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The Maillard reaction inhibitors and their biological and therapeutic significance

It is considered that the Maillard reaction in a living body takes part in various diseases related to diabetes and ageing. The inhibition of the Maillard reaction may prevent the progress of diabetic complications and slow the ageing process. Several drugs and substances of natural origin slow the formation of new glycation-induced crosslinks. One of them is aminoguanidine (Pimagedine), a small nucleophilic hydrazine compound. Its terminal amino group reacts specifically with non-protein-bound-glucose-derived intermediates of early glycation products such as 3-deoxyglucosone. This results in the formation of 3-amino-5- and 3-amino-6-substituted triazines, which prevent the further rearrangement of intermediates to protein-protein and protein-lipid crosslinks. Animal models demonstrated an aminoguanidine-mediated decrease of AGEs accumulation in the large arteries, the glomerular basement membrane and in the retina of diabetic animals (1). The treatment of diabetic animals with aminoguanidine, an inhibitor of advanced glycation (glycosylation) product formation, prevented this accumulation and diminished both early pericyte loss and the subsequent formation of acellular capillaries and microaneurysms. After 75 weeks, aminoguanidine- untreated diabetic animals developed an 18.6-fold increase in the number of acellular capillaries and formed capillary microaneurysms, characteristic pathologic features of background diabetic retinopathy. In contrast, aminoguanidine-treated diabetic animals had only 3.6-fold increase in acellular capillaries and no microaneurysms. These findings suggest that aminoguanidine may have therapeutic use in diabetic retinopathy (4). The treatment of diabetic rats for 26 weeks with aminoguanidine prevented 2.6-fold accumulation of AGEs at branching sites of precapillary arterioles (2). Aminoguanidine treatment prevented the glomerular basement membrane (GBM) thickening in experimental diabetic nephropathy (3).

Aminoguanidine also affects the nerve blood flow (NBF). The administration of aminoguanidine normalizes the reduction in sciatic nerve blood flow and more gradually reverses the electrophysiologic abnormalities in the sciatic-tibial and caudal nerves of diabetic animals. The improvement in NBF was not due to a non-specific vasodilator effect of aminoguanidine on microvessels, since this compound alone did not have a vasodilator effect on normal nerves. Aminoguanidine reverses ischaemia and more gradually improves their electrophysiology by an action on nerve microvessels (6,12). Aminoguanidine has been proposed as a drug of potential benefit in prophylaxis of the complications of diabetes. It is regarded as virtually non-toxic compound (its LD_{50} = 1800 mg / kg in rodents) but high doses of aminoguanidine irreversibly inhibit catalase and produce hydrogen peroxide, in a transition metal-catalysed process which may be partially dependent upon prior hydrolysis of aminoguanidine to semicarbazide and hydrazine (8). Therefore, chronic administration of

aminoguanidine might promote side effects related to inhibition of catalase as acatalasaemia or suppressed iodine uptake by the thyroid (1).

Aminoguanidine treatment reduces the increase in collagen stability of rats with experimental diabetes mellitus. Aminoguanidine may bind to carbonyl groups of nonenzymatic glycation products and thereby block the crosslinking process. Aminoguanidine did not reduce the formation of early nonenzymatic glycation products (aldimine and Amadori rearrangement product), whereas the amount of browning products (fluorescent compounds) was reduced in the tail tendon collagen of the diabetic rats. Aminoguanidine treatment may prevent the concomitant changes in biophysical properties of connective tissues (9).

The hypoglycaemic drug OPB – 9195, the thiazolidine derivative, reduces AGE formation and AGE-derived crosslinks in vitro and in vivo at significantly lower doses than those of aminoguanidine. This compound prevents the progression of diabetic glomerular sclerosis in diabetic rats even under conditions of persistent hyperglycaemia (1).

The antidementia drug tenilsetam (CAS 997; (+/-)-3-(2-thienyl)-2-piperazinone), successfully used for the treatment of patients suffering from Alzheimer disease, when included in the Maillard reaction, apparently inhibits protein crosslinking by AGEs *in vitro*. Tenilsetam acts via covalent attachment to glycated proteins, thus blocking the reactive sites for further polymerisation reactions. A beneficial effect of tenilsetam in Alzheimer disease could come from the interference with AGE-derived crosslinking of amyloid plaques and a decreased inflammatory response by diminished activation of phagocytosing microglia (7,10).

The dipeptide carnosine (β-alanyl-L-histidine) inhibited glycation of the model peptide Ac-Lys-His-amide by dihydroxyacetone and it protected α-crystallin, superoxide dismutase and catalase against glycation and crosslinking mediated by ribose, deoxyribose, dihydroxyacetone, dihydroxyaceton phosphate and fructose. Carnosine can prevent the formation of cross-linked antithrombin (AT-III), LDL, apoprotein (ApoB) and fibronectin. The potential anti-glycating property of carnosine suggests that this dipeptide could be considered in the treatment of diabetics, where the glycation is the initial step leading towards important pathological secondary effects. Preliminary studies indicate that carnosine can inhibit DNA / protein cross-linking and can prevent chromosomal aberrations in Chinese Hamster ovary cells. The observation that carnosine can delay senescence in cultured human fibroblasts reinforces the proposal that carnosine, usually associated with long-lived cells (i.e. neurones), may possess useful protective properties against the deleterious side effects of glucose, other sugars and oxygen (5).

Antioxidants (for instance α-tocopherol, α-lipoic acid, deferioxamine, dimethyl- sulfoxide) have been demonstrated to inhibit hyperglycaemia-induced reactive oxygen species and AGE formation *in vitro*.

Aspirin administration seems to inhibit the formation of pathological AGE crosslinks in diabetic animals and to demonstrate protective effects in age-related cataractogenesis in humans (1).

The above mentioned compounds are the Maillard reaction inhibitors but do not seem to break AGE crosslinks which have already formed. Therefore, these compounds will not be effective in patients with a long history of the disease that already resulted in extensive tissue AGE accumulations.

Many of the crosslink breakers are modified thiazolium salts. One of them is PTB (phenacylthiazolium bromide), which reacts with and cleaves covalent, AGE-derived protein crosslinks. Based on the hypothesis that the majority of AGE crosslinks formed from glucose involve an α-diketone moiety, PTB significantly attacks the carbon-carbon bond of α-diketones and thereby breaks the carbon-carbon bond between two carbonyls of AGE crosslink. PTB demonstrated the ability to reduce AGE crosslinks *in vitro* and *in vivo* (1,11).

The other substance of natural origin homocarnosine (γ-amino-butyryl-L-histidine) showed a lower reactivity than carnosine (5).

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SUMMARY

The formation of AGE crosslinks as a result of the Maillard reaction is reduced by several drugs (aminoguanidine, OPB-9195, tenilsetam, aspirin), substances of natural origin (carnosine, homocarnosine) and antioxidants. These compounds are the Maillard reaction inhibitors, but do not seem to break AGE-derived protein crosslinks, which have already formed and therefore will not be effective in patients with a long history of the disease. The first in a new class of compounds that have been shown the ability to chemically reverse the Maillard reaction is PTB. This compound breaks the carbon-carbon bond between two carbonyls of glucose-derived protein crosslinks.

Inhibitory reakcji Maillarda i ich znaczenie biologiczne i terapeutyczne

Niektóre leki (aminoguanidyna, OPB-9195, tenilsetam, aspiryna), substancje pochodzenia naturalnego (karnozyna, homokarnozyna) oraz antyoksydanty hamują tworzenie się powiązanych krzyżowo białkowych polimerów AGE. Są one inhibitorami reakcji Maillarda, lecz nie rozrywają już utworzonych polimerów AGE. W związku z tym nie są skuteczne u pacjentów przewlekle chorych. PTB jest pierwszym, nowej klasy, związkiem wykazującym zdolność do chemicznego odwracania reakcji Maillarda. Związek ten rozrywa wiązania węgiel-węgiel pomiędzy dwoma grupami karbonylowymi w powiązanym krzyżowo białkowym polimerze AGE.