Metabolic memory — the implications for diabetic complications
Pamięć metaboliczna — rola w patogenezie przewlekłych powikłań cukrzycy
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Abstract
Many important biochemical mechanisms are activated in the presence of high levels of glucose, which occur in diabetes. Large randomised studies have established that early intensive glycaemic control reduces the risk of diabetic complications. This phenomenon has recently been dubbed ‘metabolic memory’. It has been suggested that early glycaemia normalisation can halt the hyperglycaemia-induced pathological processes associated with enhanced oxidative stress and glycation of cellular proteins and lipids. The phenomenon of metabolic memory suggests that early aggressive treatment and strict glycaemic control could prevent chronic diabetic complications.

Key words: levels of glucose, metabolic memory, diabetic complications

Introduction
The toxic influence of glucose on different tissues (so called glucotoxicity) has been known for a long time [1, 2]. Experiments on animal models as long ago as the mid-1980s pointed to the phenomenon of ‘metabolic memory’. Between 2000 and 2002, the results of clinical trials showed that an early intensive therapy aimed at normalising metabolic control can reduce the negative processes in cells and minimise the risk of chronic complications [3–5]. Later multicenter studies confirmed those results [6–13].

The development of chronic complications is a result of some metabolic, hormonal, environmental or genetic action [14]. It is well known that persistent hyperglycaemia is responsible for the development of the chronic complications of a microangiopathic (retinopathy, nephropathy, neuropathy) as well as a macroangiopathic (ischaemic heart disease, cerebral and peripheral vessels diseases) nature.

Under the conditions of chronic hyperglycaemia, a non-enzymatic protein glycation, polyol pathway and oxidative stress are being activated [15]. An increased glucose concentration leads to the LDL particles modification which results in their endothelial toxicity.

Chronic hyperglycaemia and the related inflammatory state disturbs the balance between metalloproteinases and their inhibitors (MMP/TIMP) causing a pathological remodelling of the vessel walls, endothelium proliferation and arteriogenesis.

Of late, there has been discussion of the ‘hyperglycaemic memory’, a phenomenon of the pathological processes persistence related to the increase of oxidative stress, glycation of proteins and cellular lipids [16–18]. Ihnat et al. [19] have presented randomised studies on this subject. A wider discussion of this issue based on a review of the literature has been advanced by Ceriel-lo et al. [20] and Drzewoski et al. [21].

Previously brought up phenomena are being initiated as a result of hyperglycaemia’s influence already
at the beginning of the disease. Their memory is being preserved despite subsequent improvement of the metabolic control [19, 20]. Hence the importance of thorough, intensive treatment of diabetes from the moment of its diagnosis cannot be overstated. This particular, early period of the disease is, to a great degree, a predictor of the following chronic complications and the fate of the patient.

Chronic hyperglycaemia triggers many processes, e.g:
- protein kinase C and phospholipase A2 activation, leading to an increase in arachidonic acid metabolites’ production;
- an increased growth factors expression, resulting in increased vasoconstriction;
- rise of the advanced glycation end-products (AGE), increasing oxidative stress through their interaction with corresponding receptors (RAGE);
- glycation and oxidation of LDL;
- enhancement in expression of the nuclear transcription factor NFκB, adhesion molecules’ concentration rise, decrease in NO bioavailability, increase of IL-6, TNF-α and other cytokines;
- protein kinase C activation and a rise in DAG (diacylglycerol) production, leading to a lowering of the NADPH pool and generation of NO.

It is believed that after reaching a certain critical point of some disturbances (like AGE accumulation) the acceleration of retrograde changes in the cell still progresses, despite having acquired a good glycaemia control. It has been suggested that a long-lasting good metabolic control, established as soon as glucose intolerance appears, may inhibit the development of chronic complications even if subsequently the control worsens. The ‘memory’ existence awareness seems to be particularly important in children and young adults, in whom onset of the disease is usually so evident that the diagnosis is quickly established and treatment is introduced relatively fast. Therefore these patients stand a good chance of a reduction in marked chronic complications. On the other hand, older patients with diabetes type 2 are sometimes left undiagnosed and untreated for many months, sometimes even years. In this group, the level of hyperglycaemia is usually not as high as in type 1, so it can often be overlooked. Unfortunately, all chronic hyperglycaemic states lead to increased nonenzymatic glycation and oxidative stress, and the subsequent development of chronic complications.

Nonenzymatic protein glycation

Hyperglycaemia plays a crucial role in the pathomechanism of diabetic angiopathy. Its destructive influence can take place through the activation of variable metabolic pathways. A nonenzymatic protein glycation is one of them. It is a nonenzymatic binding of carbohydrates with the rich in free amino groups particles of protein. The early stages of glycation are reversible, but the process results in the emergence of advanced glycation end-products (AGE) [22, 23]. These compounds form a heterogeneous group that derives from a nonenzymatic reduction of carbohydrates with the contribution of the free amino groups, lipids and nucleic acids. AGEs have specific membrane receptors on certain types of cells.

The nonenzymatic protein glycation pathway is an important mechanism, through which hyperglycaemia damages endothelial cells. Endothelial dysfunction may play a significant role in the development of diabetic angiopathy. On the surface of endothelial cells, specific types of receptors are found (RAGE — advanced glycation end-products receptor). RAGE binds the advanced glycation end-products [24]. This connection causes an increase in oxidative stress, rise in the production of reactive oxygen species, cytokines (TNF-α, IL-1), growth factors (IGF-1, TGFβ), adhesion molecules and the activation of the transcription nuclear factor kappa-light-chain-enhancer of activated β-cells (NF-κβ). Plenty of studies point to the essential role AGE plays as a mediator in the pathogenesis of diabetes and its complications [25]. The glycation process can affect genetic material as well, leading to changes in gene expression.

The activation of the polyol pathway

In the circumstances of glucose increase in the extracellular space, a secondary glucose metabolism pathway is being activated. Aldose reductase transforms glucose into sorbitol, causing its accumulation. Sorbitol excess leads to tissue swelling and damage. Chronic hyperglycaemia intensifies glucose transformation via this cycle, and also changes the NADH/NADPH ratio and lowers the concentration of reduced glutathione. The sorbitol increase is accompanied by a drop in the intracellular myoinositol, which takes part in the signal transduction inside the cell and regulates the Na+/K+ ATPase activity.

Oxidative stress

Hyperglycaemia leads to cyclooxygenase activation, glucose autooxidation and disturbs the function of divalent metal ions. The free radicals (ROS) that are formed in the process of glucose autooxidation cause lipid and AGE oxidation, diacylglycerol-protein kinase C pathway activation and the increased thromboxane synthesis.

The action of free radicals contributes also to an increase in endothelium permeability and escalates the production of the secondary glycation end-products.
ROS cause lipid peroxidation in the cellular membranes and activate LDL oxidation, which in this way becomes toxic for endothelium. In diabetes, an increased lipid peroxides concentration can be seen. They cause vasoconstriction of vessels, especially in the heart. Free radicals can activate growth factors and release the particles that play a role in monocyte and platelet adhesion to the endothelium. They can also stimulate macrophages that release cytokines damaging endothelial cells. Many experimental studies show that ROS can induce apoptosis within the cell.

Proteoglycans metabolism disturbances

In the process of diabetic angiopathy development, the disturbances of the proteoglycans metabolism play a significant role. Glycosaminoglycans (GAG) have an important part in the pathogenesis of diabetic nephropathy. The proteoglycans are macromolecular components of the extracellular matrix. They consist of a protein core bound covalently with the glycosaminoglycan chains of the high grade of diversity. Hyperglycaemia disturbs the metabolism of the proteoglycan known as heparan sulfate. A deficiency of heparan sulfate’s (HS) leads to renal glomeruli sclerosis and accelerates atherosclerotic changes in the vessels. Moreover, GAG deficiency increases the proliferation of smooth muscle cells.

The development of the chronic complications of diabetes

The activation of nonenzymatic protein glycation

This process leads to the glycation of the basement membrane, collagen, serum proteins, DNA etc. The glycation of mitochondrial proteins might be part of the explanation of the ‘metabolic memory’ phenomenon. The glycated mitochondria that overproduce free radicals in a way different from the glucose level manner can cause mitochondrial DNA (mt DNA) damage. This leads to a further worsening of the mitochondrial state and further reactive oxygen species production, which damages the cell and sustains the activation of the pathways responsible for the chronic complications of diabetes [26]. Oxidative stress can change the expression of the mitochondrial proteins.

Advanced glycation end-products (AGE) accumulate in the vessel walls from the onset of diabetes, and this is what causes their damage. Endothelium functions disturbances play a significant role in the early stages of vascular lesions [27, 28]. Vascular complications affect both main parts of the vessel wall (the internal and the media), including not only functional but also structural changes.

The intensification of glucose metabolism via the polyol pathway

The increased activity of the polyol pathway takes place mainly in the retina, the eye pupil, peripheral nerves and renal glomeruli, i.e. in the regions of the insulin-dependent glucose transport. Sorbitol accumulation triggers a chain of reactions leading to the lowering of sodium-potassium ATPase activity, something that causes structural and functional disturbances in the organs.

Protein kinase C activation

In the cells where the expression of aldose reductase is low or none at all, hyperglycaemia causes increased diacylglycerol production, which up-regulates protein kinase C activity. The excessive activation of protein kinase C leads to functional and structural changes in the cells. Hyperglycaemia can have opposite effects on protein kinase C in different cell types. For instance, retinal pericytes which display a high expression of aldose reductase under the circumstances of hyperglycaemia begin to atrophy, which causes microaneurysms to appear. On the other hand, endothelial cells with no enzyme at all proliferate, leading to occlusion of the vessel’s lumen [29].

Oxidative stress increase

There is substantial evidence linking hyperglycaemia-induced overproduction of reactive oxygen species with increased levels of oxidative stress in diabetic patients. The MAP-kinases’ damage under the circumstances of hyperglycaemia may be one of the factors responsible. Mitogen-activated kinases (MAP, MAPK) are a group of protein serine threonine kinases which play a role in the regulation of the answer to the external stimuli that reaches the cell. In endothelial cells, the overproduction of ROS is sustained long after the normalisation of the glucose level. Many processes, such as the prolongation of protein kinase C-β (PKC-β) activation, accompany this phenomenon. These processes influence gene expression as well as division, differentiation, movement and apoptosis of the cells.

In glucose intolerance, an overproduction of the endogenous inhibitor of the vascular nitric oxide synthase (ADMA, asymmetric dimethylarginine) can occur. One of the reasons for ADMA increase may also be inhibition of the enzyme that degrades it: dimethylarginine dimethylaminohydrolase (DDAH). This enzyme is inactivated by oxidative stress. Nitric oxide (NO) plays a crucial role in maintaining vascular homeostasis. Its decreased bioavailability, which can be caused either by insulin deficiency or by defective insulin sensitivity, leads to disturbances in the structure and function of the ves-
sels. Hyperglycaemia also induces the production of some vasoconstrictive agents such as endothelin 1, which through its specific receptor causes contraction of the smooth muscle cells in the vascular wall [30].

Molecular changes in the biology of the vessel wall of the microcirculation that develop in the presence of higher than physiologic glucose concentrations on the one hand cause a change in their functions, and on the other are responsible for the ‘hyperglycaemic memory’ phenomenon. DNA damage indirectly induced by hyperglycaemia leads to the maintenance of intracellular molecular structure changes, for as long as several years [31].

The mitochondrial proteins become glycated in the period of hyperglycaemia, which causes an increase of superoxide anion production. In this case, even when the glycaemia returns to normal, the glycated mitochondria keep on producing the superoxide anion which thereby activates the same pathways involved in the development of the chronic complications of diabetes. Hence, long-lasting hyperglycaemia before the diagnosis of diabetes may already in this early period leave marks in the cells of the circulatory system and target organs, contributing to the future development of complications.

If so, this would explain the fact that the chronic complications of diabetes can appear even in patients with currently good metabolic control. Nowadays, it is known that to prevent chronic complications, one not only to maintain good metabolic control, but also to maintain an efficient treatment from the very first diagnosis.

The diagnostic usefulness of oxidative stress markers in children with diabetes type 1 has been reviewed by Krzystek-Korpacka et al. [32]. The development of the pathogenic processes related to hyperglycaemia caused either by insulin deficit and/or insulin resistance, can be seen in type 1 as well as in type 2 diabetes. The results of extensive, prospective clinical studies have been set out by Giugliano et al. [33], who stress the need for maximal glycaemia control. ‘Metabolic memory’ has its role in the occurrence of vascular complications in children as well [10, 34].

Conclusions

Very early, aggressive treatment aiming to ‘normalise’ glycaemic control is needed to reduce cellular reactive species and glycation and to minimise long-term diabetic complications.

References

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