ACTA ABP BIOCHIMICA POLONICA

Epub: No
Paper in Press
https://doi.org/10.18388/abp.2017_

Review

Molecular and biochemical mechanisms of diabetic encephalopathy

Igor Belenichev[1], Olena Aliyeva[2]✉, Olena Popazova[3] and Nina Bukhtiyarova[4]

[1]Department of Pharmacology and Medical Formulation with Course of Normal Physiology, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine; [2]Department of Medical Biology, Parasitology and Genetics, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine; [3]Department of Histology, Cytology and Embryology, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine; [4]Department of Clinical Laboratory Diagnostics, Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine

Diabetes mellitus is one of the important independent risk factors for the development of neurological disorders such as ischemic stroke, transient ischemic attacks, vascular dementia and neurodegenerative processes. Hyperglycemia plays a crucial role as a trigger in the pathogenesis of these disorders. In this review, we summarize the existing data on the molecular mechanisms of diabetic encephalopathy development, consider the features of oxidative and nitrosative stresses, changes in the thiol-disulfide system, as well as mitochondrial and endothelial dysfunction in diabetes. We focus on the role of HSP 70 in cellular responses in diabetic encephalopathy. HSP70 protein is an important component of the endogenous system of neuroprotection. It acts as an intracellular chaperone, providing the folding, retention, and transport of synthesized proteins, as well as their degradation under both normoxic and stress-induced denaturation conditions. HSP70 can be considered a molecular marker and a promising therapeutic target in the treatment of diabetes mellitus.

Keywords: diabetes mellitus, diabetic encephalopathy, thiol-disulfide system, mitochondrial dysfunction, HSP70, HIF-1a

Received: 31 July, 2023; revised: 13 October, 2023; accepted: 13 October, 2023; available on-line: ?? November, 2023

✉e-mail: aliyeva1eg@gmail.com

Abbreviations:

INTRODUCTION

Diabetes mellitus (DM) is recognized by numerous studies as an independent risk factor for ischemic stroke, transient ischemic attacks and vascular dementia (Tun *et al.,* 2017; Maida *et al.,* 2022). In some cases, it can be associated not only with cerebral vascular disease but also with neurodegenerative processes, in particular Alzheimer's disease. At the same time, diabetic neuropathy is the most common complication of diabetes mellitus and the leading factor among the causes of reduced quality of life in patients with diabetes (Feldman *et al.,* 2019; Aleidan *et al.,* 2020). One of the most difficult parts of diabetes mellitus treatment is the correction of its late neurological complications. Diabetic lesions of the nervous system inevitably occur even against the background of many years of compensation for the disease, achieved through the use of modern effective and affordable antidiabetic drugs. For example, diabetes increases the risk of acute cerebrovascular events 6 times, with a nearly three-fold increase in mortality from them (Maida *et al.,* 2022; Ergul *et al.,* 2012). The development of cerebral circulatory disorders in such patients is severe, and carbohydrate metabolism disorders are associated with high mortality and disability (Lin *et al.,* 2020; Hill-Briggs *et al.,* 2021). Chronic lesions of the brain in diabetes are called diabetic encephalopathy, which leads to a decrease in cognitive and mental functions, loss of performance and quality of life in this category of patients. The discovery of new mechanisms of many cerebrovascular diseases, in particular, disturbances of the functional state of the endothelium, inflammation of the vascular wall, and programmed cell death, has opened up opportunities for the development of effective pathogenetic correction measures. In the pathogenesis of diabetic encephalopathy, the trigger link is hyperglycemia (Shi *et al.,* 2016). An important mechanism of vascular complications against the background of hyperglycemia is the activation of the polyol pathway of glucose oxidation under the influence of the enzyme aldose reductase. As a result, glucose is converted into sorbitol under the influence of aldose reductase, which leads to depletion of NADPH and, subsequently, to depletion of the glutathione link of the thiol-disulfide system, reduction of endothelial NO synthase expression, necessary for NO synthesis. A special role in the formation of vascular complications in DM belongs to the activation of protein kinase C, and subsequently to the increase in the concentration of endothelin-1 and the production of growth factors: vascular endothelial growth factor VEGF, epidermal growth factor EGF and transformed growth factor TGF-β. Also, hyperglycemia leads to increased incorporation of glucose into the hexose substitutable pathway, resulting in increased transcription of inflammatory cytokine genes and hyperproduction of reactive oxygen species and NO. Currently, oxidative and nitrosative stress are considered a universal mechanism of development of all complications in DM, including neurodegeneration and endothelial dysfunction (Tota *et al.,* 2021; Pitocco *et al.,* 2013). Recently, experimental studies have discovered a new mechanism that explains many aspects of endothelial dysfunction and neurodegradation in DM (Sivitz & Yorek, 2010; Teodoro *et al.,* 2019; Cheng *et al.,* 2020). This is mitochondrial dysfunction, which is one of the causes of the increase in oxidative stress. Endogenous mechanisms, limiting the harmful effects of cytotoxic derivatives of NO, are provided by the thiol-disulfide system, the derivatives of which have transport properties with respect to NO, thus increasing its bioavailability. In addition, many thiols (glutathione, cysteine, methionine) can significantly limit the cytotoxicity of nitrosative stress, increasing the chance of cell survival (Kükürt *et al.,* 2021; Ren *et al.,* 2017; Aoyama*,* 2021). A significant role in the mechanisms of endogenous cyto- and neuroprotection is attributed to the proteins shaperones (HSP) especially, with mM 70 kDa (Belenichev *et al.,* 2023; Zhang *et al.,* 2022). However, their involvement in the molecular and biochemical mechanisms of the damage cascade mechanism in DM has not been fully identified; experimental data are scarce and sometimes contradictory. All this has prompted us to analyze and systematize world achievements in this direction, taking into account our modest results as well.

DIABETIC ENCEPHALOPATHY

The term "diabetic encephalopathy" (DE) was proposed by R. de Jong in 1950 and represents a persistent cerebral pathology resulting from the effects of acute, subacute and chronic vascular disorders, which are clinically manifested as neurosis-like and psychosis-like defects, organic, mild to moderate cognitive deficit (Dejong, 1950). It has been established that the most significant pathogenic factors initiating the development of DE are the duration of the disease, degree of DM, level of glycosylated hemoglobin, diastolic BP and total cholesterol (Li *et al.,* 2023; Wang *et al.,* 2020). In clinical observations and experimental equivalents of diabetes in animals, the duration of DM is associated with pathological changes in the CNS, characterized by cognitive and emotional deficits, which can be considered a factor in the development of dementia, as well as the risk of vascular brain complications (Feldman *et al.,* 2019; Aleidan *et al.,* 2020; Ergul *et al.,* 2012; Li *et al.,* 2023). A probable correlation between DM and cognitive function was established as early as 1922 (Miles & Root, 1922). Over the past 20 years, a number of studies evaluating the relationship between type 2 diabetes and cognitive function have been completed (Moheet *et al.,* 2015; Alkethiri *et al.,* 2021; Antal *et al.,* 2022; Kinattingal *et al.,* 2023). In DM, memory and attention are the most frequently impaired cognitive functions. Hypoglycemic conditions have a pronounced effect on the development of mnemonic disorders. In some cases, the development of dementia is possible. Under the term dementia, we understand a diffuse disorder of mental functions as a result of organic brain damage, manifested by primary disorders of thinking and memory, as well as secondary emotional and behavioral disorders. A diagnosis of dementia can be made when impairments of memory and other cognitive functions are pronounced to an extent that significantly interferes with the performance of professional and social activities in previous amounts and quality (Hugo & Ganguli, 2014). In its development, DE passes through several stages of its formation, which fully depend on the age of the disease: subclinical (coinciding with the debut of DM), clinical (corresponding to the age of the disease – from 2 to 5 years), subcompensation (over 5 years), severe (10–15 years) and decompensation (with the age of the disease over 20 years) (Cheon & Song, 2021; Popruga *et al.,* 2021).The clinical picture of DE is characterized by a typical triad of symptoms: headaches, dizziness, and memory impairment, which in general unite DE with other types of encephalopathies. However, DE has its own specific features: progressive cognitive decline, which is sometimes referred to as cognitive aging, and sometimes is considered as a pre-stage of Alzheimer's disease (Jayaraj *et al.,* 2020; Falvo *et al.,* 2023). Moreover, it has been established that the leading domains of cognitive impairment in type 2 DM patients are a decrease in short-term verbal memory and attention, correlating with atrophic changes in the cerebral cortex, which appear already in the early stages of diabetes and are not associated with vascular factors (Moheet *et al.,* 2015; Antal *et al.,* 2022).In addition, the clinical course of DE is characterized by frequent episodes of acute impairment of cerebral circulation, transient ischemic attacks and cerebral strokes. In particular, cerebral strokes are 6 times more frequently registered in DM patients (Maida *et al.,* 2022; Ergul *et al.,* 2012).Furthermore, chronic cerebral circulatory disorders are observed to a greater extent in patients with diabetes, leading to chronic cerebrovascular insufficiency syndrome, and the mechanisms of progressive memory decline are associated with chronic hypoxia, cerebral tissue ischemia, and neurometabolic disorders (Ergul *et al.,* 2012; Pitocco *et al.,* 2013).The concept of "brain insulin resistance", according to which insulin receptors exist in the limbic system along with neurotransmitter receptors, is of certain interest. Their role in the mechanisms of synaptic plasticity in the hippocampus has now been established. In particular, it has been shown that insulin rapidly mobilizes functional GABA-A receptors on postsynaptic membranes of hippocampal neurons and improves synaptic transmission. In addition, a regulatory role of insulin in the functioning of AMPA and NMDA receptors of hippocampal neuronal membranes has been established (Spinelli *et al.,* 2019). Insulin can act as a mediator by accelerating the synthesis and synaptic trafficking of acetylcholine, dopamine, and other mediators. With time there is a depletion of insulin receptors in the CNS and a weakening of the function of other neurotransport systems, which to some extent explains the processes of cognitive aging (Kleinridders *et al.,* 2014). In addition, it has been experimentally established that insulin also has a neuroprotective effect under conditions of oxidative stress or DM (Soto *et al.,* 2019). Pathomorphological studies have determined a decrease in the expression of insulin and insulin-like growth factor-1 (IGF) in the hippocampus, cerebellum, pons, and basal ganglia, as well as neuronal losses in the hippocampus and frontal neocortex (Jafferali *et al.,* 2000). In the brain, insulin and IGF-1 mediate numerous effects, including glucose utilization and energy metabolism, oxidative stress, genetic regulation of other neurotrophic factors and their receptors, cholinergic gene expression and tau-protein phosphorylation, and formation regulation. They also exhibit anti-inflammatory and anti-apoptotic effects (Dandona *et al.,* 2007). Decrease of insulin regulation inhibits early response genes c-fos and c-jun with subsequent expression of IGF1 and IGF2, nerve growth factor, neurotrophin-3 and their receptors (Griffiths *et al.,* 1998; Zhang & Li, 2017). Also, insulin and IGF provide neurotrophic support in the hippocampus. It is known that diabetic neurovascular pathology is a metabolic disorder whose pathogenesis is based on the lack of insulin requirement for glucose to enter both nerve tissue and the vascular wall. Hyperglycemia contributes to a significant (up to fourfold) increase in neuronal glucose levels with subsequent disruption of intracellular glucose metabolism and neuronal damage (Barrett *et al.,* 2017). This results in the development of secondary processes in the form of oxidative stress and protein glycosylation. At the same time, it was found that insulin activates the movement of GLUT4 to the plasma membrane in hippocampal neurons by mechanisms similar to those observed in peripheral tissues. It is considered that due to this, hippocampal neurons can significantly increase glucose utilization during neuronal activity growth (Cisternas *et al.,* 2019). But it was found that elevated plasma glucose levels of up to 6.1 mmol/L were associated with greater atrophy of structures associated with aging and neurodegeneration processes, in particular, the hippocampus and amygdalin. This indicates the relevance of glycemic control and correction in the subclinical course of DM or its absence. Disregarding the interdependence and similarity of pathogenesis, damages to the neuronal and vascular systems are fundamentally different, including the therapeutic approaches. Studies have established the role of hippocampal dysfunction in diabetes mellitus and its role in the development of DE (Spinelli *et al.,* 2019). In particular, it was electrophysiologically discovered that behavioral and mnemastic deviations in diabetic animals are associated with a deficit of long-term potentiality in the CA1 area of the hippocampus (Kumar, 2011). This factor, which reflects the synaptic plasticity of the hippocampus, was prevented by insulin therapy, while interventional treatment to normalize hyperglycemia had only a partial effect on long-term potentiality (Ho *et al.,* 2013). The role of hyperglycemia in the activation of damage mechanisms and activation of apoptosis in the rat hippocampus has also been established (Chen *et al.,* 2019). Induction of apoptosis in the hippocampus may be associated with an increase in the Bax/Bcl-2 and Bax/Bcl-xl ratio as well as caspase-3 activity (Liu *et al.,* 2013). It was experimentally determined that streptozotocin-induced diabetes led to cholinergic receptor dysfunction and reduced the neuroprotective activity of the GABAergic system in the hippocampus, indicating a high vulnerability of neurons of this brain formation and a relationship between the development of cognitive impairment and deficit (Sherin *et al.,* 2012).

Processes of systemic neuronal inflammation in the CNS also correlate with manifestations of cognitive deficits and are associated with increased levels of inflammatory cytokines (IL-1β, TNF-α and IL-6) against a decrease in BDNF in the hippocampus (Fourrier *et al.,* 2019; Dugue *et al.,* 2017). Long-term hyperglycemia leads to the activation of cyclooxygenase-2 expression that in turn results in the increase in biosynthesis of prostaglandin E2, which inhibits glucose-stimulated insulin secretion that disturbs cell tolerance to glucose and plays a significant role in the pathogenesis of DM. It has been experimentally established that streptozotocin-induced diabetes leads to an increase in the immunoreactivity of the inducible form of cyclooxygenase-2 (Cox-2) in the dentate gyrus and CA3-zone of the hippocampus and can thereby influence the synaptic plasticity processes in this structure (Nam *et al.,* 2011).

In general, such disorders can be the cause of rapid development of neurodegenerative changes in DM. The leading role in the pathogenesis of these complications belongs to the negative impact of oxidative stress on the function of the cells of the central nervous system, and in particular the hippocampus, provided both high intracellular glucose levels and impaired microcirculation (Kükürt *et al.,* 2021; Li *et al.,* 2023). (Fig. 1).

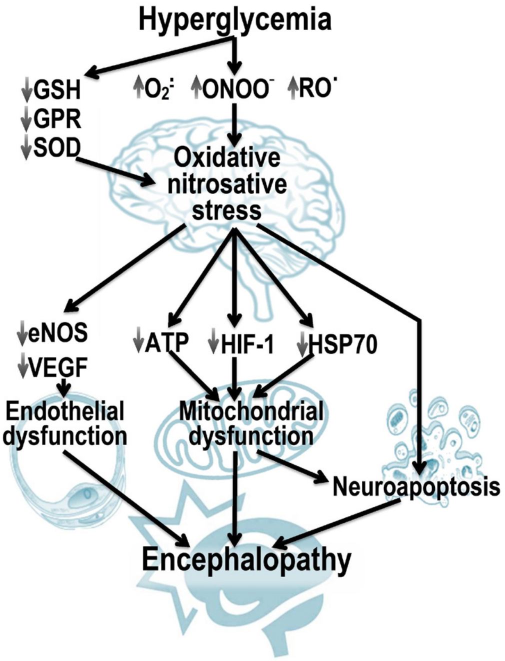

Figure 1. Molecular and biochemical cascade of links of diabetic encephalopathy pathogenesis.

OXIDATIVE STRESS

The main source of free-radical oxidation processes in DM is a state of chronic hyperglycemia. The development of neuronal dysfunction and the appearance of signs of cognitive deficit are based on disorders of carbohydrate metabolism, which lead to self-oxidation of glucose, to activation of the polyol (sorbitol) and hexozoamine pathways of glucose metabolism with intracellular accumulation of their reaction end products, to an increase in intracellular glutathione and ascorbate redox systems, as well as disorders of the metabolism of NO and prostaglandins, non-enzymatic glycosylation of proteins and formation of glycosylation end products with the subsequent development of neuroinflammatory processes and cytoxic edema of neuronal tissue (Kükürt *et al.,* 2021; Belenichev, 2013). Hypoxia observed in DM is an additional factor contributing to the increased formation of reactive oxidants. The accumulation of peroxidation products under conditions of hyperglycemia leads to the interaction of glucose with amino groups of proteins, increasing their glycosylation and oxidation (auto-oxidative oxidation). Non-enzymatic glycosylation of antioxidant defense enzymes leads to a decrease in their activity and even complete inactivation (Belenichev *et al.,* 2015). The greatest number of free radicals in the organism refers to combinations of reactive oxygen with a very short lifetime: the superoxide oxygen radical anion (O_2^-) and alkoxy radical (RO*) – 10^{-6} s, hydroxyl radical (OH^-) – 10^{-9} s, peroxyl radical (ROO) – 10^{-12} s (Collin, 2019; Edge & Truscott, 2021).

NITROXIDERGIC SYSTEM AND NITROSATIVE STRESS

The unique chemical nature and large number of intracellular targets for NO and its physiologically active oxidative-redox forms leave open the question of the way and the specificity in which the damaging effect of nitric oxide is mediated in the neuron under ischemic conditions. Numerous studies have shown the direct involvement of NO in the process of neuronal destruction in ischemia, arterial hypertension, and DM. A slight increase in NO concentration activates the synthesis of chaperone proteins and NO-dependent activation of HSP70 may constitute an important endogenous cellular defense mechanism. However, iNOS hyperexpression is suppressed by HSP70 by reducing the activation of the iNOS transcription factor (NFϰB), which leads to the limitation of nitrosative stress and neuroapoptosis (Belenichev *et al.,* 2015). Now, there is an active study of NO targets and whether NO is sufficiently cytotoxic, or whether its derivatives are more active (Aquilano *et al.,* 2011; Liu *et al.,* 2019). Studies in recent years have established that NO, and especially the products of its conversion, such as peroxynitrite (ONOO$^-$), nitrosonium ion (NO$^+$), nitroxyl (NO$^-$) and diazotrioxide (N$_2$O$_3$), are major factors in the realization of nitrosative stress, which results in direct interaction of NO with metals (hem iron of hemoglobin, myoglobin, iron-containing enzymes, as well as non-heme iron of iron-sulfur proteins and DNA, copper and zinc of active enzyme centers), and indirect interaction of NO$^+$ (S-, N-, O-nitrosation) with thiol, phenolic, hydroxyl and amino groups of proteins and DNA. Such interaction leads to receptor desensitization, inhibition of mitochondrial enzyme activity and fragmentation of nucleic acids (Belenichev *et al.,* 2015; Liu *et al.,* 2019).

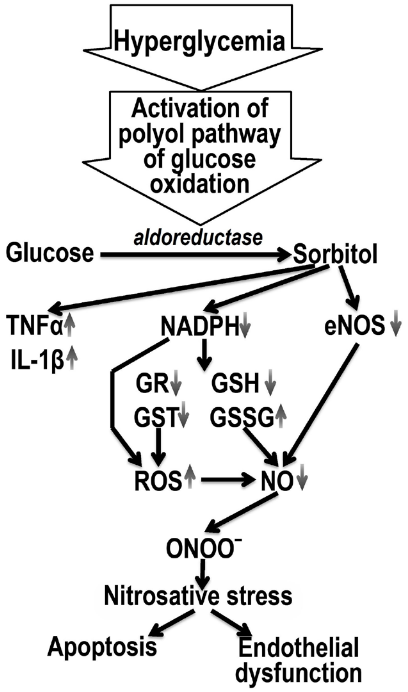

Figure 2. Disturbance in the coupling of NO/SH system in diabetes mellitus and nitrosative stress activation.

GLUTATHIONE LINK OF THE THIOL-DISULFIDE SYSTEM

Hyperglycemia promotes the activation of the sorbitol pathway of glucose metabolism, which, together with activation of NADPH oxidase, leads to depletion of the NADPH cytosolic level and, consequently, of the reduced glutathione (GSH) level (Yan, 2018). (Fig. 2). A decrease in GSH levels below normal values can serve as an indicator of impaired cellular redox status and changes in the redox-dependent regulation of genes. The consequence of this disturbance is a significant change in the mechanism of cellular redox-dependent signaling, controlled both non-enzymatically and enzymatically with the participation of glutathione transferase and glutaredoxin isoforms (Luo *et al.,* 2016; Ohiagu *et al.,* 2021). It is known that GSH is a neurotransmitter and neuromodulator (in micromolar concentrations it is an agonist of glutamate receptors; in millimolar concentrations, it modulates the SH groups of NMDA receptors). Oxidized forms of glutathione in concentrations above 200 μM decrease the expression of early response genes, and in concentrations of 5 mM or more, it activates p53-dependent apoptosis and reduces HSP levels (Belenichev *et al.,* 2020). GSH, competitively binding to nitric oxide, forms a complex in the form of S-nitrosoglutathione, which forms a depot of endogenous NO (further NO release is catalyzed by the thioredoxin system). Also, the release of NO from S-nitrosoglutathione occurs with glutamyltranspeptidase to form S-nitrosocysteinylglycine as a producer of NO. Cystine, which is reduced to cysteine, takes part in the transport of S-nitrosoglutathione. These reactions are controlled by glutathione reductase and glutathione transferase. Nitrosative stress results in oxidative modification of low molecular weight thiols, formation of homocysteine and its cytotoxic derivatives which enhance thiol oxidation (Ren *et al.,* 2017; Aoyama, 2021; Belenichev *et al.,* 2015). It should be noted that the increased intracellular levels of cytotoxic forms of NO and decreased levels of reduced glutathione may be associated with deprivation of the heat shock protein (HSP70) level (Belenichev *et al.,* 2020).The action of NO formed with the participation of mtNOS results in the opening of mitochondrial pores and the release of pro-apoptotic proteins into the cytosol. The opening of the pores is due to oxidation or nitrosylation of the thiol groups of the cysteine-dependent portion of the mitochondrial inner membrane protein (ATP/ADP-antiporter), and this converts it into a permeable nonspecific pore channel (Pavlov *et al.,* 2017). The interaction of NO with members of the Bcl-2 superfamily is also reflected in the fact that the action of nitric oxide in the cell decreases significantly the level of intracellular Bcl-2 protein, possibly through caspase-induced splitting or p53-dependent inhibition of its expression (Shamas-Din *et al.,* 2013; Fricker *et al.,* 2018; Török *et al.,* 2002). The proapoptotic effect of nitric oxide is also expressed in its induced increase in the expression of apoptogenic BaX proteins. GSH and its precursor N-acetylcysteine can modulate NF-ϰB, inhibit IL-1β expression, and exhibit anti-inflammatory effects (Belenichev *et al.,* 2020; Pavlov *et al.,* 2017). It is known that increased production of TNF-α, IL-1β, IL-6, and iNOS occurs against a background of GSH deficiency (Skelly *et al.,* 2013).

MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction (MD) has no etiological and nosological specificity and is a typical pathological process. However, it leads to disruption of mediator reuptake (noradrenaline, dopamine, serotonin), ion transport, impulse generation and conduction, protein synthesis, processes of transcription and translation, and activation of "parasitic" energy-producing reactions, resulting in significant energy expenditure in the neuronal cell. The role of MD in the development of various pathological conditions, including neurodegenerative ones, has

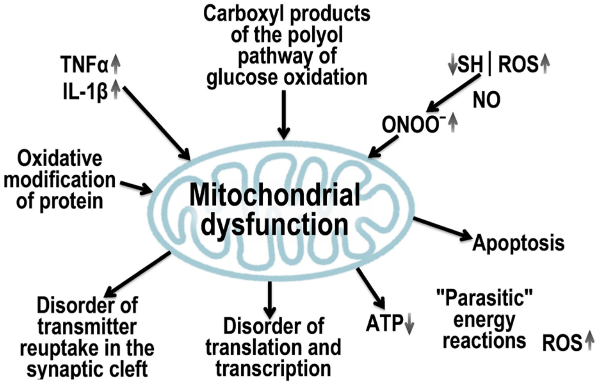

Figure 3. Formation of mitochondrial dysfunction in diabetes mellitus and its consequences.

also been confirmed in DM (Norat *et al.,* 2020; Wang *et al.,* 2020; Pessoa & Duarte, 2023).

It was experimentally determined that diabetes mellitus leads to a significant decrease in the membrane potential of rat brain mitochondria. These changes were accompanied by a decrease in the ATP content and ATP/ADP ratio in brain synaptosomes, which indicates diabetes-induced disorders in the functioning of the electron-transport chain and energy coupling of the electron transfer process with ATP synthesis (Belenichev *et al.,* 2015; Pinti *et al.,* 2019; Singh *et al.,* 2021).

In conditions of hypoperfusion of brain tissues, compensatory mechanisms are depleted and energy deficiency develops, which leads to an increase in Ca^{2+} levels in the cell cytoplasm because energy-dependent pumps that "load" Ca^{2+} into the cisterns of the endoplasmic reticulum or "unload" it from the cell are blocked. These processes activate Ca^{2+}-dependent phospholipases. One of the defense mechanisms preventing the accumulation of calcium ions in the cytoplasm is their capture by mitochondria. However, it increases their metabolic activity aimed at maintaining intramitochondrial charge and proton pumping. This is accompanied by an increase in ATP expenditure. In general, a vicious circle occurs when oxygen deficiency disrupts energy exchange and stimulates the formation of ROS damaging mitochondrial and lysosome membranes, which can lead to mitochondrial dysfunction. In turn, mitochondrial dysfunction leads to the initiation of apoptosis and irreversible damage and death of the neuron (Norat *et al.,* 2020). In addition, the key enzyme of the Krebs cycle, aconitate hydratase (aconitase), is highly sensitive to the effects of oxidative and nitrosative stress (Pessoa & Duarte, 2023). In DM its activity is significantly reduced, and this leads to impaired mitochondrial glucose oxidation, and ATP deficiency (Sivitz & Yorek, 2010; Kuretu, 2023) (Fig. 3).

ENDOTHELIAL DYSFUNCTION

Hyperglycemia is a trigger in the pathogenesis of diabetic encephalopathy. As a result of protein kinase C activation, there is an increase in the concentration of endothelin-1 and production of growth factors: vascular endothelial growth factor VEGF, epidermal growth factor EGF and transformed growth factor TGF-β (Ergul, 2011; Heydarpour *et al.,* 2020; Wu & Derynck, 2009; Chen *et al.,* 2020). Also in hyperglycemia, there is an increased incorporation of glucose into the hexose-substituted pathway, resulting in increased transcription of inflammatory cytokine genes, which also contributes to the formation of vascular inflammation and proatherogenic state (Shi *et al.,* 2016; Wang *et al.,* 2020). Currently, oxidative stress is considered the main universal mechanism of development of all complications in DM, in particular, as a result of endothelial dysfunction. Moreover, hyperglycemia-induced oxidative stress triggers damage reactions to protein structures of ion channels and receptors, as well as activation and phosphorylation of cytosolic phospholipase A2 (cPLA2) with increased formation of arachidonate and prostaglandin E2, which leads to changes in vascular permeability (Wang & Hsiao, 2020; Sun *et al.,* 2021). As a result of oxidative stress, DNA damage occurs, an obligatory stimulus for the activation of the nuclease enzyme poly(ADP-ribose) polymerase, which depletes the intracellular concentration of NAD+, reducing the level of glycolysis, slowing electron transport and ATP formation, blocking glyceraldehyde-3-fos activity, which leads to endothelial dysfunction and development of diabetic complications (Liu *et al.,* 2017; Pacher & Szabó, 2005) (Fig. 4).

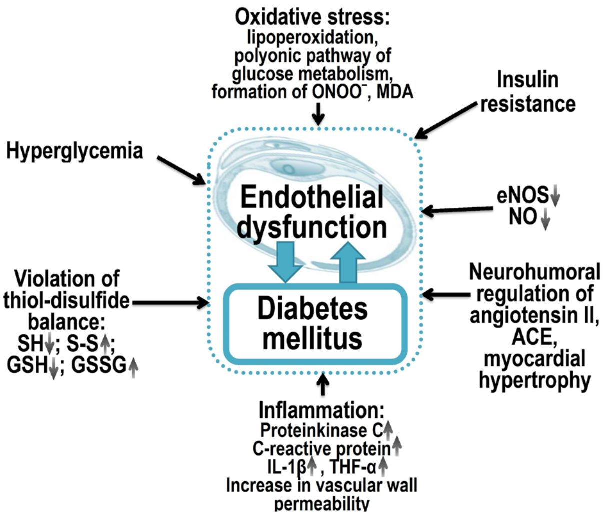

Figure 4. Pathogenesis of endothelial dysfunction in diabetes mellitus.

HEAT SHOCK PROTEINS

Clinical studies of HSP70 levels in diabetes are limited. It is known that patients with DM1 had elevated blood levels of HSP72, which decreased significantly after treatment (Ludwig *et al.,* 2014). However, another case-control study reported reduced serum HSP70 levels in type 1 diabetic patients with and without microvascular complications (Atalay *et al.,* 2004). Increased serum HSP70 levels were also found in patients with type 2 DM not treated with insulin (Nakhjavani *et al.,* 2010). A decrease in iHSP70 expression and an increase in eHSP70 expression are found in patients with obesity and metabolic diseases, including DM2. HSF-1, which is one of the HSP72 transcription factors, is also repressed in subjects with DM2 (Seibert *et al.,* 2022). HSF-1 expression in skeletal muscle was found to be five times lower in obese and DM2 patients than in a control obese group.

The family of heat shock proteins HSPs (Heat shock proteins) is considered to be one of the most studied cytoprotective factors (Kim *et al.,* 2020; Deka & Saha, 2018; Belenichev *et al.,* 2022). There is a class of proteins (chaperones) whose main function is to restore the correct tertiary structure of damaged proteins, as well as to form and dissociate protein complexes. Many chaperones are heat shock proteins, that is, proteins whose expression is initiated in response to increased temperature or other cellular stresses (Belenichev, 2013; Ortan *et al.,* 2018). HSPs act as intracellular chaperones that maintain cell proteostasis in normal and under various stress conditions (hyperthermia, hypoxia, oxidative stress, radiation, etc.).

The most interesting is the HSP70 protein as an important component of the system of endogenous cyto- and neuroprotection, which, first of all, performs the function of intracellular chaperones and provides the processes of folding, holding and transport of synthesized proteins, as well as their degradation, both in normoxia and under stress-induced denaturation (Turturici *et al.,* 2011). It is known that the heat shock protein family 70 includes: inducible/stress-inducible block HSP72/HSP70i, constitutive/physiological protein HSP73/HSC70, constitutive glucose-regulating mitochondrial protein GRP75, constitutive heme oxygenase-1 (HO^{-1}) participates in bilirubin metabolism (Belenichev *et al.,* 2023). The constitutive form of HSP70 is still present in all subcellular compartments and participates in the functioning of cell life support systems in normoxia. On the contrary, the inducible form of HSP70 appears in cells in response to stress, including ischemic stroke (Turturici *et al.,* 2011). In response to stress, ischemia, hypoxia, etc., a sharp increase in the level of HSP70 is registered, and its highest concentration is observed in vital parts of cells: nuclear, perinuclear space, mitochondria, endoplasmic reticulum, which indicates the importance of chaperone70 in protecting cells from death. As nuclear pre-ribosomes resume functioning, the concentration of HSP70 in the nucleus decreases and increases in the cell cytoplasm. Thus, the level of HSP70 can be considered as a marker of cellular and tissue damage. Hyperproduction of HSP70 in cells inhibits the development of autophagy as an alternative, more “radical” mechanism of cellular stress response (Belenichev, 2013; Ortan *et al.,* 2018). Recent studies have established a direct cytoprotective effect of HSP70, which is realized by regulating the processes of apoptosis and cell necrosis. HSP70 inhibits mitochondrial and cytoplasmic pathways of apoptosis. Thus, HSP70 inhibits the transition of procaspase 9 into active caspase 9 and disrupts apoptosome formation in the cytoplasm of cells. Against the background of HSP70 hyperexpression the level of anti-apoptotic protein Bcl-2 increases, which prevents the release of cytochrome c from mitochondria and translocation of apoptosis-inducing factor (AIF) into the nucleus preventing cell apoptosis. HSP70 protein inhibits TNFα-induced apoptosis and also effectively inhibits the development of Fas- and TRAIL- (TNF-related apoptosis-inducing ligand) mediated apoptosis in different cell types. Accumulation of HSP70 in cells increases their resistance to staurosporine, and doxorubicin, known as apoptosis inducers (Naka *et al.,* 2014). Ubiquitination of the insulin-like growth factor-1 receptor is inhibited by HSP10 and HSP60 which results in insulin-like growth factor-1 receptor signaling in cardiac muscle in streptozotacin-induced DM (Shan *et al.,* 2003). It is known that ischemia and hyperglycemia lead to the development of local inflammation. In this situation, HSP70 blocks the activation of the inflammatory transcription factor NF-ϰB and inhibits its cytokine-mediated translocation to the nucleus (Belenichev, 2013). HSP70 inhibits the production of proinflammatory cytokines (TNF-α, IL-6), inhibits the activity of matrix metalloprotein kinases (MMPs) and inducible nitric oxide synthase (iNOS) in models of ischemia *in vitro* and *in vivo* (Belenichev *et al.,* 2015). It was found that HSP70 in astrocyte culture under ischemia inhibits proapoptotic Jun N-terminal kinases (JNK) and p38 mitogen activating protein kinase (MAPK), disrupting the apoptosis signaling pathway (Giffard *et al.,* 2008). The studies demonstrated a direct relationship between HSP70 and TNFα expression levels, iNOS in microglia, and MMP-9 in astrocytes. When IL-1b interacts with receptors, the nuclear transcription factors AP-1 and NF-ϰB are activated, which alters the behavior of target cells and leads to the development of an acute cellular response, to the expression of other pro-inflammatory factors, to the stimulation of iNOS and cytotoxic NO produced by astrocytes, to an increase in mitochondrial pore permeability and to the initiation of neuroapoptosis. The IL-1b signaling pathway that enhances mechanisms of delayed neuronal death may be regulated by HSP70 (Kim *et al.,* 2020). An increase in HSP70 concentration within the physiological norm leads to an increase in IL-1β to levels necessary for its participation in cyto- and neuroprotection; while HSP70 deficiency can lead to a significant increase in IL-1. Overexpression of HSP70 attenuates IL-1β expression by inhibiting the C/EBPβ and C/EBPδ transcription factors (Senf *et al.,* 2008). HSP70 can prevent the production of inflammatory cytokines by inhibiting NF-ϰB-dependent transcription (Lyu *et al.,* 2020; Ferat-Osorio *et al.,* 2014). Many studies investigating the mechanisms of endogenous neuroprotection in ischemia show that the glutathione link of the thiol-disulfide system is reactivated against the background of an increase in the level of HSP70, and the introduction of exogenous HSP70 leads to an increase in the functional activity of the glutathione system (Belenichev *et al.,* 2020). HSP70 proteins mobilize antioxidant resources in neurons by increasing the level of both cytosolic and mitochondrial pools of reduced glutathione (Belenichev, 2013; Belenichev *et al.,* 2015; Zhang *et al.,* 2022). The data on the role of HSP in the stabilization of hypoxia-inducible factor (HIF-1a), which in conditions of ischemia is responsible for providing proliferation, apoptosis, angiogenesis, stabilization of protein molecules under oxidative stress, have recently emerged (Belenichev *et al.,* 2023). Under hypoxia conditions, HSP 70 is displaced from the complex with HIF-1a, thus, during 20–30 min of hypoxia, protecting the factor structure from targeted proteolysis. It is likely that HSP 70 is able to increase the lifetime of factor HIF-1a under pre- and post-hypoxia conditions and is required for cells to respond appropriately to oxygen deprivation under ischemic conditions (Kim *et al.,* 2020). HIF-1a determines the ability to activate the compensatory energy shunt and HSP 70 determines the ability of its long-term function. This statement is supported by the works of other researchers. It was found that one of the chaperones, the HSP 90 protein, is able to bind to the PAS domain of B-factor and stabilize it. Another cellular chaperone, HSP 70, recognizes a different structural motif of the HIF-1a molecule, the so-called oxygen-dependent degradation (ODD) domain (Dery *et al.,* 2005). It should be noted that the role of these inter-protein interactions is unclear; it is assumed that they are required for the stabilization of HIF-1a under normoxia conditions. Under hypoxia conditions, at least one of the chaperones (HSP 70) is displaced from the complex with HIF-1a by the ARNT protein, which protects the factor structure from targeted proteolysis during 20–30 min of hypoxia. Thus, HSP 70 is able to increase the lifetime of the HIF-1a factor under pre- and post-hypoxia conditions and is required for cells for an appropriate response to oxygen deprivation (Belenichev *et al.,* 2022; Belenichev *et al.,* 2023; Kim *et al.,* 2019).

Under DM, HSP levels are higher in some tissues and lower in other tissues. Defects in response to heat shock are seen in diabetic wounds. Both chaperones play important roles in cardiac defense. HSP60 expression is impaired in the heart of diabetic animals and this may contribute to diabetic cardiomyopathy (Atalay *et al.,* 2004). Also, expression of HSP72 is suppressed in streptozotacin-induced DM. A decrease of HSP70 was found in the mitochondria and cytosol of neurons in the CA1 hippocampus and sensorimotor cortex of rats with streptozotocin-induced DM (Chen *et al.,* 2013)15. Lower levels of HSP70 expression have been reported in insulin-sensitive tissues such as muscle and heart. There is evidence of decreased HSP70 protein levels in exercising diabetic animals with increased mRNA expression. Insulin resistance may contribute to a decrease in HSP70 levels in the heart and brain. It is hypothesized that increased expression of HSP70 in the brain is found in insulin sensitivity, in the brain as well as in peripheral tissues (Moin *et al.,* 2021).

HSP70 demonstrates diverse mechanisms of action on the development of inflammation and insulin resistance. Extracellular eHSP70 plays a role as a ligand for TLR2 and TLR4 in surrounding cells, which activates JNK *via* MEKK4/7 and suppresses NF-ϰB through IRAK4 activation (Mulyani *et al.,* 2020; Zhang *et al.,* 2013). eHSP70 also regulates the expression of eNOS, iNOS and other cytokines such as TNFα and IL1β (Belenichev *et al.,* 2023; Kim *et al.,* 2020; Deka & Saha, 2018; Giffard *et al.,* 2008). Activation of JNK leads to increased inflammation, triggers insulin resistance mechanisms and enhances the formation of mitochondrial dysfunction. In contrast, intracellular iHSP70 inhibits JNK activation and suppresses pathological mechanisms associated with its activation such as inflammation, insulin resistance, mitochondrial dysfunction, and ROS production (Bironaite *et al.,* 2012; Nagai & Kaji, 2023). The effect of HSP70 action depends on the iHSP70/eHSP70 ratio. A higher level of iHSP70 compared to eHSP70 leads to a decrease in inflammation processes (Krause *et al.,* 2015; Oliveira *et al.,* 2022; Seibert *et al.,* 2022; Alemi *et al.,* 2019).

LABORATORY DIAGNOSTICS

As a molecular marker in DM, it is necessary to determine the iHSP70/eHSP70 ratio in patients' serum or lymphocytes instead of total HSP70, which leads to a departure from the real picture of the pathological process. In healthy people, it is about 1 (Krause *et al.,* 2015; Seibert *et al.,* 2022). An [eHSP70]/[iHSP70] ratio of more than 5 indicates a significant pathological process – inflammation, insulin resistance, and endothelial dysfunction in DM (Mulyani *et al.,* 2020). The lower the ratio or the dynamics are more negative, the better the outcome of the disease.

PERSPECTIVES ON THE DEVELOPMENT OF PHARMACEUTICAL PRODUCTS

Such a role of chaperone proteins in cellular responses in pathological conditions raises the question of developing new drugs capable of providing modulation/protection of the genes encoding the synthesis of HSP 70 and HIF-1a proteins. Strategies aimed at modulating HSP70 in DM (prolonged exercise, pharmacological modulation of HSP70) require adherence to and maintenance of iHSP70 expression, thus preventing progression toward more severe DM and allowing restoration of insulin sensitivity. Thus, HSP70 is attractive as a therapeutic target in the treatment of DM.

Declarations

Author contributions. IB designed the research. IB and OA wrote the original manuscript. OP and NB performed the literature search and revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed a potential conflict of interest.

REFERENCES

Aleidan FAS, Ahmad BA, Alotaibi FA, Aleesa DH, Alhefdhi NA, Badri M, Abdel Gader AG (2020) Prevalence and risk factors for diabetic peripheral neuropathy among saudi hospitalized diabetic patients: a nested case-control study. *Int J Gen Med* **13**: 881–889. https://doi.org/10.2147/IJGM.S273807

Alemi H, Khaloo P, Rabizadeh S, Mansournia MA, Mirmiranpour H, Salehi SS, Esteghamati A, Nakhjavani M (2019) Association of extracellular heat shock protein 70 and insulin resistance in type 2 diabetes; independent of obesity and C-reactive protein. *Cell Stress Chaperones* **24**: 69–75. https://doi.org/10.1007/s12192-018-0942-x

Alkethiri K, Almtroudi T, Jurays AB, Abanumay F, Aldammas M, AlKhodheer M, Iqbal M, Habib SS, Bashir S (2021) The relationship between type 2 diabetes mellitus with cognitive functions. *Heliyon* **7**: e06358. https://doi.org/10.1016/j.heliyon.2021.e06358

Antal B, McMahon LP, Sultan SF, Lithen A, Wexler DJ, Dickerson B, Ratai EM, Mujica-Parodi LR (2022) Type 2 diabetes mellitus accelerates brain aging and cognitive decline: Complementary findings from UK Biobank and meta-analyses. *Elife* **11**: e73138. https://doi.org/10.7554/eLife.73138

Aoyama K (2021) Glutathione in the brain. *Int J Mol Sci* **22**: 5010. https://doi.org/10.3390/ijms22095010

Aquilano K, Baldelli S, Cardaci S, Rotilio G, Ciriolo MR (2011) Nitric oxide is the primary mediator of cytotoxicity induced by GSH depletion in neuronal cells. *J Cell Sci* **124**: 1043–1054. https://doi.org/10.1242/jcs.077149

Atalay M, Oksala NK, Laaksonen DE, Khanna S, Nakao C, Lappalainen J, Roy S, Hänninen O, Sen CK (2004) Exercise training modulates heat shock protein response in diabetic rats. *J Appl Physiol* **97**: 605–11. https://doi.org/10.1152/japplphysiol.01183.2003

Belenichev IF, Aliyeva OG, Popazova OO, Bukhtiyarova NV (2023) Involvement of heat shock proteins HSP70 in the mechanisms of endogenous neuroprotection: the prospect of using HSP70 modulators. *Front Cell Neurosci* **17**: 1131683. https://doi.org/10.3389/fncel.2023.1131683

Belenichev I F (2013) The Role of heat shock proteins in realization of molecular biochemical mechanisms of neuroprotection. *Pharm Drug Toxicol* **36**: 72–80

Belenichev IF, Aliyeva EG, Popazova OO (2022) Experimental substantiation of new target links in complex therapy of prenatal cns damage. pharmacological modulation of HSP70-dependent mechanisms of endogenous neuroprotection. *Neurotherapeutics* **19**: 1414–1431. https://doi.org/10.1007/s13311-022-01298-5

Belenichev IF, Cherniy VI, Nagornaya EA, Pavlov SV, Cherniy TV (2015) *Neuroprotection and neuroplasticity*. Logos, Kyiv

Belenichev IF, Chekman IS, Nagornaya EA, Gorbacheva SV, Gorchakova NA, Bukhtiyarova NV, Reznichenko NU, Feroz S (2020) *Thiol-disulfide System: Role in Endogenous Cyto- and Organoprotection, Pathways of Pharmacological Modulation*. Yuston Publishing House, Kyiv

Bironaite D, Pivoriunas A, Venalis A (2012) Upregulation of iHsp70 by mild heat shock protects rabbit myogenic stem cells: involvement of JNK signalling and c-Jun. *Cell Biol Int* **36**: 1089–1096. https://doi.org/10.1042/CBI20120143

Chen HY, Ho YJ, Chou HC, Liao EC, Tsai YT, Wei YS, Lin LH, Lin MW, Wang YS, Ko ML, Chan HL 92020) The role of transforming growth factor-beta in retinal ganglion cells with hyperglycemia and oxidative stress. *Int J Mol Sci* **21**: 6482. https://doi.org/10.3390/ijms21186482

Chen YW, Hsieh PL, Chen YC, Hung CH, Cheng JT (2013) Physical exercise induces excess hsp72 expression and delays the development of hyperalgesia and allodynia in painful diabetic neuropathy rats. *Anesth Analg* **116**: 482–490. https://doi.org/10.1213/ANE.0b013e318274e4a0

Chen Z, Guo H, Lu Z, Sun K, Jin Q (2019) Hyperglycemia aggravates spinal cord injury through endoplasmic reticulum stress mediated neuronal apoptosis, gliosis and activation. *Biomed Pharmacother* **112**: 108672. https://doi.org/10.1016/j.biopha.2019.108672

Cheng H, Gang X, Liu Y, Wang G, Zhao X, Wang G (2020) Mitochondrial dysfunction plays a key role in the development of neurodegenerative diseases in diabetes. *Am J Physiol Endocrinol Metab* **318**: E750–E764. https://doi.org/10.1152/ajpendo.00179.2019.

Cheon SY, Song J (2021) The association between hepatic encephalopathy and diabetic encephalopathy: the brain-liver Axis. *Int J Mol Sci* **22**: 463. https://doi.org/10.3390/ijms22010463

Cisternas P, Martinez M, Ahima RS, William Wong G, Inestrosa NC (2019) Modulation of glucose metabolism in hippocampal neurons by adiponectin and resistin. *Mol Neurobiol* **56**: 3024-3037. https://doi.org/10.1007/s12035-018-1271-x

Collin F (2019) Chemical basis of reactive oxygen species reactivity and involvement in neurodegenerative diseases. *Int J Mol Sci* **20**: 2407. https://doi.org/10.3390/ijms20102407

Dandona P, Chaudhuri A, Mohanty P, Ghanim H (2007) Anti-inflammatory effects of insulin. *Curr Opin Clin Nutr Metab Care* **10**: 511–517. https://doi.org/10.1097/mco.0b013e3281e38774

Dejong RN (1950) The nervous system complications of diabetes mellitus, with special reference to cerebrovascular changes. *J Nerv Ment Dis* **111**: 181–206. http://dx.doi.org/10.1097/00005053-195011130-00001

Deka K, Saha S (2018) Regulation of Mammalian HSP70 Expression and Stress Response. In *Regulation of heat shock protein responses. Heat shock proteins,* Asea A, Kaur P eds, vol 13*,* pp 3–25. Cham, Springer. https://doi.org/10.1007/978-3-319-74715-6_1

Dery MA, Michaud MD, Richard DE (2005). Hypoxia-inducible factor 1: Regulation by hypoxic and non-hypoxic activators. *Int J Biochem Cell Biol* **37**: 535–540. https://doi.org/10.1016/j.biocel.2004.08.012

Dugue R, Nath M, Dugue A, Barone FC (2017) Roles of pro- and anti-inflammatory cytokines in traumatic brain injury and acute ischemic stroke. In *Mechanisms of Neuroinflammation,* Chapter 9, Abreu GEA eds. IntechOpen. https://doi.org/10.5772/intechopen.70099

Edge R, Truscott TG 92021) The reactive oxygen species singlet oxygen, hydroxy radicals, and the superoxide radical anion - examples of their roles in biology and medicine. *Oxygen* **1**: 77–95. https:// doi.org/10.3390/oxygen1020009

Ergul A, Kelly-Cobbs A, Abdalla M, Fagan SC (2012). Cerebrovascular complications of diabetes: focus on stroke. *Endocr Metab Immune Disord Drug Targets* **12**: 148–158. https://doi.org/10.2174/187153012800493477

Ergul A (2011) Endothelin-1 and diabetic complications: focus on the vasculature. *Pharmacol Res* **63**: 477–482. https://doi.org/10.1016/j.phrs.2011.01.012

Barrett EJ, Liu Z, Khamaisi M, King GL, Klein R, Klein BEK, Hughes TM, Craft S, Freedman BI, Bowden DW, Vinik AI, Casellini CM (2017) Diabetic microvascular disease: an endocrine society scientific statement. *J Clin Endocrinol Metab* **102**: 4343–4410, https://doi.org/10.1210/jc.2017-01922

Falvo E, Giatti S, Diviccaro S, Cioffi L, Herian M, Brivio P, Calabrese F, Caruso D, Melcangi RC (2023) Diabetic encephalopathy in a preclinical experimental model of type 1 diabetes mellitus: observations in adult female rat. *Int J Mol Sci* **24**: 1196. https://doi.org/10.3390/ijms24021196

Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, Bril V, Russell JW, Viswanathan V (2019) Diabetic neuropathy. *Nat Rev Dis Primers* **5**: 42. https://doi.org/ 10.1038/s41572-019-0097-9

Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, Thornton PL, Haire-Joshu D (2020) Social determinants of health and diabetes: a scientific review. *Diabetes Care* **44**: 258–279. https://doi.org/10.2337/dci20-0053

Ferat-Osorio E, Sánchez-Anaya A, Gutiérrez-Mendoza M, Boscó-Gárate I, Wong-Baeza I, Pastelin-Palacios R, Pedraza-Alva G, Bonifaz LC, Cortés-Reynosa P, Pérez-Salazar E, Arriaga-Pizano L, López-Macías C, Rosenstein Y, Isibasi A (2014) Heat shock protein 70 down-regulates the production of toll-like receptor-induced pro-inflammatory cytokines by a heat shock factor-1/constitutive heat shock element-binding factor-dependent mechanism. *J Inflamm* **11**: 19. https://doi.org/10.1186/1476-9255-11-19

Fourrier C, Singhal G, Baune B (2019) Neuroinflammation and cognition across psychiatric conditions. *CNS Spectrums* **24**: 4–15. https://doi.org/10.1017/S1092852918001499

Fricker M, Tolkovsky AM, Borutaite V, Coleman M, Brown GC (2018) Neuronal cell death. *Physiol Rev* **98**: 813–880. https://doi.org/10.1152/physrev.00011.2017

Giffard RG, Han RQ, Emery JF, Duan M, Pittet JF (2008) Regulation of apoptotic and inflammatory cell signaling in cerebral ischemia: the complex roles of heat shock protein 70. *Anesthesiology* **109**: 339–448. https://doi.org/10.1097/ALN.0b013e31817f4ce0

Griffiths MR, Black EJ, Culbert AA, Dickens M, Shaw PE, Gillespie DA, Tavaré JM (1998) Insulin-stimulated expression of c-fos, fra1 and c-jun accompanies the activation of the activator protein-1 (AP-1) transcriptional complex. *Biochem J* **335**: 19–26. https://doi.org/10.1042/bj3350019

Heydarpour F, Sajadimajd S, Mirzarazi E, Haratipour P, Joshi T, Farzaei MH, Khan H, Echeverría J (2020) Involvement of TGF-β and autophagy pathways in pathogenesis of diabetes: a comprehensive review on biological and pharmacological insights. *Front Pharmacol* **11**: 498758. https://doi.org/10.3389/fphar.2020.498758

Ho N, Sommers MS, Lucki I (2013) Effects of diabetes on hippocampal neurogenesis: links to cognition and depression. *Neurosci Biobehav Rev* **37**: 1346–1362. https://doi.org/10.1016/j.neubiorev.2013.03.010

Hugo J, Ganguli M (2014) Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. *Clin Geriatr Med* **30**: 421–442. https://doi.org/10.1016/j.cger.2014.04.001

Jafferali S, Dumont Y, Sotty F, Robitaille Y, Quirion R, Kar S (2000) Insulin-like growth factor-I and its receptor in the frontal cortex, hippocampus, and cerebellum of normal human and alzheimer disease brains. *Synapse* **38**: 450–459. https://doi.org/10.1002/1098-2396(20001215)38:4<450::AID-SYN10>3.0.CO;2-J

Jayaraj RL, Azimullah S, Beiram R (2020) Diabetes as a risk factor for Alzheimer's disease in the Middle East and its shared pathological mediators. *Saudi J Biol Sci* **27**: 736–750. https://doi.org/10.1016/j.sjbs.2019.12.028

Kim JY, Barua S, Huang MY, Park J, Yenari MA, Lee JE (2020) Heat Shock Protein 70 (HSP70) induction: chaperonotherapy for neuroprotection after brain injury. *Cells* **9**: 2020. https://doi.org/10.3390/cells9092020

Kim JY, Huang M, Lee JE, Yenari MA (2019) Role of Heat Shock Proteins (HSP) in neuroprotection for ischemic stroke. In *Heat Shock Proteins in Neuroscience. Heat Shock Proteins,* Vol 20, Asea A, Kaur P eds, Cham, Springer. https://doi.org/10.1007/978-3-030-24285-5_6

Kinattingal N, Mehdi S, Undela K, Wani SUD, Almuqbil M, Alshehri S, Shakeel F, Imam MT, Manjula SN (2023) Prevalence of cognitive decline in type 2 diabetes mellitus patients: a real-world cross-sectional study in Mysuru, India. *J Pers Med* **13**: 524. https://doi.org/10.3390/jpm13030524

Kleinridders A, Ferris HA, Cai W, Kahn CR (2014) Insulin action in brain regulates systemic metabolism and brain function. *Diabetes 1* **63**: 2232–2243. https://doi.org/10.2337/db14-0568

Krause M, Heck TG, Bittencourt A, Scomazzon SP, Newsholme P, Curi R, Homem de Bittencourt PI Jr (2015) The chaperone balance hypothesis: the importance of the extracellular to intracellular HSP70 ratio to inflammation-driven type 2 diabetes, the effect of exercise, and the implications for clinical management. *Mediators Inflamm* **2015**: 249205. https://doi.org/10.1155/2015/249205

Kükürt A, Gelen V, Başer Ö, Deveci H, Karapehlivan M (2021) *Thiols: Role in Oxidative Stress-Related Disorders*. IntechOpen. https://doi.org/10.5772/intechopen.96682

Kumar A (2011) Long-term potentiation at CA3-CA1 hippocampal synapses with special emphasis on aging, disease, and stress. *Front Aging Neurosci* **3**: 7. https://doi.org/10.3389/fnagi.2011.00007

Kuretu A, Arineitwe C, Mothibe M, Ngubane P, Khathi A, Sibiya N (2023) Drug-induced mitochondrial toxicity: Risks of developing glucose handling impairments. *Front Endocrinol* **14**: 1123928. https://doi.org/10.3389/fendo.2023.1123928

Li Y, Liu Y, Liu S, Gao M, Wang W, Chen K, Huang L, Liu Y (2023) Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. *Signal Transduct Target Ther* **8**: 152. https://doi.org/10.1038/s41392-023-01400-z

Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, Song X, Ren Y, Shan PF (2020) Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Sci Rep* **10**: 14790. https://doi.org/10.1038/s41598-020-71908-9

Liu C, Liang MC, Soong TW (2019) Nitric oxide, iron and neurodegeneration. *Front Neurosci* **13**: 114. https://doi.org/10.3389/fnins.2019.00114

Liu G, Wang T, Wang T, Song J, Zhou Z (2013) Effects of apoptosis-related proteins caspase-3, Bax and Bcl-2 on cerebral ischemia rats. *Biomed Rep* **1**: 861–867. https://doi.org/10.3892/br.2013.153

Liu C, Vyas A, Kassab MA, Singh AK, Yu X (2017) The role of poly ADP-ribosylation in the first wave of DNA damage response. *Nucleic Acids Res* **45**: 8129–8141, https://doi.org/10.1093/nar/gkx565

Ludwig MS, Minguetti-Camara VC, Heck TG, Scomazzon SP, Nunes PR, Bazotte RB, Homem de Bittencourt PIJ (2014) Short-term but not long-term hypoglycaemia enhances plasma levels and hepatic expression of HSP72 in insulin-treated rats: an effect associated with increased IL-6 levels but not with IL-10 or TNF-alpha. *Mol Cell Biochem* **397**: 97–107. https://doi.org/10.1007/s11010-014-2176-2

Lyu Q, Wawrzyniuk M, Rutten VPMG, van Eden W, Sijts AJAM, Broere F (2020) Hsp70 and NF-kB mediated control of innate inflammatory responses in a canine macrophage cell line. *Int J Mol Sci* **21**: 6464. https://doi.org/10.3390/ijms21186464

Maida CD, Daidone M, Pacinella G, Norrito RL, Pinto A, Tuttolomondo A (2022) Diabetes and ischemic stroke: an old and new relationship an overview of the close interaction between these diseases. *Int J Mol Sci* **23**: 2397. https://doi.org/10.3390/ijms23042397

Miles WR, Root HF (1922) Psychologic tests applied to diabetic patients. *Arch Intern Med* **30**: 767–777. https://doi.org/10.1001/archinte.1922.00110120086003

Moheet A, Mangia S, Seaquist ER 2015) Impact of diabetes on cognitive function and brain structure. *Ann N Y Acad Sci* **1353**: 60–71. https://doi.org/10.1111/nyas.12807

Moin ASM, Nandakumar M, Diane A, Dehbi M and Butler AE (2021) The role of heat shock proteins in type 1 diabetes. *Front Immunol* **11**: 612584. https://doi.org/10.3389/fimmu.2020.612584

Mulyani WRW, Sanjiwani MID, Sandra, Prabawa IPY, Lestari AAW, Wihandani DM, Suastika K, Saraswati MR, Bhargah A, Manuaba IBAP (2020) Chaperone-based therapeutic target innovation: Heat Shock Protein 70 (HSP70) for type 2 diabetes mellitus. *Diabetes Metab Syndr Obes* **13**: 559–568. https://doi.org/10.2147/DMSO.S232133

Nagai M, Kaji H (2023) Thermal effect on heat shock protein 70 family to prevent atherosclerotic cardiovascular disease. *Biomolecules* **13**: 867. https://doi.org/10.3390/biom13050867

Naka K K, Vezyraki P, Kalaitzakis A, Zerikiotis S, Michalis L, Angelidis C (2014) Hsp70 regulates the doxorubicin-mediated heart failure in Hsp70-transgenic mice. *Cell Stress Chaperones* **19**: 853–864. https://doi.org/10.1007/s12192-014-0509-4

Nakhjavani M, Morteza A, Khajeali L, Esteghamati A, Khalilzadeh O, Asgarani F, Outeiro TF (2010) Increased serum HSP70 levels are associated with the duration of diabetes. *Cell Stress Chaperones* **15**: 959–964. https://doi.org/10.1007/s12192-010-0204-z

Nam SM, Yi SS, Yoo KY, Park OK, Yan B, Song W, Won MH, Yoon YS, Seong JK (2011) Differential effects of treadmill exercise on cyclooxygenase-2 in the rat hippocampus at early and chronic stages of diabetes. *Lab Anim Res* **27**: 189–195. https://doi.org/10.5625/lar.2011.27.3.189

Norat P, Soldozy S, Sokolowski JD, Gorick CM, Kumar JS, Chae Y, Yağmurlu K, Prada F, Walker M, Levitt MR, Price RJ, Tvrdik P, Kalani MYS (2020) Mitochondrial dysfunction in neurological disorders: Exploring mitochondrial transplantation. *NPJ Regen Med* **5**: 22. https://doi.org/10.1038/s41536-020-00107-x

Ohiagu F, Chikezie P, Chikezie C (2021) Pathophysiology of diabetes mellitus complications: Metabolic events and control. *Biomed Res Ther* **8**: 4243–4257. https://doi.org/10.15419/bmrat.v8i3.663

Oliveira AA, Priviero F, Webb RC, Nunes KP (2022) Increased eHSP70-to-iHSP70 ratio disrupts vascular responses to calcium and activates the TLR4-MD2 complex in type 1 diabetes. *Life Sci* **310**: 121079. https://doi.org/10.1016/j.lfs.2022.121079

Ortan P, Akan OY, Hosgorler F (2018) Heat Shock Protein70 in Neurological Disease. In *HSP70 in Human Diseases and Disorders. Heat Shock Proteins,* Vol 14, pp 57–69, Asea A, Kaur P eds. Cham, Springer. https://doi.org/10.1007/978-3-319-89551-2_3

Pacher P, Szabó C (2005) Role of poly(ADP-ribose) polymerase-1 activation in the pathogenesis of diabetic complications: endothelial dysfunction, as a common underlying theme. *Antioxid Redox Signal* **7**: 1568–1580. https://doi.org/10.1089/ars.2005.7.1568

Pavlov SV, Belenichev IF, Nikitchenko YV, Gorbachova SV (2017) Molecular bio-chemical mechanisms of HSP 70-mediated cytoprotection in pathologies of ischemic origin. *Bull Probl Biol Med* **1**: 61–67

Pessoa J, Duarte AI (2023) Overcoming mitochondrial dysfunction in neurodegenerative diseases. *Neural Reg Res* **18**: 1486–1488. https://doi.org/10.4103/1673-5374.360279

Pinti MV, Fink GK, Hathaway QA, Durr AJ, Kunovac A, Hollander JM (2019) Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. *Am J Phys-Endocr Metab* **316**: E268–E285. https://doi.org/10.1152/ajpendo.00314.2018

Pitocco D, Tesauro M, Alessandro R, Ghirlanda G, Cardillo C (2013) Oxidative stress in diabetes: implications for vascular and other complications. *Int J Mol Sci* **14**: 21525–21550. https://doi.org/10.3390/ijms141121525

Popruga A, Mykhaylychenko T, Samarchenko L, Bobyrova L (2021) Mathematical model of diabetic encephalopathy in diagnosis of complicated forms of diabetes mellitus. *Int J Endocr (Ukr)* **13**: 420–423. https://doi.org/10.22141/2224-0721.13.6.2017.112882

Ren X, Zou L, Zhang X, Branco V, Wang J, Carvalho C, Holmgren A, Lu J (2017) Redox signaling mediated by thioredoxin and glutathione systems in the central nervous system. *Antioxid Redox Signal* **27**: 989–1010. http://doi.org/10.1089/ars.2016.6925

Seibert P, Anklam CFV, Costa-Beber LC, Sulzbacher LM, Sulzbacher MM, Sangiovo AMB, Dos Santos FK, Goettems-Fiorin PB, Heck TG, Frizzo MN, Ludwig MS (2022) Increased eHSP70-to-iHSP70 ratio in prediabetic and diabetic postmenopausal women: a biomarker of cardiometabolic risk. *Cell Stress Chaperones* **27**: 523–534. https://doi.org/10.1007/s12192-022-01288-8

Senf SM, Dodd SL, McClung JM, Judge AR (2008) Hsp70 overexpression inhibits NF-kappaB and Foxo3a transcriptional activities and prevents skeletal muscle atrophy. *FASEB J* **22**: 3836–3845. doi: 10.1096/fj.08-110163

Shamas-Din A, Kale J, Leber B, Andrews DW (2013) Mechanisms of action of Bcl-2 family proteins. *Cold Spring Harb Perspect Biol* **5**: a008714. https://doi.org/10.1101/cshperspect.a008714

Shan YX, Yang TL, Mestril R, Wang PH (2003) Hsp10 and Hsp60 suppress ubiquitination of insulin-like growth factor-1 receptor and augment insulin-like growth factor-1 receptor signaling in cardiac muscle: implications on decreased myocardial protection in diabetic cardiomyopathy. *J Biol Chem* **278**: 45492–45498. https://doi.org/10.1074/jbc.M304498200

Sherin A, Anu J, Peeyush KT, Smijin S, Anitha M, Roshni BT, Paulose CS (2012) Cholinergic and GABAergic receptor functional deficit in the hippocampus of insulin-induced hypoglycemic and streptozotocin-induced diabetic rats. *Neuroscience* **202**: 69–76. https://doi.org/10.1016/j.neuroscience.2011.11.058

Shi J, Dong B, Mao Y, Guan W, Cao J, Zhu R, Wang S (2016) Review: Traumatic brain injury and hyperglycemia, a potentially modifiable risk factor. *Oncotarget* **7**: 71052–71061. https://doi.org/10.18632/oncotarget.11958

Singh R, Mohapatra L, Tripathi, AS (2021) Targeting mitochondrial biogenesis: a potential approach for preventing and controlling diabetes. *Futur J Pharm Sci* **7**: 212. https://doi.org/10.1186/s43094-021-00360-x

Sivitz WI, Yorek MA (2010) Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. *Antioxid Redox Signal* **12**: 537–577. https://doi.org/10.1089/ars.2009.2531

Skelly DT, Hennessy E, Dansereau M-A, Cunningham C (2013) A systematic analysis of the peripheral and CNS effects of systemic LPS, IL-1β, TNF-α and IL-6 challenges in C57BL/6 mice. *PLoS ONE* **8**. https://doi.org/10.1371/annotation/90c76048-2edd-4315-8404-4d9d8cbd411e

Soto M, Cai W, Konishi M, Kahn CR (2019) Insulin signaling in the hippocampus and amygdala regulates metabolism and neurobehavior. *Proc Natl Acad Sci USA* **116**: 6379–6384. https://doi.org/10.1073/pnas.1817391116

Spinelli M, Fusco S, Grassi C (2019) Brain insulin resistance and hippocampal plasticity: mechanisms and biomarkers of cognitive decline. *Front Neurosci* **13**: 788. https://doi.org/10.3389/fnins.2019.00788

Sun GY, Geng X, Teng T, Yang B, Appenteng MK, Greenlief CM, Lee JC (2021) Dynamic role of phospholipases A2 in health and diseases in the central nervous system. *Cells* **10**: 2963. https://doi.org/10.3390/cells10112963

Teodoro JS, Nunes S, Rolo AP, Reis F, Palmeira CM (2019) Therapeutic options targeting oxidative stress, mitochondrial dysfunction and inflammation to hinder the progression of vascular complications of diabetes. *Front Physiol* **9**: 1857. https://doi.org/10.3389/fphys.2018.01857

Török NJ, Higuchi H, Bronk S, Gores GJ (2002) Nitric oxide inhibits apoptosis downstream of cytochrome *c* release by nitrosylating caspase 91. *Cancer Res* **62**: 1648–1653

Tota Ł, Matejko B, Morawska-Tota M, Pilch W, Mrozińska S, Pałka T, Klupa T and Malecki MT (2021) Changes in oxidative and nitrosative stress indicators and vascular endothelial growth factor after maximum-intensity exercise assessing aerobic capacity in males with type 1 diabetes mellitus. *Front Physiol* **12**: 672403. https://doi.org/10.3389/fphys.2021.672403

Tun NN, Arunagirinathan G, Munshi SK, Pappachan JM (2017) Diabetes mellitus and stroke: A clinical update. *World J Diabetes* **8**: 235–248. https://doi.org/ 10.4239/wjd.v8.i6.235

Turturici G, Sconzo G, Geraci F (2011) Hsp70 and its molecular role in nervous system diseases. *Biochem Res Int* **2011**: 618127. https://doi.org/ 10.1155/2011/618127

Wang C, Li J, Zhao S, Huang L (2020) Diabetic encephalopathy causes the imbalance of neural activities between hippocampal glutamatergic neurons and GABAergic neurons in mice. *Brain Res* **1742**: 146863. https://doi.org/10.1016/j.brainres.2020.146863

Wang MH, Hsiao G, Al-Shabrawey M (2020) Eicosanoids and oxidative stress in diabetic retinopathy. *Antioxidants (Basel)* **9**: 520. https://doi.org/10.3390/antiox9060520

Wang W, Zhao F, Ma X, Perry G, Zhu X (2020) Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. *Mol Neurodegener* **15**: 30. https://doi.org/10.1186/s13024-020-00376-6

Wu L, Derynck R (2009) Essential role of TGF-beta signaling in glucose-induced cell hypertrophy. *Dev Cell* **17**: 35–48. https://doi.org/10.1016/j.devcel.2009.05.010

Luo X, Wu J, Jing S, Yan LJ (2016) Hyperglycemic stress and carbon stress in diabetic glucotoxicity. *Aging Dis* **7**: 90–110. https://doi.org/10.14336/AD.2015.0702

Yan LJ (2018) Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. *Animal Model Exp Med* **1**: 7–13. https://doi.org/10.1002/ame2.12001

Zhang Y, Zhang X, Shan P, Hunt CR, Pandita TK, Lee PJ (2013) A protective Hsp70-TLR4 pathway in lethal oxidant lung injury. *J Immunol* **191**: 1393–403. https://doi.org/10.4049/jimmunol.1300052

Zhang Y, Li H (2017) Reprogramming interferon regulatory factor signaling in cardiometabolic diseases. *Physiology* **32**: 210–223. https://doi.org/10.1152/physiol.00038.2016

Zhang H, Gong W, Wu S, Perrett S (2022) HSP70 in Redox homeostasis. *Cells* **11**: 829. https://doi.org/10.3390/cells11050829