appropriate model for early-onset diabetes research. In Akita, Japan, they were made using the inbred strain C57BL/6. Their protein folding is abnormal, resulting in toxic beta cells, and they possess a mutation in the Ins2+/C96Y gene that leads to the demise of pancreatic beta cells [73, 74]. Polydipsia, hypoinsulinema, hyperglycaemia, and polyuria are some of the symptoms. Early-onset diabetes in Akita mice is autosomal dominantly inherited and is not accompanied by obesity or insulitis. When compared to non-diabetic animals, the Akita diabetic mice have significantly lower amounts of circulating insulin [75].

The genetic model of the ZDF rats was created in 1991 when Diabetic Fatty Rats were produced from an outbred Zucker rat colony in Indianapolis, USA. The leptin receptor gene (fa) on chromosome 5 has a simple autosomal recessive mutation that causes hyperglycaemia, insulin resistance, and obesity [76, 77]. It is noteworthy that between the ages of four and eight weeks, these rats exhibited significant insulin and glucose resistance. At eight to ten weeks of age, they exhibit obvious signs of diabetes, with fasting blood glucose levels reaching 500 mg/dL.

Goto-Kakizaki rats were produced by regularly crossing Wistar rats with Wistar rats that had the highest glucose tolerance limit in the normal distribution. They are regarded as a non-obese model and acquire peripheral insulin resistance within 56 days for the date of birth [75, 77]. They exhibit moderate hyperglycaemia early in life. Type 2 diabetes is induced using this approach.

Surgically induced model

This frequently used model involves removing of entire of or partly the pancreas to cause diabetes in rodents. The beta cells' capacity for regeneration is investigated. When 90% of the pancreas is surgically removed, hyperglycaemia results and partial loss of the organ is more significantly studied, while insulin dependent diabetes mellitus occurs from the complete removal of the pancreas [78]. Despite being frequently utilised, this model results in the loss of additional pancreatic enzymes and alpha and delta cells in addition to beta cells. This approach is intrusive as well.

Virus induced model

Absolutely like humans, mice also have insulin-dependent diabetes. Male ICR Swiss mice were observed and presence of the D variant encephalomyocarditis in them was found. It confirmed the Swiss mice are vulnerable to its diabetogenic effects. First, the cause of viral infection was identified in the 1960s by Gamble *et al.* as juvenile onset diabetes. Diabetes is brought on by the viruses Coxsackie virus and D-variant encephalomyocarditis [79]. Coxsackie virus damages the mice's pancreatic acinar cells. This virus infects mice due to tissue damage and inflammation. The infection responsible for the activation of latent auto-reactive T cells originates indirectly from islet antigen sensitization [80].

While D-Encephalomyocarditis virus damages the beta cells of pancreas in some inbred mouse strains. The chances of success are increased by first administering an immunosuppressive agent to the mice followed by viral infection [81].

Hormone induced method

Growth hormone can induce diabetes with development of renal complications [82]. Steroid diabetes is a condition that can result from the usage of corticosteroids. Prednisolone and dexamethasone are the two glucocorticoids that cause steroid diabetes the most frequently [83, 84]. In rats, intraperitoneal administration of dexamethasone twice daily at a dosage of 2 to 5 mg/kg causes the development of NIDDM [85].

Summary of common rodent models commonly being used for experimental induction of diabetes are summarised in Table 2.

Discussion

Diabetic neuropathy is one of the most prevalent and debilitating chronic complications of diabetes mellitus and is associated with significant morbidity,

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Table 2: Rodent models commonly used for experimental induction of diabetes.

Induction method	Animal model (type/species)	Key feature
Chemically induced	Streptozotocin model	β-cell destruction
	Alloxan model	Free radicals
	Dithizone model	Zinc interaction
Spontaneously induced	NOD mouse	Autoimmune
	LETL rat	Autoimmune
	BB rat	Complications
	KDP rat	Autoimmune
Genetically induced	Akita mouse	Early-onset
	ZDF rat	Obesity
	Goto-Kakizaki rat	Non-obese
Surgically induced	Pancreatectomy model	Pancreas removal
Virus induced	Encephalomyocarditis virus	β-cell damage
	Coxsackie virus	Acinar damage
Hormone induced	Dexamethasone-treated rat	Insulin resistance

mortality, and reduction in quality of life [86, 87]. Among its various forms, diabetic peripheral neuropathy (DPN) and diabetic neuropathic pain (DNP) are the most commonly reported manifestations, characterized by progressive nerve damage, sensory loss, burning pain, tingling sensations, numbness, and motor dysfunction, predominantly affecting the lower extremities in a symmetric and length-dependent manner [86, 88]. Earlier considered an asymptomatic and underdiagnosed complication, recent advances in diagnostic techniques and clinical awareness have enabled earlier detection and intervention [87, 89]. The pathogenesis of diabetic neuropathy is highly complex and multifactorial, involving chronic hyperglycaemia, oxidative stress, mitochondrial dysfunction, neuroinflammation, microvascular impairment, altered lipid metabolism, and activation of polyol and protein kinase C pathways, which collectively contribute to neuronal degeneration and impaired nerve conduction [88–90]. Current therapeutic strategies mainly focus on glycaemic control and symptomatic pain management using agents such as pregabalin, duloxetine, gabapentin, tricyclic antidepressants, and certain antidiabetic medications with neuroprotective potential; however, these therapies are often inadequate in reversing the underlying neuronal damage [87, 91]. Recent scientific literature emphasizes the importance of targeting inflammatory mediators, oxidative stress pathways, ion channels, and neurotrophic signalling mechanisms for developing more effective disease-modifying therapies [90–92].

Furthermore, diabetic neuropathy imposes a substantial economic burden on healthcare systems worldwide due to long-term treatment requirements, hospitalization, disability, and reduced work productivity [86, 87]. Experimental animal models have become indispensable tools for understanding the molecular and cellular mechanisms underlying diabetic neuropathic pain and for evaluating novel therapeutic interventions [93]. Streptozotocin-induced diabetic rodents, genetic diabetic mouse models, and high-fat diet-induced models are widely utilized to mimic human diabetic neuropathy and study alterations in peripheral and central nervous systems [94, 95]. These models have significantly contributed to identifying biomarkers, inflammatory pathways, and neuroprotective agents that may help prevent or delay neuropathic progression [90, 94]. Recent studies also highlight emerging therapeutic approaches including stem cell therapy, gene therapy, nanotechnology-based drug delivery systems, antioxidant therapy, and phytoconstituent-based interventions for improving nerve regeneration and reducing neuropathic pain [91, 93,95]. Although animal models cannot fully replicate the complexity of human diabetes and neuropathy, they continue to provide valuable insights into disease progression and therapeutic development [94]. Therefore, continued translational research integrating experimental models, molecular

biology, and advanced pharmacological approaches remains crucial for developing safer and more effective strategies for diabetic neuropathy management [93, 95].

Conclusion

Diabetic neuropathy is a major complication of diabetes mellitus associated with severe morbidity, chronic pain, and reduced quality of life. Existing therapies primarily provide symptomatic relief and fail to completely reverse neuronal damage or disease progression. Current research highlights the critical role of oxidative stress, inflammation, and metabolic dysfunction in the pathogenesis of diabetic neuropathy. Animal models remain essential for understanding disease mechanisms and evaluating novel therapeutic interventions.

Conflict of interest

The authors declare no conflict of interest.

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