Carbonyl stress

High concentration of the reactive carbonyl species leads to proceeding destruction of the organs. The reason could be increased production of the carbonyl species or decreased elimination (disorder of aldehyde dehydrogenase which catalyses the oxidation of aldehydes) and excretion.

Carbonyl species are related to oxidative stress, hyperlipidemia and hyperglycemia. Examples of carbonyl species are glyoxal, glycoaldehyde, hydroxynonenal, methylglyoxal, 2-deoxyglukoson. These compounds can be created from sugars, amino acids and fats.

Excretion of the carbonyl species takes place in the kindeys. Enzymes which can eliminate carbonyl compounds are for example aldosa reduktasa, aldehyd dehydrogenasa a glyoxylat. All these enzymes require redox coenzymes GSH, NADPH, NADH.

AGEs (advanced glycation end products)

Carbonyl species react non enzymatically with amino groups of the proteins (Maillard reaction) with production of AGEs as the resault.

AGEs represent heterogeneous group of substances that includes pentosidine, GOLD (glyoxal-lysine dimmer), MOLD (methylglyoxal-lysine dimmer).

For AGEs is typicall yellow-brown pigmentation and fluorescence. AGEs are able to modify biological structures. They react through their specific receptors (for example RAGE receptor). AGEs are important in patogenesis of chronic deseases and their complications, for example diabetes mellitus, chronic kidney desease, atherosclerosis, neurodegenerative diseases and the others.

Proteins transformed to the AGEs change their physical and chemical properties. These changes include change of the solubility, charge, lower isoelectric point, crosslinking (bondings linking one protein to another), increased resistance to the heat denaturation and stability against low pH.

RAGE receptor

RAGE is a transmembrane protein that works as a receptor for advanced glycation end products. It belongs to the immunoglobulin superfamily. RAGE often appears on the endothelial cells in regions affected by atherosclerosis, on macrophages and microglial cells of the brain tissue.

AGEs-RAGE interaction

Interaction between AGEs-RAGE causes intracellular signalization. It also leads to the oxidative stress and activation of the MAP-kinase pathway. Both of these mechanismes activate transcription factors, for example NF-κB, that can trigger the cascade reaction.

Effect of the RAGE receptors in an organism

Activation of the NF-κB factor stimulates the production of the cytokines (IL-1, TN-α, interferon γ) and growth factors (IGF-1, PDGF). As a result the expression of the adhesion molecules, level of the cell proliferation and vascular permeability increase. Migration of the macrophages and endothelin production are also stimulated. Synthesis of the colagen IV, proteoglycans and fibronectin are increased. In area of the inflammation fagocytes start producing carboxymethyllysine (CML).

Negative impacts of AGEs

Complications providing diabetes mellitus

Chronic changes during the diabetes are consequence of hyperglycemia, which leads to the high protein glycation and subsequently to the oxidative and carbonyl stress. The result of these stresses is high production of the AGEs and ALEs.

This mechanism is not the only reason of the negative impacts during the diabetes. Glycemia itself causes the dysfunction of metabolism of the fats and the level of AGEs and ALEs is increased by non-enzymatic glycation. It's important to understand that complications during the diabetes don't have only one certain reason but a complex of connected processes.

Changes in metabolism

Non-enzymatic glycation - Maillard reaction.

Intracellular hyperglycemia develops in the tissues where insulin is not required (lens, nervous tissue, kidneys). Glucosa is transformed into sorbitol and fructose, that causes hyperosmolarity and osmotic damage of the cells. Sorbitol damages the ion pumps and causing the neuropathia and aneurysm in the retina.

Macrovascular complications

Accelerated development of the atherosclerosis causes the CAD (coronary artery disease) which leads to the ischemic disease of the lower extremities.

Microvascular complications

Nephropathy leads to the kidney failure. Deposits are storaged in the basal membrane, as the result it gets thicker and its charge changes. Growth factors are released and the vascular permeability rises, mesangial matrix expandes and also gets thicker. Cell wall proteins are modified by the crosslinking. Glycation and oxidation of the LDL molecules and collagen lead to the destruction of the endothelium.

Retinopathy manifests in several forms. Non-proliferative form is characterised by microaneurysms, light bleedings, exsudation, edema. Avascular sections and bleeding are typicall for the preproliferative form. Preproliferative form is characterised by angiogenesis, fibrosis and vitreous haemorrhage.

Other complications

- Diabetic foot – is caused by neuropathy, neuromuscular deseases and simultaneous damage of the large and small blood vessels. In this case it comes to edema, ulcer disease, infection, necrosis and gangrene of the tissues.
- Diabetic neuropathy.
- Hypertension.

Complications providing chronic kidney desease

Diabetic nephropathy

Carbonyl stress damages kidneys with AGEs and ALEs which modify biological structures, otherwise it comes to diabetic nephropathy. Kidneys become dysfunctional and incapable of normal catabolite excretion, regulation of the ion, water and acid-base balance.

Amyloidosis related to hemodialysis.

Oxidative and carbonyl stress effects the modification of the β-2-microglobulin, which is a part of the amyloid deposits. This attracts monocytes and macroohages which start to produce cytokins.

Connection with peritoneal dialysis

Carbonyl sress is also important for peritoneal dialysis where it comes to autooxidation of the glucose which leads to generation of dicarboxyl products, subsequent production of the AGEs and peritioneal dialysis failure. This situation can be prevented by separation of the glucose from the electrolyte solution.

Uremia

Uremia is effected by carbonyl and oxidative stress and leads to the production of the carbonyl compounds (glyoxal, glycoaldehyde, methylglyoxal, 3-Deoxyglucosone), radical reaction products (hydroperoxide, NO, os-LDL), AOPP – advanced oxidation protein products and AGEs – advanced glycation end products. In uremic plasma are accumulated pentosidine, GOLD, MOLD and ALEs – advanced lipoperoxidation end products).

- Insufficient clearance of the oxygen radicals;
- reduced antioxidative protection (enzymes and their cofactors, antioxidative vitamins, depletion of the thiols, hypoalbuminemia - related to malnutrition).

Complications providing atherosclerosis

Atherosclerosis is a pathological process of damaging of the blood vessel's walls and progression of the atheromatous plaques. Both of these mechanismes can gradually cause the stenosis and closure of the artery and subsequently cause ischemia of the tissues. Pathogenesis of atherosclerosis is affected by many of processes following each other.

The affect of lipoprotein molecules

Lipoprotein molecules (LDL, VLDL) circulating in blood permeate to the subendothelial layer of the blood vessel. These molecules can be modified by glycation, oxidative stress or carbonyl stress with formation of the glycated, glycooxidated and oxidated LDL. All of them interact with proteogycans in the extracellular matrix and cause the structural modifications of the proteins and crosslinking.

Increased amount of extracelular matrix leads to thickening of endothelium. Endothelium damage increases procoagulant activity (adhesion and aggregation of platelets). Inflammation manifests in this region, anti-inflammatory cytokines and factors (TNFα, IL-1) are produces as a response. Synthesis of NO is blocked, the ability

of the wall to dilatate decreases.

The affect of macrophages

Macrophages also play an important role in the atherosclerosis development. These cells are provided by scavenger receptors on their surface. Scavenger receptors help to accumulate LDL molecules and cholesterol inside the cells. Macrophage engulf these molecules and turn into the foam cells. Foam cells release fats to the extracellular region (creation of the atherosclerotic plaques) and produce the growth factors for the smooth muscule cells. Besides they produce oxygen radicals and hydrolases that cause further modifications of the proteins.

Modified LDL molecules cause the chemotaxis of the monocytes (support the expression of VCAM and further adhesion proteines in smooth muscule cells). The next step is adhesion of the monocytes to the wall and permeation between the wall layers where they transform into macrophages. Macrophages then turn into the foam cells and that is the way atherosclerotic plaque creates. Foam cells inside the atherosclerotic plaque die by necrosis. This can cause instability and disintegration of the plaque. As the result increases the risk of thrombosis and further related complications.

Theraphy and reduction of the carbonyl stress

Nowadays therapy of the carbonyl stress is aimed at intervention of carbonyl stress compounds production. One of the medications is for example aminoguanidine.