

# Advanced glycation products

**Advanced glycation products (AGEs)** are a heterogeneous group of substances, including pentosidine, GOLD (glyoxal-lysine dimmer) and MOLD (methylglyoxal-lysine dimmer).

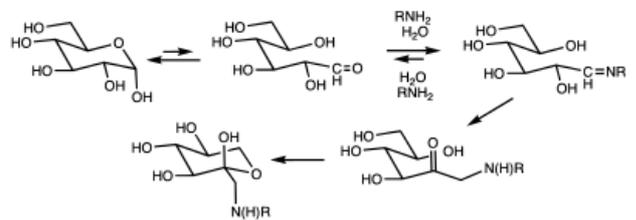
They are characterized by **yellow-brown pigmentation** and fluorescence. They are able to **modify biological structures**. They react with specific receptors, for example **RAGE**. They are important in the pathogenesis of late complications of diabetes mellitus and chronic diseases such as chronic renal failure, atherosclerosis, neurodegenerative diseases and others.

Proteins **change their physical and chemical properties** during their glycation and subsequent changes. They include for example changing solubility, charge and isoelectric point, chain crosslinking, increased resistance to thermal denaturation and stability against decrease in pH .

AGEs arise as advanced products of non-enzymatic protein glycation. This process is closely related to oxidative stress and carbonyl stress.

## Non-enzymatic glycation

In non-enzymatic glycation of proteins, the **free amino groups of proteins** (especially the lysine and arginine side groups, to a lesser extent the histidine side groups) react with the **carbonyl groups** of reducing sugars without the catalytic action of enzymes. This reaction was first described by Louis Maillard, who observed the browning of proteins when heated with sugars.



Glycation

## Maillard reaction

### Initiation

The reaction is initiated by non-enzymatic condensation of the aldehyde group of the reducing sugar and the amine group to form aldimine (Schiff base). The reaction proceeds rapidly and equilibrium occurs within a few hours. This reaction is easily reversible.

### Promotion

Schiff's base undergoes chemical rearrangement within a few days to form more stable structures, which are referred to as **Amadori products**. These structures have the character of **ketoamine**. Amadori's products are to some extent reversible, but their balance is significantly shifted in the direction of their creation. Steady state occurs within 20 - 30 days.

Other reactions can form carbonyl compounds such as glyoxal, methylglyoxal, deoxyglucosone.

Deoxyglucosone is formed at higher pH, when Amadori products enolize in the position between the second and third carbon and thus eliminate the amine from the first carbon. These compounds are **highly reactive** and are intrinsic promoters of non-enzymatic glycation, which cause **irreversible molecular changes in proteins**.

### Formation of advanced glycation products

In the last phase, Amadori products or other compounds react with the free amino groups of long-lived proteins (collagen, elastin, myelin). Advanced glycation products - **AGE-compounds** - are formed. Their formation is practically irreversible and AGEs permanently damage the tissues in which they are **stored**.

## Oxidative stress

An imbalance between the formation of reactive forms and antioxidants that remove them from the body. The resulting equilibrium is shifted in favor of reactive forms.

Reactive forms include hydroxyl radical, superoxide and compounds formed from Cl, NO<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, Fe, Cu, as well as herbicides, pesticides and others. These substances damage biological structures - lipids (lipoperoxidation), proteins (protein cross-linking), sugars (glycosylation) and nucleic acids (DNA mutations).

Antioxidants (ascorbic acid, vitamin E, selenium, Beta-carotene ) can be removed from the body.

## Carbonyl stress

An increase in reactive carbonyl compounds leads to **gradual organ damage**. It can be caused by their increased production or their reduced degradation (elimination error - aldehyde dehydrogenase) and subsequent excretion.

Carbonyl compounds are very closely related to oxidative stress, hyperlipidemia and hyperglycemia. Carbonyl compounds include **glyoxal, glycoaldehyde, hydroxynonenal, methylglyoxal and 2-deoxyglucosone**. These compounds can be formed from carbohydrates, amino acids and fats.

## RAGE receptor

RAGE is a transmembrane protein that serves as a receptor for advanced glycation products. They belong to the immunoglobulin superfamily. It most commonly occurs on endothelial cells (areas typically affected by atherosclerosis), macrophages, and microglia in brain tissue.

### AGEs-RAGE interaction

Interactions between AGEs-RAGE cause intracellular signaling. It also leads to oxidative stress and activation of MAP kinases. These two mechanisms lead to the activation of transcription factors such as NF- $\kappa$ B (nuclear factor kappa B). NF- $\kappa$ B affects the expression of genes important for immunity, inflammatory response, cell growth, cell death and embryonic development.

### Effect of RAGE receptor in the body

Activation of NF- $\kappa$ B stimulates the production of cytokines (IL-1, TN- $\alpha$ , interferon  $\gamma$ ) and **growth factors** (IGF-1, PDGF). This results in the expression of adhesive molecules, increased cell proliferation and increased vascular permeability. It also stimulates macrophage migration, endothelin production. The synthesis of collagen IV, proteoglycans and fibronectin increases. At the site of inflammation, it stimulates the formation of carboxymethyllysine (CML) in phagocytes.

## Negative effects of AGEs in the organism

### Complications of Diabetes mellitus

Chronic changes in diabetes are the result of hyperglycemia, which leads to increased **protein glycation** and subsequent oxidative and carbonyl stress. Carbonyl and oxidative stress alone leads to the formation of AGEs and ALEs.

However, this mechanism is not the only one that leads to organ damage in diabetes. For example, **hyperglycemia alone increases the amount of AGEs and ALEs** (non-enzymatic glycation) - a disorder of lipid metabolism. It should be noted that the development of complications in diabetes is not caused by a single mechanism. It is a **complex** and to some extent cascading process that is highly interconnected.

### Metabolic changes

Non-enzymatic glycation - Maillard reaction.

Intracellular hyperglycemia occurs in tissues where insulin is not required (eye lens, nerve tissue, kidneys). Glucose is metabolized to sorbitol and fructose, which causes hyperosmolarity of the cells and the resulting **osmotic damage of the cell**. Sorbitol also **damages ion pumps**, leading to neuropathies and aneurysms in the retina.

### Macrovascular complications

Accelerated development of atherosclerosis, which leads to coronary heart disease and chronic ischemic disease of the lower limbs.

### Microvascular complications

Nephropathy leads to kidney failure. Deposits are stored in the basement membrane, which leads to its thickening and charge change. Furthermore, growth factors are secreted, vascular permeability increases, densification and mesangial matrix increase. Vascular wall proteins are modified (crosslinking). Glycation and oxidation of LDL particles (low-density lipoprotein) and collagen occurs, leading to endothelial damage.

### Retinopathy

- Non-proliferative form - microaneurysms, minor bleeding, exudates, edema.
- Preproliferative form - avascular sections, area hemorrhages.
- Proliferative form - formation of new blood vessels, fibrosis, vitreous hemorrhage.

### Cardiovascular complications

Modification of vascular wall proteins (crosslinking). There is increased extracellular matrix production, glycation and oxidation of LDL particles, as well as endothelial damage (collagen glycation).

Other complications include arterial damage (weakening of the vessel wall, changes in vascular permeability) and atherosclerosis.

### Complications of other systems

- Nervous system - The accumulation of AGEs in pyramidal cells (neurons) is probably related to Alzheimer's disease, in general it can be said to be a neurodegenerative disease.
- Respiratory system - Chronic lung diseases.
- GIT - Liver cirrhosis.
- Joints - Rheumatoid arthritis.

## Therapeutic options effect of reducing the formation of AGEs

Prevention of negative effects of AGEs in the body can be prevented in general at 3 levels:

1. **Development of AGEs** - Careful compensation of diabetes (diet, reduction of hyperglycemia and hyperlipidemia, reduction of oxidative stress).
2. **Chemical degradation of cross-linked proteins.**
3. **AGEs-RAGE interactions** - Effect on anti-RAGEAb receptor effect. Increased expression of soluble AGE receptor (sRAGE) - inhibitor of AGEs toxic effects. Its expression is increased by some angiotensin converting enzyme (ACEI) inhibitors, such as ramipril or perindopril. Some antidiabetics block RAGE signaling (pioglitazone, empagliflozin ).

There are ongoing studies on the effects of AGEs and their side effects. In this context, we can include substances such as taurine, carnosine, aspirin, pyridoxamine, aminoguanidine or alpha-lipoic acid.

## Links

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