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Mitochondria Function in Diabetes – From Health to Pathology – New Perspectives for Treatment of Diabetes-Driven Disorders

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1. Introduction

A few words about mitochondria ….

Mitochondria are active intracellular structures that collide, divide, and fuse with other mitochondria. Mitochondria exist as branched-chain reticulum networks, but can also exist as punctuated structures. Their distribution within the cells is quite diverse, is regulated by the interactions with the cytoskeleton and maintained by the balance between mitochondrial fusion and fission.
Mitochondria play crucial physiological functions that underlie the distortions of fragile balance between health and disease. In recent years, the role of mitochondria has gained much interest in the field of diabetic pathology since mitochondrial abnormalities were found in insulin resistance and in both types of diabetes.

A few words about hyperglycaemia and diabetes….

Hyperglycaemia, resulting from uncontrolled regulation of glucose metabolism, is widely recognized as the causal link between diabetes and diabetic complications. Diabetes mellitus has been classified into two forms. Type 1 diabetes, which accounts for about 10% of all cases of diabetes, is caused by autoimmune destruction of pancreatic β-cells that implies insulin deficiency. Type 2 diabetes, the more prevalent form of diabetes, is considered a heterogeneous disease due to the multiplicity of factors that cause the observed phenotype. It results from the combination of insulin resistance and/or a β-cell secretory defects. The explosive increase in the prevalence of type 2 diabetes is predicted in the nearest future. It is considered that about 220 millions people all over the world may suffer from the condition, and an equal number is thought to be "prediabetic", having early symptoms and not yet full manifestation of the disease.

A few words about impact of hyperglycaemia on mitochondria …..

Hyperglycaemia has been indicated as one of the main causes of altered mitochondrial function in diabetic individuals (animals and humans). Rather huge variation in the extent of damage has been observed and attributed to both the type and duration of diabetes studied. General consensus points out to the formation of glycation products as a crucial mechanism, by which hyperglycaemia affects mitochondrial and cellular function in diabetes.

Hyperglycaemia elicits an increased ROS production, presumably to the major extent originating from mitochondrial respiratory chain. ROS play a central role in mediating various metabolic defects associated with a diabetic state. Therefore, the inhibition of ROS production and/or enhancement of ROS scavenging might prove to be beneficial therapies. Alterations in metabolic regulators and glucose-stimulated insulin secretion are also associated with mitochondrial dysfunction in diabetes.

Impairments in mitochondrial function are intrinsically related to diabetes. The prevailing hypothesis is that hyperglycaemia-induced increase in electron transfer donors (NADH and $FADH_2$) may increase electron flux through the mitochondrial electron transport chain. Consequently, the ATP/ADP ratio and hyperpolarisation of the mitochondrial membrane (electrochemical potential difference) also become increased. This high electrochemical potential difference generated by the proton gradient leads to partial inhibition of the electron transport in the complex III, resulting in the augmented electron flow towards coenzyme Q. In turn, this drives partial reduction of O_2 to generate the free radical anion superoxide. It is accelerated reduction of coenzyme Q and generation of ROS that are believed to constitute the fundamental source for mitochondrial dysfunction that plays a critical role in diabetes-related metabolic disorders and tissue histopathology.

A few words about oxidative stress…..

Oxidative stress has been implicated as a major contributor to both the onset and the progression of diabetes and its associated complications. Some of the consequences of an oxidative environment may be the development of insulin resistance, β-cell dysfunction, impaired glucose tolerance, and mitochondrial dysfunction, which can ultimately lead to the diabetic disease state. Experimental and clinical data suggest an inverse association between insulin sensitivity and ROS levels. Oxidative stress can arise from a number of different sources, like the disease state or lifestyle, including episodes of ketosis, sleep restriction, and excessive nutrient intake. Oxidative stress can be reduced by controlling calorie intake, hyperglycaemia and mitochondrial metabolism.

It is now established that 90% of intracellular ROS are generated by mitochondria. The mitochondrial respiratory chain is the principal source of cellular oxygen radicals (ROS), such as superoxide anion radicals and hydroxyl radicals. The primary factor governing mitochondrial ROS generation is the redox state of the respiratory chain. If the membrane potential across the inner mitochondrial membrane rises above a certain threshold value, a massive stimulation of ROS generation occurs. Electrons leak mainly from the complexes I and III of the electron transport chain (ETC) and thereby generate incompletely reduced forms of oxygen. The rise in a membrane potential may occur as a consequence of augmented delivery of electrons to the respiratory chain, which results from either increased glucose or fatty acid oxidation or as a result of altered ETC stoichiometry. Consequently, an increased reverse electron flow occurs. Also, there is an evidence that increased cytosolic generation of ROS might precipitate increased mitochondrial ROS. The balance between the genesis of physiological mitochondrial ROS and antioxidant defenses may thus become disturbed, causing numerous pathological events, and finally leading to cell death.

A few words about an interesting association between mitochondrial ATP production and ATP deficiency in pathology….

Mitochondria are the primary source of ATP production in every cell. Therefore, disruption of mitochondrial respiratory function is regarded as a key event in the development of pathologic complications due to ATP depletion in different tissues, like for instance in heart tissue in diabetic patients. However, no general consensus has been raised about the occurrence of mitochondrial defects under diabetic conditions. Evidence associating

diabetes with impaired mitochondrial respiratory function in the liver, heart and kidney of diabetic animals dates back more than 45 years. Despite this long history of research, we have still no comprehensive knowledge on the nature and extent of mitochondrial dysfunction in diabetics, as well as about the mechanisms linking this secondary metabolic abnormality with the primary metabolic defect in insulin and hyperglycaemia. The relationship between mitochondrial dysfunction and diabetic pathology has also not yet been defined and elucidated.

In summary…..

In this chapter we discuss how to possibly modulate the "vicious circle" established between mitochondria, oxidative stress and hyperglycaemia. The potential application of some existing and some new agents possessing promising anti-glycation properties to reduce glycation phenomenon and to increase the antioxidant defense system by targeting mitochondria is discussed. Moreover, this chapter outlines various mechanisms present in mitochondria that may lead to the development of diabetes. Intervention and therapy that alter or disrupt these mechanisms may serve to reduce the risk of development of this pathology.

2. Impact of hyperglycaemia on cellular biochemistry/metabolism – overview of the recent achievements in the field

Glycation and oxidative stress are two important processes known to play a key role in the etiopathology of complications in numerous disease processes. Oxidative stress, either via increasing reactive oxygen species (ROS), or by depleting the antioxidants, may modulate the genesis of glycated proteins *in vitro,* as well as *in vivo*.

2.1 Hyperglycaemia – the basic knowledge on Louis Maillard's discovery

Glycation (non-enzymatic N-glycosylation) is an endogenous process that contributes to the post-translational modification of proteins. It is slow under normal physiological conditions, giving rise to the presence of lysine- and arginine-derived glycation adducts in cellular and extracellular proteins. Inside cells, the impact of glycation is countered by high turnover and short half-life of numerous cellular proteins. In long-lived extracellular proteins, however, glycation adducts accumulate with age (Sell et al., 1996). Then, some of these adducts may be removed by enzymatic repair mechanisms, whilst all are removed by degradation of the glycated proteins. Degradation of extracellular glycated proteins requires specific recognition by receptors, internalisation and proteolytic processing. There are specific receptors, AGE receptors, which fulfill this role (Thornalley, 1998).

The Maillard reaction is named after Louis Maillard, who discovered over 80 years ago that some amines and reducing carbohydrates react to produce brown pigments (Ellis, 1959). The Maillard reaction proceeds via three major stages (early, advanced and final stage) and is dependent upon factors such as pH, time, temperature, as well as type and concentrations of reactants. Maillard reactions occur both *in vivo* and *in vitro*, and are associated with the chronic complications of diabetes, aging and age-related diseases (Edeas et al., 2010). The first step of this reaction typically involves the nucleophilic addition of a reducing sugar to a primary amine group (e.g. as found on a lysine or at the N-terminus of a protein). In this stage a reversible Schiff base is formed, which can undergo a slow irreversible rearrangement to form more stable Amadori product that accumulates over time (Fig. 1). The total amount of such accumulated products is known to be dependent on the type of sugar that is causing the glycation, the incubation time and sugar concentration, as well as the type protein that is being modified (Barnaby et al., 2011).

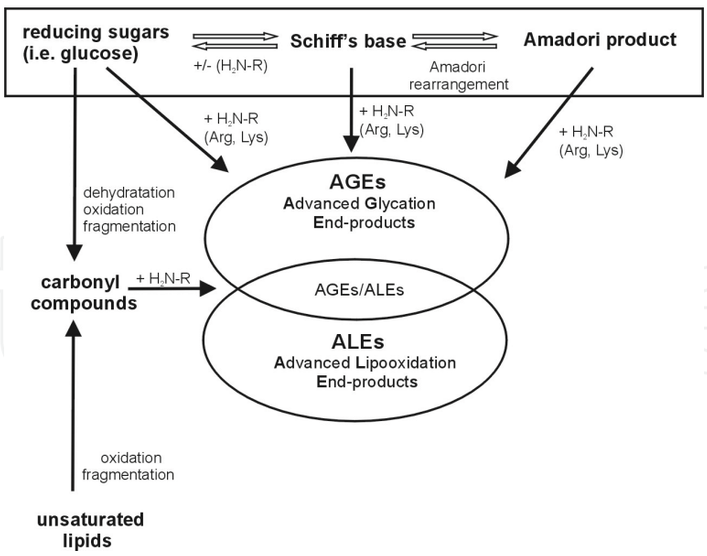

Fig. 1. General scheme of Maillard pathways in diabetic organism.

The first product of Maillard reaction is a simple glycosylamine, which readily undergoes the Amadori rearrangement to produce 1-amino-1-deoxy-2-ketoses. The large body of literature on these reactions is due to the multitude of possible reaction pathways and products, including fragmentations of the carbohydrates and formation of aromatic compounds from cyclisation/dehydration processes (Hodge, 1955). Reducing disaccharides also undergo this reaction, and it is a well-documented process for the degradation of lactose during the heating of milk. Reducing carbohydrates such as glucose, maltose, and lactose are tautomers and are in equilibrium with their more reactive aldehyde forms; nonreducing carbohydrates, such as mannitol, sucrose and trehalose, are not subject to Maillard reactions. Although early scientists believed that only primary aromatic amines were capable to become glycated, subsequent research has shown that nearly all primary and secondary amines, both aromatic and aliphatic, are capable of this reaction (Wirth et al., 1998).

Fragmentation of glucose adducts in early glycation processes establishes many parallel glycation pathways that lead to the subsequent formation of the so-called **A**dvanced **G**lycation **E**nd-products (AGEs). Analogous oxidation and dehydration reactions have been found in glycation by other hexose and pentose derivatives. Glyoxal, methylglyoxal and 3-deoxyglucosone (3-DG)-derived AGEs may be present in proteins glycated by glucose. Methylglyoxal-derived AGEs are common to proteins modified by glucose and by the authentic α-oxoaldehyde. Indeed, similar binding to AGE receptors has been found for these proteins. The formation of α-oxoaldehydes from monosaccharides, Schiff's bases and fructosamines suggests that AGEs may be formed at all stages of glycation (Westwood et al., 1999). AGEs alter structure and functions of proteins. It has been shown that the formation of AGEs *in vivo* contributes to several pathophysiological impairments associated with aging and diabetes mellitus, such as chronic renal insufficiency, Alzheimer's disease, nephropathy, neuropathy and cataract (Ravelojaona et al., 2007).

2.2 Impact of AGEs on human organism – undesirable effects on our health

Glycation of amino-groups on small or large cell constituents induces a number of undesirable effects in a plethora of age-related pathologies, overall referred to as glycation-induced health

hazards and including cardiovascular diseases, kidney insufficiencies, retinopathy, or effects of AGEs on embryonic development, as observed in diabetes-related gravidities. As such reactions proceed with a speed proportional to the concentrations of the interacting substances, hyperglycaemia is an important factor for its acceleration (Urios et al., 2007).
It is very important to remember that Maillard products derive also from ''ready made'' ingested food. Table 1 shows the contents of Maillard products in some foods (expressed as N^{ε}-carboxylysine), as selected from data published by Goldberg et al. (2004).

Name of the selected food	AGE content [U/g]*
Bread Whole wheat, crust, toasted	1.39
Corn flakes	2.32
Peanut Butter Chocolate	32
Popcorn, microwave	336
Butter	265
Fruits:	
Apple	127
Apple baked	445
Banana	87
Vegetables:	
Broccoli, carrots, celery	2.26
Carrots, canned	103
Pepper, mushrooms	2.66
Tomato, raw	234
Liquids:	
Milk, whole	48
Formula, infant	486
Human milk, fresh	52
Apple juice	20
Orange juice, carton	56
Beverages:	
Coffee, instatnt	53
Tea	19
Cola	65
Condiments:	
Ketchup	103
Mustard	29
Vinegar sauce, white	377
Cheese:	
Feta	84
Mozzarella	17
Parmesan	169
Hamburger, fast food	54

*AGE denotes N-carboxymethyllysine (CML)-like immunoreactivity, assessed by enzyme-linked immunosorbent assay using monoclonal antibody 4G9.

Table 1. The content of Maillard products in the selected victuals.

The Maillard reaction between reducing sugars and amino acids is a common reaction in foods, which undergo thermal processing. Desired consequences, like the formation of flavor and brown color of some cooked foods, but also the destruction of essential amino acids and the production of anti-nutritive compounds, require to consider the relevant mechanisms for controlling of Maillard reaction intermediates and final products. Processes such as roasting, baking or frying rely on favorable effects of the Maillard reaction, such as color and flavor formation, whereas during drying, pasteurisation and sterilisation the occurrence of the Maillard reaction is unfavorable. Nutritional losses of essential amino acids that are involved in the reaction, as well as the formation of reaction products are among those unwanted effects (Jaeger et al., 2010).

There is a limited number of studies that have been used to investigate the health effects of dietary Maillard neoformed compounds in humans. Some observational studies have been carried out to address the question of absorption, biodistribution and elimination of dietary Maillard Reaction Products (MRP), and to observe the associations between food exposure to MRPs and their *in vivo* levels.

Some reports have shown that in tobacco leaves, which are dried in the presence of sugars, the Maillard reaction cascade leads to a formation of glycated and oxidative derivatives. These compounds are inhaled during the smoking, after that they are absorbed by lungs and conjugated with serum proteins. It was evidenced that total serum AGE level in cigarette smokers is significantly higher in comparison with non-smokers. However, the highest level of AGEs was detected in the arteries and ocular lenses in diabetic smokers (Vlassara & Palace, 2002).

Furthermore, high AGE levels were observed in industrially preprocessed foods from animal products, like frankfurters, bacon, and powdered egg whites, compared with the unprocessed forms. Across all categories, exposure to higher temperature most of all raised the AGE content (for equal food weights). The temperature level appeared to be more critical than the duration. Also, microwaving increased AGE content more rapidly compared with conventional cooking methods (Peppa et al., 2002). Based on the above data, it is well evidenced that dietary glycoxidation products may constitute an important link between the increased consumption of animal fat and meat and the subsequent development of diabetic complications. However, the problem of AGEs' presence in food is well known, and therefore presently scientists call to use diets containing low contents of these compounds undesirable for out health.

Paradoxically, because of the metabolic demands of the brain, the human body has an obligatory requirement for glucose, approaching 200 g/day. The blood glucose concentration is tightly regulated by homeostatic regulatory systems and maintained between 40 mg/dl (2.2 mmol/l) and 180 mg/dl (10.0 mmol/l). Hypoglycaemia below the lower limit may result in coma, seizures, or even death. Hyperglycaemia, exceeding the upper limit, is associated with immediate glycosuria and caloric loss, as well as long-term consequences, like retinopathy, atherosclerosis, renal failure, etc. Under normal physiological conditions hyperglycaemia stimulates insulin secretion, promoting uptake of glucose by muscles and adipose tissue (Chiu & Taylor, 2011).

Nevertheless, several studies suggest that some MRPs present in foods could have beneficial effects on human health. For instance, the melanoidins are brown Maillard polymers, which seem to have functional properties in food products and are also capable of inhibiting growth of a tumour cell line in culture (Marko et al., 2003). In addition, it was also found recently that a selection of foods rich in MRPs could inhibit the oxidation of LDL *in vitro*.

The high diversity of the MRPs formed in the very diverse food matrices makes it impossible to classify all of them as glycotoxins. It is admitted that they have different beneficial or detrimental biological activities. Thus, more well-controlled clinical experiments are needed to establish the role of the ingested MRPs, pure or added to food matrices, following acute or chronic exposures (Tessier & Birlouez-Aragon, 2010).

2.3 The role of Reactive Oxygen Species (ROS) in glycation process

Free radicals in biological materials were discovered less than 60 years ago. Soon thereafter, Denham Harman hypothesized that reactive oxygen radicals may be formed as by-products of enzymatic reactions *in vivo.* In 1956 he described free radicals as a Pandora's box of evils that may account for gross cellular damage, mutagenesis, cancer, and, last but not the least, the degenerative process of biological aging (Harman, 1956). Presently, the list of cell and tissue disorders caused by free radicals is very long and the diseases, such as diabetes and/or impairments in mitochondria functions, also belong to the "victims" of ROS attack.

Glycation and oxidative stress are closely linked, and both phenomena coincide in a vicious process referred to as ''glycoxidation''. In all steps of glycoxidation there is a massive generation of oxygen-free radicals, some of them being common with lipidic peroxidation pathways. Besides, glycated proteins, and especially their advanced adducts, activate membrane receptors, such as RAGE, and induce an intracellular oxidative stress and a pro-inflammatory status. Glycated proteins may modulate functions of cells involved in oxidative metabolism and induce inappropriate responses. Finally, some oxidative products (reactive aldehydes such as methylglyoxal) or lipid peroxidation products (malondialdehyde) may bind to proteins and amplify glycoxidation generated lesions (Hunt et al., 1998).

Recently, oxygen free radicals, antioxidant defences and the cellular redox status have been considered as central players in pathogenesis of diabetes. The role of glycaemic control on the pro-oxidant/antioxidant balance deserves special attention. Metabolic disturbances and oxidative stress seem to be closely related, improved glycaemic control being associated with a lowered pro-oxidant status (Wierusz-Wysocka et al., 1995).

It was also evidenced that there is a relationship between oxidative stress and insulin resistance observed in diabetes. Hyperinsulinaemia increases the concentrations of ROS, which, in turn, may be responsible for the impaired intracellular insulin actions. Amongst ROS, hydrogen peroxide has been shown to contribute to insulin receptor signaling, and may play a key role in the modulation of the signalling transduction pathways regulated by insulin through coupled receptors.

Consequently, the inactivation of hydrogen peroxide by catalase could represent a critical step for the removal of intracellular ROS in insulin-producing cells. On the other side, the inhibition of catalase under conditions of insulin resistance could also represent an adaptive response to maintain the homeostasis of intracellular hydrogen peroxide as an intermediate of the insulin-activated physiological processes. Overall, relationships between ROS and diabetes seem extremely complex (Bonnefont-Rousselot, 2002).

A second source of ROS formation is an excessive production of AGEs, especially due to a hyperglycaemia-induced overproduction of methylglyoxal. AGEs are also able to produce oxygenated free radicals via complex biochemical mechanisms. AGEs have been shown to interact with their specific receptors (RAGE) and thus they induce oxidative stress, enhance vascular cell adhesion molecule type 1 (VCAM-1) expression, and increase endothelial adhesiveness for monocytes. This overproduction of AGEs appears to play a key role in the pathogenesis of diabetic complications. In particular, the accumulation of two AGEs

biomarkers, namely carboxymethyllysine and pentosidine, has been related to the severity of diabetic nephropathy and the so-called 'carbonyl stress'. The toxic effects of AGEs result from structural and functional alterations in proteins, especially the cross-linking of proteins, and from their interactions with RAGEs leading to the enhanced formation of oxygen free radicals (Miyata et al., 2001; Singh et al., 2001).

2.4 Diabetes – a frequent disease or an epidemic?

In 1993 the World Health Organisation (WHO) Ad Hoc Diabetes Reporting Group published standardized global estimates for the prevalence of diabetes and impaired glucose tolerance in adults, based on data from 75 communities in 32 countries. These estimates provided, for the first time, comparable information on the prevalence of abnormal glucose tolerance from many populations worldwide. However, they did not meet the needs of those who frequently refer to the WHO diabetes program for information on the number of people with diabetes in a particular country/community, nor did they take account of future trends in the burden of diabetes (King & Rewers, 1993). Therefore, a further study has been undertaken that links data from the global database collected by WHO with demographic estimates and projections issued by the United Nations to estimate the number of people with diabetes in all countries of the world at three points in time, i.e., the years 1995, 2000, and 2025. The results of this study suggest that for the world as a whole, between the years 1995 and 2025, the adult population will increase by 72%, prevalence of diabetes in adults will increase by 35%, and the number of people with diabetes will increase by 122% (Fig. 2). For the developed countries, there will be an 11% increase in the adult population, a 27% increase in the prevalence of adult diabetes, and a 42% increase in the number of people with diabetes. For the developing countries, there will be an 82% increase in the adult population, a 48% increase in the prevalence of adult diabetes, and a 170% increase in the number of people with diabetes (King et al., 1998).

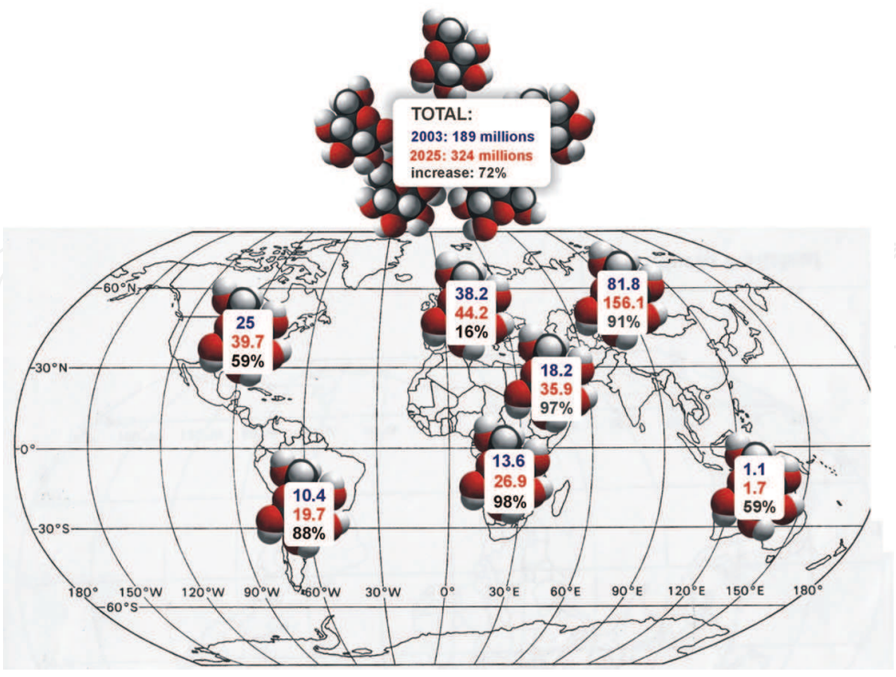

Fig. 2. Global projections for the diabetes epidemic in years 2003-2025.

It is well known that diabetes is one of the most costly and burdensome chronic diseases of our time and is a condition that is increasing in epidemic proportions throughout the world. The prevalence of abnormal glucose tolerance in any population is of public health concern, since diabetes may increase disability burden and health care utilisation.

The relationship between blood glucose concentration in diabetes and the incidence of disease complications was demonstrated in large epidemiological studies. Accurate metabolic control in diabetes is not always feasible, and therefore the issue of molecular mechanisms underlying the damaging effects of hyperglycaemia on body cells and tissues, as well as the possibilities of their pharmacological inhibition, are of the utmost importance in a diabetological practice and anti-diabetic treatment.

The complications resulting from the disease are a significant cause of morbidity and mortality and are associated with the damage or failure of various organs such as eyes, kidneys, and nerves. Although the treatment of diabetes has become increasingly sophisticated, with over a dozen pharmacological agents available to lower blood glucose, a multitude of ancillary supplies and equipment available, and a clear recognition by health care professionals and patients that diabetes is a serious disease, the normalisation of blood glucose for any appreciable period of time is seldom achieved. In addition, in well-controlled so called "intensively" treated patients, serious complications still occur, and the economic and personal burden of diabetes remains (Turner et al., 1999).

Nowadays, diabetes is treated not only as a disease, but as an epidemic. However, as a discipline, diabetes epidemiology is relatively young. The first significant gathering of researches interested in diabetes epidemiology took place just in 1978. Then, in the relatively short span of 2 decades, epidemiology studies have had a profound impact on diabetes research, care and prevention. This explosion of interest and activity in the epidemiology of diabetes should contribute to an effective reduction in the number of patients with this disease.

3. Mitochondria – the relationship between the structure and the function

Mitochondria are multifunction organelles, which play a key role in both the proper functioning of the cell and normal cell death scenario (Kuznetsov & Margreiter, 2009, as cited in McBride et al., 2006). Their main role is the production of adenosine triphosphate (ATP) through metabolic processes involving tricarboxylic acid cycle (TCA) and the electron transport chain (ETC). Most cellular ATP is generated in the process of oxidative phosphorylation, which is possible thanks to the 'sophisticated machinery' located in the inner mitochondrial membrane. Mitochondria participate in the regulation of redox state and calcium homeostasis in cell. Cations of calcium regulate some mitochondrial processes, such as enzyme activity, i.e. pyruvate dehydrogenase, or metabolic rate. These organelles participate in biosynthesis of amino acids, vitamin cofactors, fatty acids and neurotransmitters (Waldbaum & Patel, 2009). Many other biochemical reactions are associated with the functioning of these structures, including synthesis of heme group and some steps of steroid synthesis. Also, a part of the processes occurring in the urea cycle take place there (Pinti et al. 2010). Mitochondria have critical function in the control of apoptotic and necrotic cell death and in most types of cells they are also a major site of reactive oxygen species (ROS) generation (Duchen, 2004). ROS are involved in many signaling pathways. Most of them are second messengers that trigger different cellular events, such as cytokine

secretion or activation of transcription factors, but in excess they can contribute to the formation of defects in mitochondria, as well as in a whole cell (Edeas et al., 2010a).

3.1 Mitochondrial structure and biogenesis

Mitochondria are encapsulated by two membranes, each with different structure and function, separated by intermembrane space, in which some important proteins involved in the mitochondrial bioenergetics and/or cell death are located (Fig. 3) (Duchen, 2004, Borutaite, 2010). The outer membrane contains porins, which make it permeable to molecules smaller than 5-6 kDa (Waldbaum & Patel, 2009). Compounds such as water, O_2, CO_2, and NH_3 easily pass through the membrane, but hydrophilic metabolites and all inorganic ions in order to get over this membrane require the participation of specific channels and carrier proteins. Such a transport is generally based on the exchange of molecules, i.e. ADP is exchanged for ATP and P_i (inorganic phosphate) for OH^- (Szewczyk & Wojtczak, 2002). The mitochondrial inner membrane contains enzymes facilitating an oxidative phosphorylation (OXPHOS). This complex of enzymes consists of four oxidoreductases involved in respiratory electron transport (Complexes I - IV) and the ATP synthase complex (Complex V).

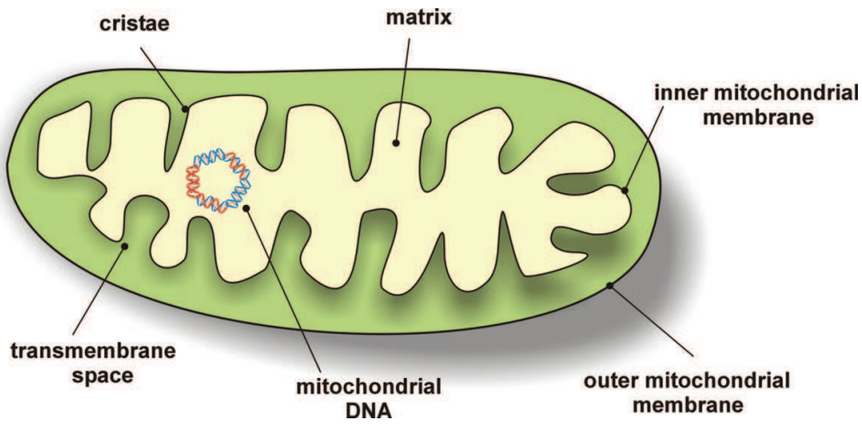

Fig. 3. Mitochondria structure and components.

Until recently, the inner membrane has been described as a multiple infolded structure forming cristae and containing numerous mitochondrial proteins (Duchen, 2004). However, electron tomographic analyses of a variety of mitochondria (both isolated and observed *in situ* in various cell types) have provided overwhelming evidence showing the need of some changes in the perception of the structure of these organelles. These infoldings or rather invaginations are not randomly spaced in the membrane, as often considered, but resemble microcompartments, which face each other in the peripheral region of the membrane. The narrow junctions are wide enough to pass metabolites and many soluble proteins (Mannella, 2008). However, the number of cristae junctions and the morphology of the intercristal space depends on the metabolic state of mitochondria (Logan, 2006). Isolated mitochondria usually occur in one of two morphologic states, condensed or orthodox. The first one is characterized by contracted, very dense matrix and wide cristae. In the second state matrix is expanded and cristae compartments are more compact. Osmotic and metabolic changes in mitochondria are responsible for these alterations. It is believed that mitochondrial inner

membrane topology is regulated by the cell to improve mitochondria capacity in their response to stimuli (Mannella, 2008).

Tissue cells contain from a few dozen to several thousands of mitochondria and their number is associated with cell energy demands. Organs such as heart, muscles or brain contain the largest number of mitochondria. Mitochondria are very dynamic structures, which can divide, undergo fusion and can take the form of the network of elongated and interconnected filaments. The phenomena of fission and fusion have an impact on mitochondrial shape, size and number (Logan, 2006). The division and replication of mitochondria is under control of the nucleus and is somehow associated with division and replication of nuclear DNA. Replication of mitochondria requires coordination between the process of mtDNA replication and synthesis of proteins encoded in both genomes (nucleus and mitochondrial). The production of both types of proteins must be synchronized to preserve their functionality.

3.2 Electron transport chain and ATP synthesis

Mitochondrial ATP production involves three main steps: a) the enzymatic "combustion" of acetyl in tricarbolxylic acid cycle (TCA), b) the electron transport chain activity and c) ATP synthase action. Energy released during this cycle is used to reduce the electron carriers NAD^+ to NADH and FAD^{2+} to FADH (Duchen, 2004). Electrons from NADH and $FADH_2$ are transferred to the respiratory chain - a coupled enzyme systems composed of four complexes (Complex I - IV). Complex I (NADH dehydrogenase) is the major entrance point of electrons to respiratory chain and is composed of two domains. One domain, localized in withe membrane, is involved in proton translocation across the bilayer, and the other, matrix-exposed domain, is responsible for oxidation of NADH. $FADH_2$ is the donor of electrons to succinate dehydrogenase (Complex II) which is the second entrance point of electrons to the ETC. Electrons from both complexes are transferred on mobile intermediate – ubiquinone, which is converted to reduced form - ubiquinol. The flow of electrons from ubiquinol is directed through the Complex III, also known as ubiquinol-cytochrome c reductase, to another carrier - cytochrome c, which transfers electrons to Complex IV - cytochrome c oxidase. Finally, at the very end of the respiratory chain, Complex IV reduces the oxygen to water in sequential four-electron transfer (Adam-Vizi & Chinopoulos, 2006). The oxidation of NADH and $FADH_2$ provides the energy to transport protons from mitochondrial matrix into the intermembrane space by the proton pumps (Complexes I, III, IV). The difference in the proton concentration, and thus the difference in the electric charge across the inner mitochondrial membrane creates the electrochemical potential gradient, also called an electrochemical proton gradient or a 'proton-motive force', which is mainly expressed as a mitochondrial transmembrane potential (Nazaret, 2008). The structure of mitochondrial electron transport and the scheme showing ATP production by mitochondria was introduced in Fig. 4.

Energy needed to phosphorylate ADP by ATP synthase comes from the entry of protons back into the matrix through the proton channel of this complex. This process is called oxidative phosphorylation (Frey & Mannella, 2000). ATP is then transported to the cytoplasm by the adenine nucleotide translocase (ANT). However, there are several mechanisms that may lead to the loss of mitochondrial potential, including an inhibition of respiration, failure in substrate supply and uncoupling mechanisms that cause proton leak across the membrane.

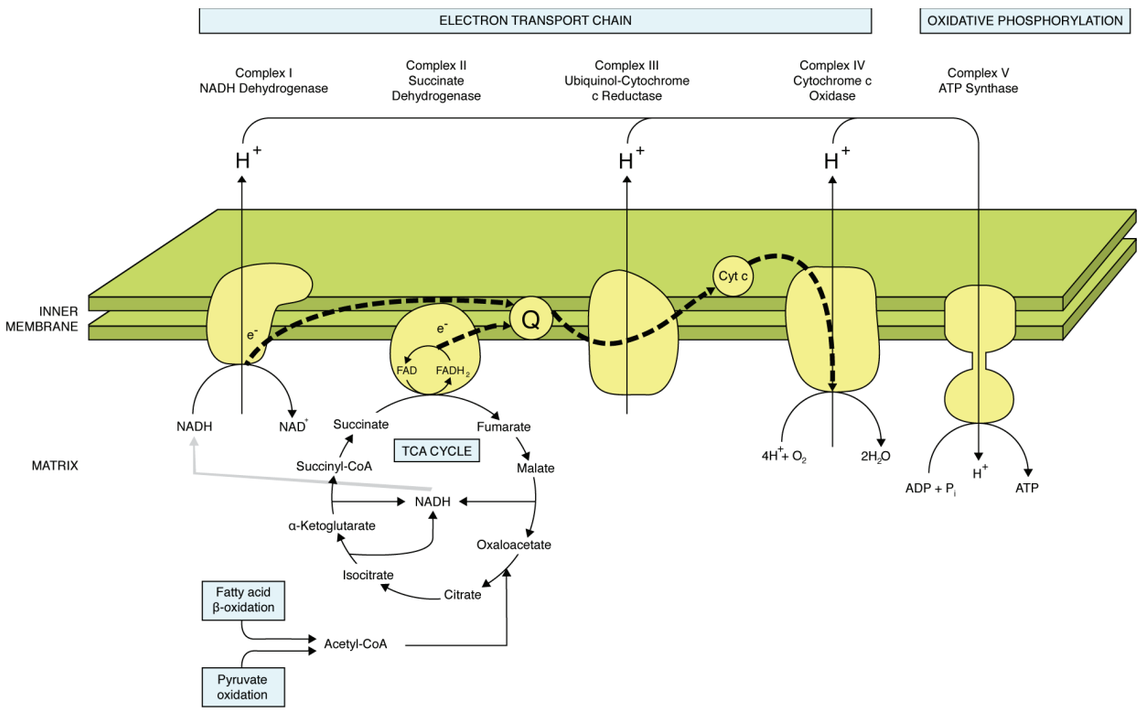

Fig. 4. The general mechanism leading to oxidative phosphorylation is as follows: high-energy electrons (marked as e-) derived from NADH and $FADH_2$, are moving along the respiratory chain composed of four protein complexes (Complex I - IV) and two additional electrons carriers: ubiquinone (coenzyme Q, **Q**), a small molecule freely moving in the inner mitochondrial membrane layer, and cytochrome c (**Cyt c**), localized in the intermembrane space attached to the inner membrane. Part of the energy released in this process is used up in the action of proton pumps transporting protons (H^+) from matrix to the intermembrane space. Across the inner membrane electrochemical gradient of protons is formed. Protons tend to return to the mitochondrial matrix and restore alignment of H^+ concentration on both sides of the membrane. When they pass back through transmembrane protein complex – ATP synthase - the energy of their movement is used for the synthesis of ATP from ADP and inorganic phosphate ($\mathbf{P_i}$).

3.3 Free radical generation by mitochondria

Oxidative metabolism and ATP synthesis are closely associated with ROS generation in mitochondria. These organelles consume 80–90% of cell's oxygen during oxidative phosphorylation. The electron transport chain is the main source of ROS in functioning mitochondria. Approximately 0.2–2% of the oxygen taken up by a cell is converted by mitochondria to ROS. Superoxide ($O2^{\bullet -}$) is the main product of these transformations, and it is then converted to hydrogen peroxide (H_2O_2) by spontaneous dismutation or by superoxide dismutase (SOD). Glutathione peroxidase or catalase, in turn, convert hydrogen peroxide into water. If this change does not occur, in the presence of divalent cations H_2O_2 can undergo Fenton's reaction to produce even more harmful hydroxyl radical ($\bullet OH$). Oxygen can be reduced to superoxide in one-electron step, theoretically, at each step of the respiratory chain, but in reality two major sites of superoxide generation are Complex I and Complex III (Paradies et al., 2010, as cited in Murphy, 2009). There is a considerable experimental support for two mechanisms of ROS production by complex I. The first one is

the production of ROS as a consequence of so-called reverse electron transfer (RET) in the mitochondrial respiratory chain. RET is a set of redox reactions in the mitochondrial ETC that allows electrons to flow from coenzyme Q to NAD^+ instead to oxygen. The other one takes place under normal conditions, whereas most of the energy from the creation of mitochondrial potential difference is used to generate ATP through ATP synthase. This process causes collapse of the proton gradient. The amplitude of the electrochemical proton gradient regulates the flow of electrons through the ETC. When the electrochemical potential gradient is high, for instance under conditions of high glucose concentrations, the life of electron transport intermediates that are involved in superoxide formation, such as ubisemiquinone, is prolonged. The reason of such condition is that the activities of of ETC proton pumps depend on the proton gradient across the inner membrane and the membrane itself – two components of proton-motive force (Duchen, 2004).

3.4 Free radical targets and the oxidative vicious circle

Mitochondria are continuously exposed to action of reactive oxygen species so they need to have a system that will prevent them against destructive effect of oxidative damage. In fact, mitochondria are equipped in complicated multi-leveled ROS defense network consisting of enzymes and non-enzymatic antioxidants. They contain a high concentration of glutathione, α-tocopherol and manganese-containing superoxide dismutase (MnSOD). The role of MnSOD is the dismutation process of superoxide radical to H_2O_2. The product of MnSOD reaction is detoxified by other enzymes, i.e. catalase, which converts H_2O_2 into O_2 and H_2O. Mitochondria possess also another system capable of efficient superoxide removal - the cytochrome c, which is than regenerated (oxidized) by its natural electron acceptor, cytochrome c oxidase (Complex IV). In intact mitochondria, superoxide may be efficiently scavenged by intramitochondrial antioxidant defences (Duchen, 2004). An imbalance between oxidants and antioxidants induces oxidative stress responsible for alteration of biomolecules and intracellular signaling pathways present in every cell (Edeas et al., 2010a). Mitochondria are a major source of ROS generation, but what is important, they are also its major target (Duchen, 2004). Mitochondrial membrane lipids, mainly long-chain polyunsaturated fatty acids (PUFAs), are also susceptible to oxidative stress. PUFAs are basal components of mitochondrial phospholipids. The sensitivity of PUFAs to oxidation increase with the increasing number of double bonds per fatty acid molecule. Peroxidation of membrane phospholipids causes alterations in their structure and consequently may disrupt organisation of the lipid bilayer. It contributes also to changes in membrane fluidity and/or permeability, and causes changes in the mitochondrial membrane potential, in respiratory capacity and in oxidative phosphorylation. ROS are also responsible for alterations in proteins, which may manifest by changes in their structure, proteolytic susceptibility and spontaneous fragmentation. Oxidative damage especially affects the mitochondrial electron transport chain and, when the ETC enzymes stop working properly, the ROS production increases. This may result in the incomplete oxygen consumption, reduced production of ATP, and finally overproduction of ROS (Waldbaum & Patel, 2009).

4. Mitochondrial physiology in diabetes

Mitochondria are provided with a variety of bioenergetic functions mandatory for the regulation of intracellular energy production. Alteration of bioenergetic activities may have drastic consequences on cellular function through the perturbation of energetic charge and balance of the cell (Fig. 5).

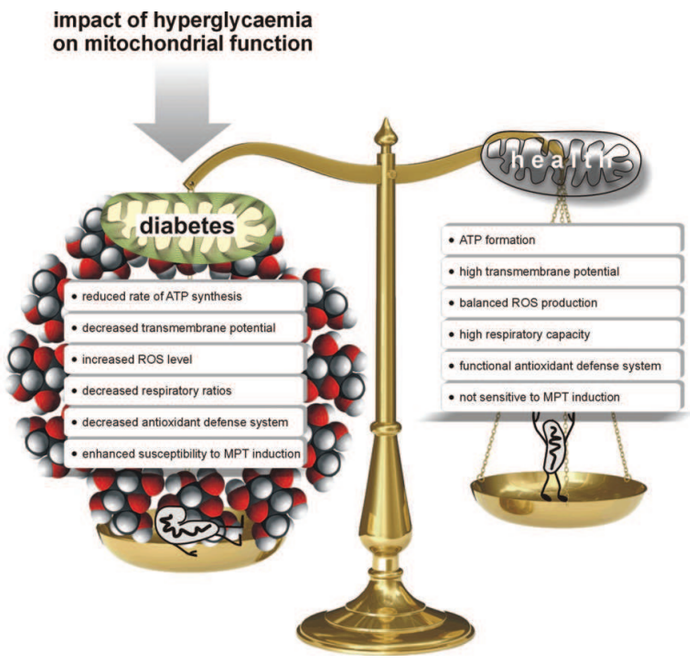

Fig. 5. The overall impact of the burden of hypergycaemia in diabetes on functioning of mitochondria.

Abnormalities of mitochondrial metabolism causing human disease have been recognised for more than 40 years. Numerous reports clearly indicate the association between mitochondrial dysfunction and diabetes. Nevertheless, some mechanisms of mitochondrial role in this pathology still requires further elucidation. Therefore different animal model studies are involved in the investigation of explaining these unknown mechanisms. There are several models of experimental diabetes that mimic two common types of diabetes. Streptozotocin-induced diabetes is a widely accepted animal model for type 1 diabetes, resulting from the inability of the pancreatic beta cells to produce insulin. For the research on type 2 or the insulin resistant state, resulting from the inefficient use of insulin by the tissues to regulate blood glucose concentration, some genetically manipulated animal models (e.g. Zucker fatty rats (ZFR), *ob/ob* (obese) mice, CP (corpulent) rats, GK (Goto-Kakizaki) rats, Akita mice) may be utilized (Srinivasan & Ramarao, 2007).

4.1 Mitochondrial dysfunction and diabetes type 1

Streptozotocin (STZ) is a naturally occurring chemical that is particularly toxic to the insulin-producing β cells of the pancreas in mammals and is used to generate Type 1 diabetes in the experimental model. Animals with diabetes induced by STZ exhibit increased mitochondrial oxidative stress and dysfunction. Other agent, alloxan, a toxic glucose analogue, is also used in order to generate type 1 of diabetes. Alloxan selectively destroys insulin-producing cells in the pancreas when administered to rodents and many other animal species, and has been shown to cause also mitochondrial dysfunction. Alloxan-treated severe diabetic rats were shown to exhibit impaired mitochondrial phosphorylative activities and low mitochondrial oxidation–reduction states (Yamamoto et al., 1981). In one month old alloxan-diabetic animals the enzyme activity of the mitochondrial membrane marker, F_0F_1-ATPase, was found to be decreased. Insulin treatment caused hyperstimulation of the activity, whereas in late-stage

diabetes the catalytic efficiency of the enzyme was increased and became decreased upon insulin treatment (Patel & Katyare, 2006).
Mitochondrial dysfunction in diabetic rats can be succinctly summarized into: decreased mitochondrial 3'-AMP forming enzyme activity, increased oxidative and nitrosative stress, decreased oxygen consumption, loss in mitochondrial transcriptional capacity, increased HMG-CoA synthase, increased levels of pyruvate and dicarboxylate transporters, increased degradation of ATPase, changes in phospholipid composition, increased pyruvate carboxylase activity, increased fatty acid beta oxidation and ultrastructure alterations.

4.2 Mitochondrial dysfunction and diabetes type 2

Type 2 diabetes is the most common metabolic disease in the world, and its prevalence much exceeds the prevalence of type 1 diabetes. Among different causes leading to diabetes the role of mitochondria is considered substantial. Disorders of the mitochondrial electron transport chain, overproduction of ROS and lipoperoxides or impairments in antioxidant defenses are encountered in type 2 diabetes. Increased ROS levels lead to generalized oxidative damage to all mitochondrial components. Moreover, it is well established that mitochondrial function is required for normal glucose-stimulated insulin secretion from pancreatic β cells. However, the studies in humans suggest that more subtle defects in mitochondrial function may also play a role in the pathogenesis of insulin resistance and type 2 diabetes (Fig. 6) (Luft, 1994).

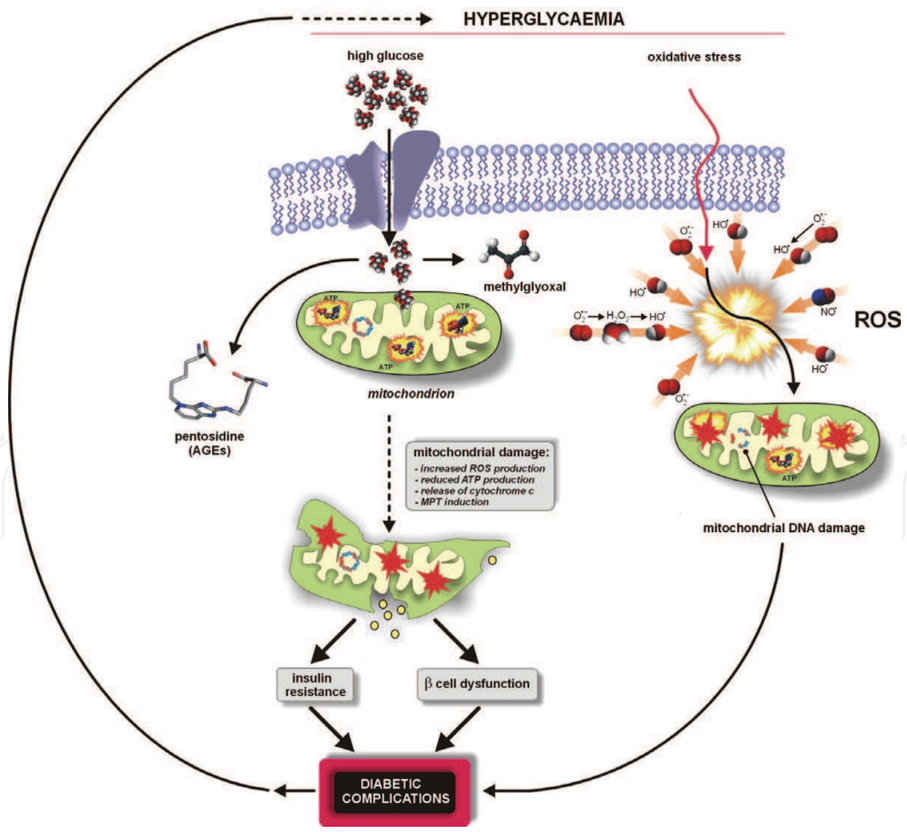

Fig. 6. Relationships among hyperglycaemia, mitochondrial damage, oxidative burst and diabetic complications.

Some data support the hypothesis that insulin resistance in humans arises from defects in mitochondrial fatty acid oxidation, which in turn leads to increased intracellular fatty acid metabolites that disrupt insulin signaling (Petersen et al., 2003). Alternatively, the reduction in mitochondrial oxidative phosphorylation activity in insulin-resistant individuals could be due not to mitochondrial loss, but rather to a defect in mitochondrial function. This hypothesis is supported by muscle biopsy studies. In one such study, the activity of mitochondrial oxidative enzymes was found to be lower in type 2 diabetic subjects, and in another, the activity of mitochondrial rotenone-sensitive nicotinamide adenine dinucleotide oxidoreductase [NADH:O(2)] was found to be lower (Lowell & Shulman, 2005).

4.3 Alterations in cardiac mitochondria observed in diabetes

Cardiovascular diseases are the predominant cause of death in patients with diabetes mellitus. Underlying mechanism for the susceptibility of diabetic patients to cardiovascular diseases still remains unclear. Elevated oxidative stress was detected in diabetic patients and in animal models of diabetes. Hyperglycaemia, oxidatively modified atherogenic lipoproteins, and advanced glycation end products act in a concerted action together with oxidative stress, and cumulatively contribute to progression of late diabetic complications. Mitochondrial dysfunction increases electron leak and the generation of ROS from the mitochondrial respiratory chain (MRC). High levels of glucose and lipids impair the activities of MRC complex enzymes. Furthermore, increased activity of NADPH oxidase (NOX), which generates superoxide from NADPH in cells, was detected in diabetic patients (Shen, 2010).

Because mitochondria constitute 20–30% of the cardiac myocytes, one of the potent causes for heart malfunctioning in diabetes is the impaired mitochondrial function and consequently the decreased ATP generation (Rolo & Palmeira 2006).

Many reports evidenced that diabetic hearts show impaired mitochondrial function, decreased ATP generation, decreased oxidative capacity, increased ROS, abnormal morphology, increased UCP-3 level, decreased mitochondrial calcium uptake and increased susceptibility to MPT induction (Fig. 5).

Distortions in cardiac mitochondrial bioenergetics are known to occur in both human types of diabetes and in models of diabetes in animals. Reduced mitochondrial calcium uptake was observed in heart mitochondria from STZ-treated rats. This was related to enhanced susceptibility to MPT induction rather than damage to the calcium uptake machinery. Interestingly, heart mitochondria from GK rats were less susceptible to the induction of MPT, showing larger calcium accumulation before the overall loss of mitochondrial impermeability. Different approaches of antioxidant administration in GK rats (vitamin E or coenzyme Q_{10}) showed no success in reversing the diabetic phenotype (Oliveira et al., 2003).

Diabetic heart failure may be causally associated with alterations in cardiac energy metabolism. Fuel selection and capacity for ATP production in the normal and failing heart are dictated by several metabolic regulatory events at the level of gene expression. Decline in the capacity for ATP, as caused by progressive impairment of mitochondrial function, is a gradual step in the progression to heart failure of any cause. Fetal heart depends on glucose and the adult heart on glucose and fatty acids. The switch between fatty acid oxidation and glucose in the adult heart leads to a healthy metabolic situation (Huss & Kelly, 2005). In the insulin-resistant and diabetic heart, fatty acid oxidation is increased and glucose utilisation

is diminished. Long-term consequence of fatty acid oxidation is mitochondrial dysfunction. A number of mechanisms may be responsible for enhanced fatty acid utilisation in type 2 diabetic hearts, such as increased fatty acid uptake into the cell and mitochondria, increased UCP-3 expression, and stimulation of peroxisome proliferator-activated receptor-α (PPARα) (Fig. 7) (Rolo & Palmeira, 2006).

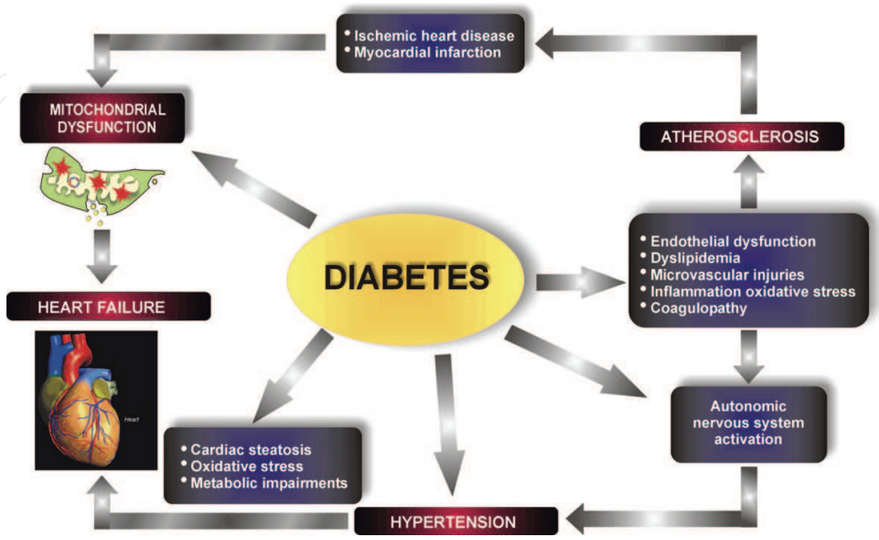

Fig. 7. The role of cardiac mitochondria in the development of heart failure in a course of diabetes.

Diabetes-associated metabolic disorders may cause the mitochondrial dysfuntion and upregulation of NOX in the cardiovascular system, which lead to increased ROS production and oxidative stress in vasculature and blood circulation. ROS may directly oxidize or indirectly regulate molecules related to atherosclerosis and thrombosis. Mitochondrial NOX, or its regulators may be considered as potential drug targets for the prevention and/or treatment of diabetic cardiovascular complications.

5. Therapeutic approaches to reduce diabetic complications

Patients with diabetes mellitus are usually treated with a combination of pharmacological agents and habitual approach, i.e. their lifestyle modification. The development of new antidiabetic agents, such as insulin analogs and incretin-based therapies, has led to treatment strategies that enable numerous patients with diabetes to improve their lifestyles.

5.1 Use of insulin in a common diabetes therapy – its advantages and disadvantages

Type 1 diabetes mellitus is underlied by the shortage of insulin, which plays a crucial role of carbohydrate and fat metabolism. Its absence causes rather a complex array of serious impairments in patients' health, e.g. hiperglycaemia, ketoacidosis, coma and even death. Hence, the injection of exogenous insulin to diabetic individual is essential to: (a) maintain a normal glucose concentration and (b) avoid the advanced microvascular complications, such as retinopathy, nephropathy or neuropathy.

Insulin was discovered by Banting and Best and this event was a milestone in the treatment of patients with diabetes (Bliss, 1982). Initially, bovine, porcin and even some fish analogues were applied to avoid diabetic ketoacidosis. However, gradually the scientists were

challenged by the uprising problems in patients injected with animal insulins (mainly because of their rather high impurity and immunogenicity) and were forced to develop a new class of insulins. Improved techniques used for insulin purification combined with other compounds like protamine and zinc, enabled to manufacture protamine insulin with the prolonged time of activity and later, the more stable protamine zinc insulin (Hagedorn et al., 1936). Moreover, further scientific discoveries shed light on better understanding of insulin structure and activity and initiated a new avenue to design human insulin analogues characterized by the properties of prolonged hormone activity in a bloodstream.

At present, there are few types of short-acting insulin analogues used in anti-diabetes therapy, and among them:

- **insulin lispro** (Humalog manufactured by Elli Lilly and Company), which was approved and launched into the market in 1996. Its modified amino acid sequence provides faster absorption, which is essential to ameliorate postprandial glucose level. The studies revealed that the activity peak of lispro appears in 1 hour after using and lasts for next 3-4 hours (Howey et al., 1994)
- **insulin glulisine** (Apidra manufactured by Sanofi-Aventis), which possesses asparagine at position B3 and glycine at position B29 in amino acid chain (Garg et al., 2005).
- **insulin aspart** (NovoRapid manufactured by Novo Nordisk), in which proline is replaced with aspartic acid what facilitates its faster absorption (Mudaliar et al., 1999).

Long-acting insulin analogues are crucial to mimic the endogenous insulin secretion. Thereby a specific modification of insulin structure was essential to obtain longer acting analogues. There are two approaches leading to diminish absorption: the first one is to change the isoelectric point of insulin and the second one is to acetylate a hydrophobic residue with fatty acid.

- **insulin glargine** (Lantus, Sanofi-Aventis) exemplifies a long-acting insulin analogue, in which asparagine is substituted by glycine at position A21 and the position B30 is enriched with two molecules of arginine at B31 and B32 (Bolli & Owens, 2000). These alterations have an impact on the structure and an isoelectric point of insulin, contributing to a decrease in its solubility after injection. Finally, the result of these changes is the product, which acts about 20 hours (Heise et al., 2002).
- **insulin detemir** (Levemir, Novo Nordisk) is characterized by long acting properties (17-20 hours) obtained as a result of acetylation with fatty acid at the position B29 and by removal of threonine at B30 (Havelund et al., 2004).

After long years of experience and observations, nowadays, multiple daily injection program is believed to be the most reasonable approach in modern diabetic treatment in order to mimic the physiological insulin release. However, it implies that patients have to undertake more inconvenient therapy resulting from the scheduled injections of both short- and long-acting insulins. To deal with this problem, clinicians and patients may choose an alternative method, which requires biphasic insulin analogues administration.

Patients with pre-diagnosed type 2 diabetes should take seriously into account the radical change of their lifestyle in order to cause a delay of possible medical intervention. Under conditions when diet or changing a lifestyle may not be sufficient enough, additional pharmacological treatment is required to avoid a severe consequence of this disease.

Nowadays, medicine is focused on delivery a large number of drugs. From pharmacological point of view, these compounds should be effective in improving insulin efficiency or

effective in enhancing its secretion from pancreas. Among those substances are: sulfonylureas, biguanides, thiazolidinediones, meglitinides, α-glucosidase inhibitors, amylin analogues, incretin hormone mimetics and dipeptidyl peptidase 4 inhibitors.

- **sulfonylureas** belong to the drugs most frequently used in diabetes treatment. It is known that these oral hypoglycaemic agents interact with β-cell pancreas cells causing insulin secretion, insulin sensitivity amelioration, as well as glucose synthesis reduction. However, in order to treat patients using sulfonylureas, an endogenous secretion of insulin at the same/similar level and a balanced diet are required (Gerich, 1989)
- **metformin**, representing a class of biguanides, is a commonly used oral hypoglycemic agent for the treatment of type 2 diabetes. Metformin is also known as an inhibitor of high glucose- or AGEs-induced ROS generation (Bellin et al., 2006)
- **thiazolidinediones (glitazones, TZD)**, oral anti-diabetic drugs, are based on the improving of adipose tissue and muscle sensitivity to insulin treatment (Day, 1999). However, troglitazone, one of the class of thiazolidinediones, was taken off the market since the hepatotocity has been noticed (Watkins & Whitcomb, 1998).

Development of the obesity associated with diabetes requires using a novel combination treatment, which aims at retarding the microvascular and macrovascular complications occurring in diabetes and obesity. Therefore, some anti-diabetic agents have been indicated to maintain an adequate glucose level in an organism suffering from diabetes. The number of anti-diabetic drugs delivered by subcutaneous injection increases constantly and to date there are numerous agents already launched into market, as well as others, tested in the clinical trials (Fig. 8).

- **glucagon-like-peptide-1 agonist (GLP-1)**, one of the first among subcutaneous drugs used in medicine. Its beneficial effect was achieved by suppression of glucagon secretion and weight loss. Unfortunately, it soon appeared that in the organism GLP-1 was active only 2 min. It was the main reason why scientists started to work on improved GLP-1 analogues.
- **exenatide and liraglutide** were introduced into market in the year 2005 and 2009, respectively, as novel GLP-1 analogues. Each of them decreases HbA_{1c} level and provides the weight loss. The main difference between these agents is their half-lives in a circulation. Exenatide yields therapeutic effect in 4-6 hours, whereas half-life of liraglutide was enhanced to 12-15 hours (Gentilella et al., 2009).
- **bromocriptin** belongs to drugs used in the treatment of Parkinson disease. However, recently it has been shown that this therapeutic agent ameliorates insulin sensitivity, leading to enhancing glucose control and lowering the incidence of hypoglycaemia (Pijl et al., 2000). Although bromocriptin provides weight loss and diminishes concentration of plasma triglyceride and free fatty acids, it was evidenced that after using bromocriptin the patients suffer from several side effects, like nausea, hypotension and psychiatric disturbances.

Diabetes mellitus has been associated with the increased mortality risk due to non-diabetic factors, like several types of solid tumours, including the cancers of colon, breast and pancreas. Similar associations have been noted for central obesity and other conditions associated with increased levels of circulating insulin. These observations have given rise to the hypothesis that growth of these tumours, which are characterised by abnormal expression and function of the insulin–IGF-1 series of receptors, may be promoted by the trophic action of insulin interacting with these receptors. The cancer risk associated with diabetes may also be influenced by therapy in a given diabetic individual: for example, the

risk of colon cancer is higher in individuals on insulin, patients on metformin are less likely to be diagnosed with cancer, and the risk of mortality from solid tumours is lower for metformin than for exogenous insulin or sulfonylureas. As a recognition dawns that cancer should be numbered among the complications of diabetes, the possibility that therapies for diabetes may influence tumour progression is likely to attract the increasing interest and concern. Furthermore, the observation that both endogenous insulin and exogenous insulin therapy are associated with tumour progression raises the questions as to the safety of the insulin analogues, which have subtly modified receptor binding properties and may accelerate the growth and proliferation of both healthy and tumour cell lines in culture.

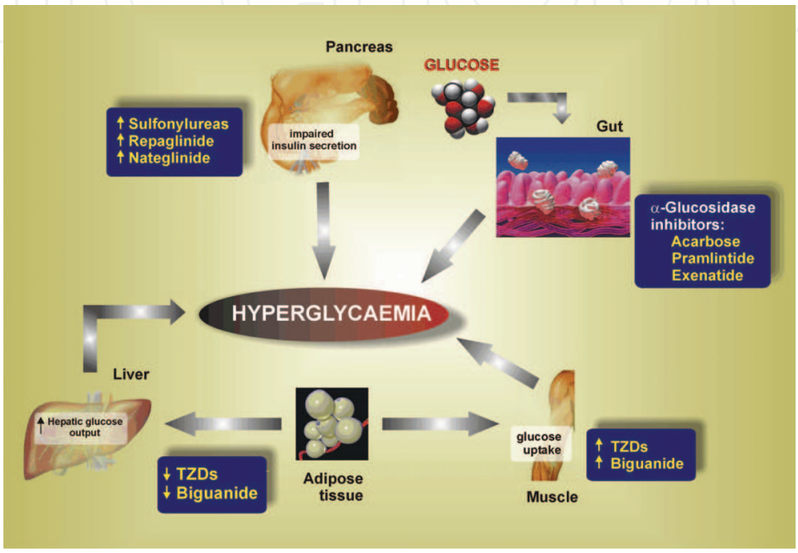

Fig. 8. Sites of action of major oral therapeutical agents used in the treatment of type 2 diabetes. Pharmacological therapies aimed at: inhibiting carbohydrate breakdown in the gut (α-glucosidase inhibitors), stimulating insulin secretion (sulfonylureas, repaglinide, nateglinide), suppressing hepatic gluconeogenesis (thiazolidinediones, biguanide), or accelerating skeletal muscle glucose metabolism (thiazolidinediones, biguanide) exhibit beneficial effects on fasting and/or postprandial plasma glucose, and consequently concord overall metabolic control in type 2 diabetic patients. Thus, a need for concerted combination therapy to successfully control a burden of hyperglycaemia in a majority of DM2 patients becomes a growing expectation by physicians and other health caregivers.

5.2 New agents – new hopes and new perspectives

The growing number of people with diabetes still requires novel combined treatments aimed at retardation of microvascular and macrovascular complications in the future. Therefore, anti-diabetic complications agents are sought to maintain an adequate glucose level in an organism. The number of anti-hyperglycaemic drugs delivered by subcutaneous injection increases constantly and to date there are numerous agents launched into market and examined in clinical trials. However, no such compounds/drugs that could be successfully applied in the treatment of diabetes have emerged hitherto, as the validated outcomes of clinical trials. Intensive studies are continued in order to develop a modern formula for effective amelioration of a burden associated with diabetes and late diabetic complications in diabetic patients in the future.

Studies on the formation of AGEs have been conducted with the goal to find promising pharmacological agents used in prevention or curing diabetic complications. The main target for these agents is to retard the formation of AGEs or to brake the AGE cross-links formed during Maillard reaction.

In order to prevent the AGEs formation the following therapeutic inhibitors have been developed and studied:

- **pyridoxamine (PM)**, a form of vitamin B_6, is thought to inhibit AGEs structures by capturing redox metal ions (Voziyan et al., 2003). In order to examine the anti-diabetic properties of PM under *in vivo* conditions, the model of diabetes mellitus induced by streptozotocin (STZ) was applied. The results of PM administration demonstrated the reduction in hyperglycaemia level and improvement in the plasma lactate/puryvate ratio. The decreased amounts of AGEs have also been noted (Degenhard et al., 2002). Moreover, it was also revealed that PM can act as inhibitor of protenuria and hyperlipidaemia in diabetes mellitus type 1 (Voziyan, 2005).
- **benfotiamine** is a derivative of vitamin B_1, which is involved in a limitation of methylglyoxal formation and lowering of AGEs accumulation (Gadau et al., 2006).
- **ALT-711** is a new stable analogue of N-phenal thiazolinium bromide (PTB). Its mechanism of action is based on preventing metal-catalyzed glycation (Price et al., 2001).
- **Acetylsalicylic acid (Aspirin®), salicylates and ibuprofen** possess an anti-inflammatory properties, which are important in the decreasing of the risk of cataract in people suffering from diabetes. As a radical scavengers, they may reduce the level of free radicals and/or chelate metal ions (Dinis et al., 1994).
- **chromium** deficiency is associated with the blood sugar irregularities of diabetes. Recent studies have demonstrated that chromium is effective in treating various types of diabetes, including types 1 and 2, gestational, and steroid-induced diabetes. Treatment of type 2 diabetes with chromium has led to improvement in blood glucose, insulin, and haemoglobin A_{1c} (HbA_{1c}) levels. The use of organic chromium complexes has been found to give superior results when compared to inorganic salts. Chromium has been found to be effective in reversing diabetes caused by the therapeutic use of glucocorticoids. Chromium picolinate (600 μg/day) was effective in lowering blood glucose almost twice (from 13.9 mM/L to 8.3 mM/L) in 47 of 50 patients. This therapy in patients was also able to reduce the doses of insulin and/or hypoglycaemic medications by half within one week from the beginning of chromium supplementation (Lamson & Plaza, 2002)

Among the newest agents tested in both *in vitro* and *in vivo* studies are poly(amido)amine PAMAM dendrimers and β-resorcylidene aminoguanidine (RAG), a derivative of aminoguanodine.

- **PAMAM dendrimers** are widely studied all over the world in almost every field of science. Their unique structure with nucleophilic character provided by surface amino groups may play an important role in the prevention or amelioration of hyperglycaemia. The ability of conjugation of PAMAM dendrimers to certain biologically relevant molecules makes them promising agents for using in biomedicine area, either as drugs or drug delivery systems. Experimental *in vitro* studies revealed that dendrimers appear very effective in scavenging glucose and reducing protein glycation (Fig. 9) (Labieniec & Watala, 2010). It was also evidenced that PAMAM dendrimer G4 administrated to rats with streptozotocin-diabetes acted as glucose scavenger and suppressed the accumulation of AGEs products, as well as some other markers of oxidative and carbonyl stress (Labieniec et al., 2008).

- **aminoguanidine** was the most promising oral antihyperglicaemic agent based on antioxidant capability and reduction of carbonyl reactive intermediates (Brownlee et al., 1986). Nevertheless, the B_6 vitamin depletion and oxidative stress production after using of aminoguanidine by patients with diabetes has been recorded, and therefore this compound was removed from clinical trials. Since then, new analogues of aminoguadine were synthesized in order to avoid the undesirable side effects of aminoguanidine itself. **β-resorcylidene aminoguanidine (RAG)** is one of these analogues, which seems to be the most promising and effective antioxidative and anti-diabetic agent amongst the others tested hitherto. The majority of studies have demonstrated that RAG is able to limit diabetes-associated long-term complications (protein glycation, AGEs formation, ROS level). Scientists suggest that RAG acts not only as antioxidative and/or anti-diabetic agent (Waczulíková et al., 2000, Vojtaśśak et al., 2008), but has also been shown to act as antithrombotic compound, independently of its anti-glycation activities (Watala et al., 2009).

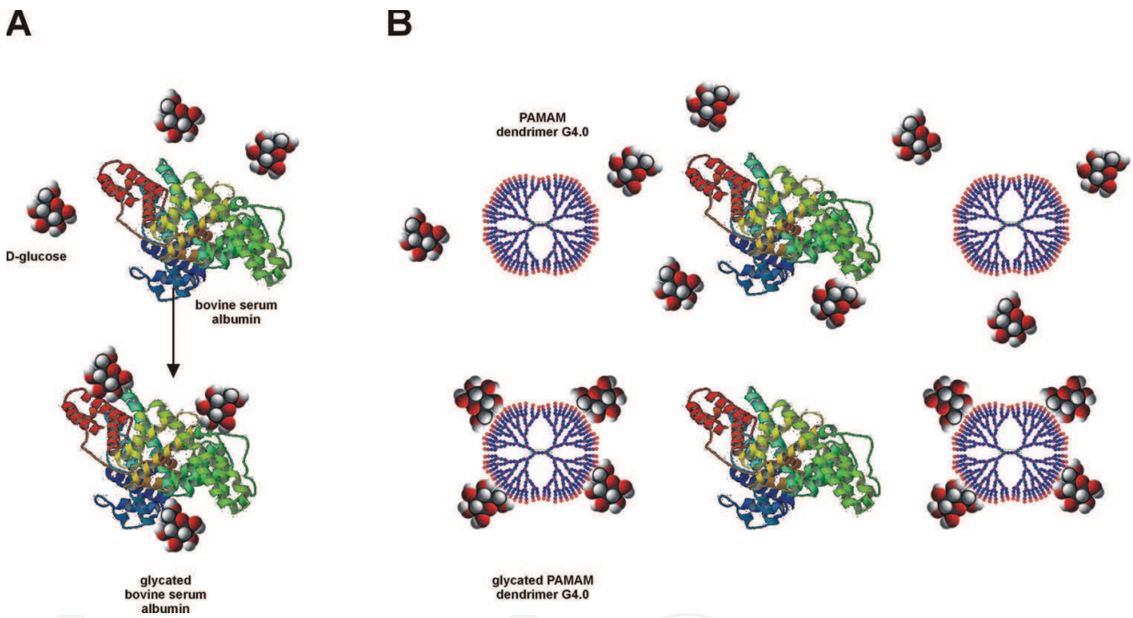

Fig. 9. The proposed mechanism of anti-glycation action of poly(amido)amine dndrimers (PAMAM).

Under conditions of excessive glucose the model protein (bovine serum albumin, BSA) undergoes extensive glycation (A), which becomes retarded and reduced to a large extent in the presence of poly(amido)amine dndrimers, generation 4.0 (PAMAM G4.0).

6. Conclusion

Diabetes is not merely a disease of impaired insulin sensitivity or insulin release, but may be a global metabolic dysfunction, including, among others, the collapse of the mitochondrial energy system. The role of the mitochondria in the metabolism associated with the pathophysiology of diabetes seems unique, mainly because a generation of ROS (which seem a natural part of mitochondrial physiology) constitutes a major treat in the development of diabetic sequelae. ROS play the central role in mediating various metabolic

defects associated with the diabetic state. Therefore, inhibition of ROS production and/or enhancement of ROS scavenging will prove to be beneficial therapies. Hyperglycaemia elicits an increased ROS production, presumably from the mitochondrial respiratory chain. An important challenge for future research is to determine whether strategies aimed to improving mitochondrial functionality by using agents with anti-diabetic properties might have therapeutic potential in the treatment of diabetes. On the other hand, the better understanding of mitochondrial biology is still needed to facilitate the judicious selection and development of compounds/agents, which could be used as "mitochondrial drugs". Further studies are certainly required to better understand how these novel compounds and mitochondria may interact with each other, and how our understanding of such interaction might be utilized for the impaired mitochondrial functioning in the presence of diabetes. These investigations should also determine, which genetic, environmental, pharmacological and nutritional factors are possibly involved in an individual patient's susceptibility and, which treatments can be used safely in those patients, who suffer from heavy diabetes and are crushed by the burden of advanced long-term complications.

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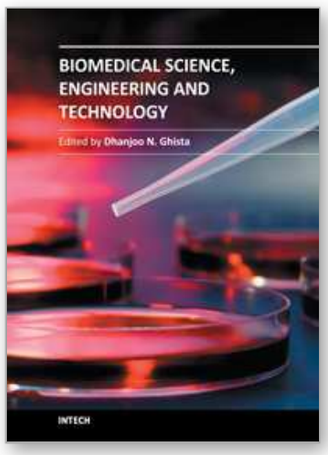

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