J Biochem Tech (2013) 5(1): 666-672
ISSN: 0974-2328

Newer insights in drugs inhibiting formation and accumulation of advanced glycation end products

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Received: 28 May 2013 / Received in revised form: 3 June 2013, Accepted: 3 June 2013, Published online: 30 June 2013

Abstract

It is now well established that non enzymatic glycation leads to formation of Amadori products which over course of time leads to formation of advanced glycation end products (AGEs). Accumulation of AGEs is very toxic and can have direct and indirect effects in the pathogenesis of various diseases including diabetes, alzheimer's disease, rheumatoid arthritis etc. Hence, to curb these harmful effects, a number of natural and synthetic compounds are being investigated so as to reduce clinically the impact of AGEs. Here, various AGE inhibitors and breakers published till date are being reviewed. Also, potential novel therapies are also being explored.

Keywords: AGEs, Maillard reaction, Amadori products, Glycation inhibitors, Carbonyl trapping agents, AGE breakers

Introduction

Glycation described by Louis–Camille Maillard is the non-enzymatic reaction between amino groups of proteins, lipids and nucleic acids with carbonyl group of reducing sugars (Reynolds 1963; Takeuchi and Yamagishi 2009). The glycation primarily occurs at intra-chain lysine residues of proteins (Watkins, Thorpe et al. 1985) and involves the condensation reaction of the carbonyl group of reducing sugar aldehydes with α- and ε-amino groups of lysine residues. The nucleophilic addition reaction rapidly forms Schiff base (an aldimine) and this reaction is followed by a molecular rearrangement and the formation of a N-substituted glycosylamine which lead to Amadori products (1-amino, 1-deoxy, 2-ketose), such as rearrangement of fructose-lysine to form stable ketoamine derivatives (Takeuchi and Yamagishi 2009). Over the course of days to weeks, these Schiff bases and Amadori products subsequently degrade into alpha dicarbonyl compounds, such as 3-deoxyglucosone, methylglyoxal, and glyoxal (Frye, Degenhardt et al. 1998).

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The alpha dicarbonyl compounds have the ability to react with amino, sulfhydryl and guanidine functional groups in proteins and the reaction results cross-linking of targeted proteins (Lo, Westwood et al. 1994). These alpha dicarbonyl compounds can also react with lysine and arginine functional groups on proteins, leading to the formation of stable AGE compounds, such as *N*ε-(carboxymethyl)lysine (CML), which are non-fluorescent AGEs (Ahmed, Thorpe et al. 1986). Glyoxal and methylglyoxal can be formed by glucose auto-oxidation and by reaction of glycolipids with arginine or lysine resulting in the formation of: N-(carboxy-alkyl)lysine, N-(carboxylmethyl)lysine, N-(carboxyl-ethyl)lysine, imidazole, glyoxal lysine dimer (Gold), methyl glyoxal lysine dimer (Mold).

These alpha-dicarbonyl compounds react more strongly than their parent sugars with amino group of proteins to form inter and intra-molecular cross-links of proteins called AGEs. Hence, Amadori-modified proteins, an early glycation product, undergo further reactions through a number of pathways and give rise to AGEs (Thornalley, Battah et al. 2003) which are irreversible (Schmidt, Yan et al. 1999). In the Maillard reaction, reactive oxygen species (ROS) and free metal ions were the chief stimulators, and chelators were identified as potent inhibitors of browning and cross-linking of proteins by sugar.

Therapeutic interventions

The discovery of AGE inhibitors and breakers and understanding their possible mechanism of actions is really a challenging task considering the complexity of glycation cascade. AGE inhibitor must possess the property of trapping highly reactive intermediates in AGEs formation in glycation pathway. Also, these inhibitors should arrest the formation of AGEs at carbonyl stress stage or after formation of reactive protein adducts. Also, these drugs should possess a property of selectivity i.e. not interfering with aldehyde or

ketone metabolism. Therapeutic approaches are prevention and inhibition of AGE formation so as to inhibit its accumulation and to break crosslinks of AGES after their formation to prevent adverse consequences of AGEs accumulation.

Prevention of AGEs

Dietary antioxidants

Drugs that could inhibit formation of AGEs, include dietary antioxidants such as vitamin C, vitamin E (α–tocopherol), benfotiamine, (a synthetic S-acyl derivative of thiamine) and pyridoxamine (vitamin B_6 family) (Rahbar and Figarola 2003). Although the mechanism of action is not known, these bind to sugars or proteins and inhibit Amadori product formation and subsequently inhibit AGEs formation. Their anti-oxidant function would decrease formation of free radicals which stimulate autoxidation of sugars (Vinson and III 1996).

Vitamin C (ascorbate) as well as its free radical semihydroascorbate forms complexes with proteins via ionic bonding (Bensch, Koerner et al. 1981). *In vitro* erythrocyte glycation have demonstrated that the carbonyl group of ascorbic acid competes with that of glucose for binding with protein (Davie, Gould et al. 1992). Also, vitamin C alone or in citrus extract could inhibit sorbitol pathway in human diabetic subjects. Thus, vitamin C affects both sorbitol and glycation pathway and thus is beneficial in diabetic complications (Vinson and III 1996).

Vitamin E, a powerful antioxidant, was earlier shown to be an anti-glycating agent *in vitro* (Ceriello, Giugliano et al. 1988). Because of its *in vitro* lipid peroxidation inhibiting property, it arrests the glycation of haemoglobin (Jain 1993). Ceriello demonstrated that it can be used as an *in vivo* supplementation in diabetes (Ceriello, Giugliano et al. 1991).

Vitamins C and E synergistically inhibit glycation and AGEs accumulation, more effectively than either vitamin alone, further proving that the inhibition is due to their anti-oxidant property (Vinson and III 1996). Besides inhibiting the oxidation of Amadori products, both vitamins can also inhibit lipid peroxidation and carbohydrates oxidation (Hunt, Smith et al. 1990; Wolff, Jiang et al. 1991).

Nicotinamide is a potent antioxidant and decreases severity of streptozotocin (STZ) induced diabetes in rats (Yamada, Nonaka et al. 1982). Pyridoxal is a competitive inhibitor and binds to proteins via its aldehyde group (Khatami, Cernadas et al. 1990). It has been used in human diabetics in high doses to decrease glycated haemoglobin (Solomon and Cohen 1989). Carnosine (β-alanyl-histidine), a natural dipeptide is another *in vitro* and *in vivo* inhibitor of AGE formation which is widely distributed in mammalian tissues. Possible mechanisms of actions include its role as an anti-oxidant, metal-chelator, SOD mimetic and free radical scavenger (Hipkiss, Michaelis et al. 1994; Hipkiss 1998). Inositol forms glucosyl-inositol complex with lens protein and is reported to be an inhibitor of glycation of lens crystalline protein (Ramakrishnan, Sulochana et al. 1999).

Thiamine and benfotiamine are potential AGE inhibitors. Glycation pathway could also be activated by glycolytic intermediates including glyceraldehyde 3-phosphate. Thiamine supplementation channelizes glyceraldehyde 3-phosphate from glycolytic pathway to anaerobic glycolytic pentose phosphate pathway by increasing transketolase activity and hence could serve as novel inhibitors of glycation. Benfotiamine is a lipid soluble derivative of thiamine which inhibits glycation pathways by activating transketolase (Hammes, Du et al. 2003) and could reverse methylglyoxal derived AGEs (Balakumar, Rohilla et al. 2010)**.** High doses of thiamine and benfotiamine have shown to reduce the incidence of diabetic complications in rats, including retinopathy and dyslipidaemia (Hammes, Du et al. 2003; Babaei-Jadidi, Karachalias et al. 2004); benfotiamine have also given promising results in clinical trials (Balakumar, Rohilla et al. 2010).

A phytoestrogen found naturally in grapes, resveratrol (3, 4, 5-trihydroxystilbene), inhibits proliferation and accumulation of AGEs as well as collagen synthesis (Mizutani, Ikeda et al. 2000). Curcumin, active principle of turmeric, has anti-inflammatory and anti-oxidant properties and has also proved its AGE inhibiting potential. In diabetic rats it has shown interference with collagen cross-linking (Sajithlal, Chithra et al. 1998).

AGE Inhibitors

Aminoguanidine (AG)

AG (pimagedine) was the first AGE inhibitor, introduced by Brownlee et al. in 1986, and was the first to be studied both in *vivo* and in *vitro* (Brownlee, Vlassara et al. 1986). It is a hydrazine-like small molecule which traps or scavenges reactive electrophilic carbonyl intermediates, by forming stable triazine adducts with glyoxal, methylglyoxal and 3-deoxyglucosone (Thornalley, Yurek-George et al. 2000), with the most prominent effect on methylglyoxal (Thornalley 2003). AGE inhibitors must be present at a high concentration so as to trap chemical intermediates in the Maillard reaction continuously; Since AG has a short half-life (1 hour), it has to be used in high doses (typically 1 g/L in drinking water) during experiments. AGE prevents diabetic complications in rats by inhibiting arterial wall cross linking, leading to increased vascular elasticity and an improved left ventricular-arterial coupling (Huijberts, Wolffenbuttel et al. 1993). After extensive studies on experimental diabetic (type 1 & 2) animal models, AG not only emerged as an potent AGE inhibitor but also prevented diabetic complications including nephropathy, neuropathy and vasculopathy (Thornalley 2003). In both type 1 and type 2 diabetic rats, it prevented albuminuria and mesangial expansion, and hence diabetic nephropathy (Soulis-Liparota, Cooper et al. 1991; Yamauchi, Takei et al. 1997; Birrell, Heffernan et al. 2002). Development of retinopathy was prevented in diabetic dogs in a five-year study with AG therapy (Kern and Engerman 2001). Also, in diabetic rats it prevented abnormal endothelial cell proliferation and micro-aneurysms (Hammes, Martin et al. 1991). In high doses, AG improved the diminishing blood flow in nerves of the diabetic rats, and enhanced the nerve conduction velocity (Miyauchi, Shikama et al. 1996; Schmidt, Dorsey et al. 1996).

Clinical trials carried out with this drug did not exhibit significant beneficial results on the progression of overt nephropathy. Although it reduced proteinuria but risk of rise in creatinine could not be reduced (Abdel-Rahman and Bolton 2002). Unfortunately in type 1 diabetes patients, treatment was ended due to serious complications. Serious adverse effects were formation of antinuclear antibodies, abnormalities in liver function test, gastrointestinal disturbances, rare vasculitis and pernicious like anaemia in patients treated with high doses (Freedman, Wuerth et al. 1999; Nilsson 1999). Its interference with B6 metabolism is another major limitation (Miyata, van Ypersele de Strihou et al. 2002). Also, renal and pancreatic tumours have been reported in diabetic rats undergoing treatment (Boel, Selmer et al. 1995).

Besides inhibiting AGEs, it has both anti- and pro- oxidant effects on lipid peroxidation (Philis-Tsimikas, Parthasarathy et al. 1995),

and also chelates metal ions (Price, Rhett et al. 2001). It also inhibits nitric oxide synthase (Southan and Szabo 1996), and has lipid lowering effects (Degenhardt, Alderson et al. 2002). Main drawback of using AG as an AGE inhibitor is its non-specificity and high reactivity with which it scavenges other carbonyl-containing compounds. Since its discovery, very little data has been published for the use of this drug in humans. The interpretation of the effect of this drug in clinical trials is therefore still debatable.

Pyridoxamine

In a search for less toxic AGE inhibitor, vitamer in B6 family (Pyridoxamine) was explored by Hudson and colleagues (Booth, Khalifah et al. 1996; Booth, Khalifah et al. 1997). Besides inhibiting AGE formation from sugars, like AG, pyridoxamine also blocks synthesis of AGEs from glycated proteins (Khalifah, Baynes et al. 1999). Described as a post-Amadori AGE inhibitor *in vitro*, the possible mechanisms of action of pyridoxamine include: 1) blocks oxidation of Amadori products; 2) traps reactive carbonyl and dicarbonyl compounds and inhibits the formation of irreversible AGEs, and ALEs (advanced lipoxidation end products) in lipid peroxidation pathway; 3) chelates metal ions; and 4) scavenges ROS (Voziyan and Hudson 2005).

Like AG, pyridoxamine prevents nephropathy (Degenhardt, Alderson et al. 2002), retinopathy (Stitt, Gardiner et al. 2002), peripheral neuropathy (Metz, Alderson et al. 2003) and vascular complications (Khalifah, Baynes et al. 1999; Voziyan and Hudson 2005) in diabetic rats. However, unlike AG, Pyridoxamine is non-toxic in rats and humans (Khalifah, Baynes et al. 1999). Pyridoxamine is superior to AG, in correcting renal complications (as measured by serum creatinine and total proteins), as well as in controlling hypertriglyceridemia and hypercholesterolemia in diabetic rats (Degenhardt, Alderson et al. 2002). Pyridoxamine is thus another potential drug which may find use in treating diseases in which inflammation and oxidative stress lead to modification of proteins.

Other carbonyl trapping agents

There are other novel agents, structurally similar to AG, with carbonyl trapping property. These agents include ALT-946 and 2, 3-diaminophenazine (2, 3 DAP). Their mechanism of action is still not very clear. ALT-946, N-(2-acetamidoethyl) hydrazine-carboximidamide hydrochloride, having hydrazine group in its structure, is a more potent inhibitor than AG but has similar renoprotective effects and fewer side effects than AG (Forbes, Soulis et al. 2001; Wilkinson-Berka, Kelly et al. 2002). 2, 3 DAP, in diabetic rats, inhibits hypertrophy of mesenteric vessels (Soulis, Sastra et al. 1999). They have shown great results in animal studies but in clinical trials their role is being explored.

Other in vitro carbonyl trapping agents with nucleophilic functional groups include tenilsetam, penicillamine, carnosine, and possibly lipoic acid which have been proved effective in rodent diabetic models. These compounds also have potent chelating activity, measured by inhibition of metal-catalyzedascorbate oxidation, contributing to their AGE-inhibitory activity. There is no data available of their in *vivo* AGE inhibitory activity (Nagai, Murray et al. 2012). Tenilsetam, (+)-3-(2-thienyl)-2-piperazine, a cognition-enhancing drug was also shown to be an effective AGE inhibitor. It inhibits cross-linking of proteins by reacting with sugars and glycated proteins (Shoda, Miyata et al. 1997).

Aromatic compounds

Recently, aromatic compounds (LR 90, LR 9 and LR 74) having ureido and carboxamide functional groups were discovered with AGEs inhibitory activity. LRs were named after their developers as Lalezari-Rahbar (LR) compounds (Rahbar and Figarola 2003). They are better *in vitro* anti-glycating agents than AG and pyridoxamine (Schalkwijk 2007). These compounds do not have carbonyl trapping actions as they lack nucleophilic group. Instead their mechanism of action of inhibiting AGEs is through metal chelation activity. Hence, they inhibit metal-catalyzed ascorbate oxidation. LR-90 also inhibits activation of nuclear factor-kB, suggesting that they have varied effects on inflammation besides carbonyl trapping (Nagai, Murray et al. 2012). By decreasing AGE concentration in serum and kidney glomeruli, these compounds inhibits progression of nephropathy in diabetic rats. Albuminuria, mesangial expansion and protein cross-linking in collagen tissues were also decreased (Schalkwijk 2007). Furthermore, these compounds have lipid lowering effects and in type 1 diabetic rats, these agents protects renal disease and dyslipidemia (Figarola, Scott et al. 2003; Figarola, Scott et al. 2005). Clinical trials are being carried out using these drugs.

AGE breakers

Developing the concept of breaking AGE cross-links was a pharmacological breakthrough. Crosslinking between AGEs and proteins, such as collagen and elastin, causes stiffening of arteries and affects cardiovascular system. Left ventricular diastolic dysfunction develops which could lead to cardiac hypertrophy and ultimately cardiac failure. N -phenacylthiazolium bromide (PTB) was the first cross-link breaker reported in 1996 by Alteon (Vasan, Zhang et al. 1996). The main reason for its failure was its instability in aqueous solutions (Thornalley and Minhas 1999). Another potential cross-link breaker named ALT-711 (alagebrium), a PTB analog, was developed which had the advantage of stability over PTB. ALT-711, a small easily synthesized compound (3-phenacyl-4, 5-dimethylthiazolium chloride) was developed for heart failure and systolic hypertension. In diabetic rats, ALT-711 increases cardiac output and improves left ventricular diastolic function, by decreasing cardiovascular stiffening (Vasan, Zhang et al. 1996; Asif, Egan et al. 2000; Vaitkevicius, Lane et al. 2001; Candido, Forbes et al. 2003). It improves atherosclerosis and cardiac expression of brain natriuretic peptide in experimental animal models (Forbes, Yee et al. 2004). Also, in diabetic rats, this drug retarded nephropathy (Forbes, Thallas et al. 2003). Recently, pyridiniumanalogs TRC4186 and TRC4149 were also developed to break AGE cross-links (Chandra, Shiwalkar et al. 2009; Joshi, Gupta et al. 2009).

The proposed mechanisms of action of AGE breakers include releasing albumin from preformed AGE-albumin-collagen complexes, and dissociation of immunoglobulin adducts from red cells of diabetic rats. AGE breakers prevent collagen cross-linking and/or reverse the cross-links once they are formed (Wolffenbuttel, Boulanger et al. 1998; Susic 2007). AGE breakers are potent chelators as well (Price, Rhett et al. 2001). ALT 711 is the age breaker being tested in humans. Its further study is still warranted.

OPB 9195 [(±)-2-isopropylidenhydrazono-4-oxo-thiazolidin-5-ylacetalinide] is a synthetic thiazolidine derivative structurally similar to PTB. Not only it breaks cross-links, it decreases AGE production and inhibits cross-linking of AGEs *in vitro*, as well (Nakamura, Makita et al. 1997; Wilkinson-Berka, Kelly et al. 2002). Like PTB, it is unstable in aqueous solution (Thornalley, Langborg et al. 1999). OPB 9195 have been useful in preventing retinopathy,

neuropathy and nephropathy in diabetic rats (Nakamura, Makita et al. 1997; Wilkinson-Berka, Kelly et al. 2002), but have not been of much help in clinical trials because of its instability.

Exploring the existing drugs in AGE inhibition

Furthermore, some drugs which are developed for other therapeutic interventions have been demonstrated to be potent inhibitors of glycation and AGE formation.

Oral hypoglycemics

Metformin (dimethyl biguanide), an oral hypoglycemic drug, is structurally similar to AG. It has both *in vivo* and *in vitro* inhibitory activity and the possible mechanism of its action includes trapping of methylglyoxal and other dicarbonyl compounds generated during glycation (Ruggiero-Lopez, Lecomte et al. 1999; Rahbar, Natarajan et al. 2000; Beisswenger and Ruggiero-Lopez 2003). It inhibits glycation at multiple steps with maximum effect in post Amadori stages (Rahbar, Natarajan et al. 2000). Type 2 diabetes patients after metformin treatment exhibited a significant decrease in their serum methylglyoxal levels (Beisswenger, Howell et al. 1999). It significantly reduced the accumulation of AGEs in the lens and renal cortex of STZ-induced diabetic rats. By reducing carbonyl stress and accumulation of toxic AGEs, it plays a role in reducing diabetic complications (Tanaka, Goto et al. 1999).

Pioglitazone, another oral hypoglycemic drug, a member of the thiazolidinedione group, is also a powerful AGE inhibitor *in vitro*. It is similar to metformin in trapping dicarbonyl compounds. It also has metal-chelation property (Rahbar, Natarajan et al. 2000).

Drugs having anti-inflammatory/ anti-oxidant/ metal chelation property

Anti-inflammatory drugs such as acetylsalicylic acid, ibuprofen, indomethacin and diclofenac inhibits oxidative stress and hence are reported to be inhibitors of glycation (Shastri, Thomas et al. 1998; Caballero, Gerez et al. 2000; Sobal and Menzel 2000). Desferoxamine (Monnier 2003; Rahbar and Figarola 2003), hyaluronic acid (Neumann, Schinzel et al. 1999) and flavonoids (Wu and Yen 2005) have also shown inhibiting activities against AGE formation, possibly by repressing oxidative stress. Since iron is involved in the pathogenesis of diabetes, specific iron chelators such as desferoxamine have shown great results in treatment of diabetes, both in animal models and in clinical studies (Liu, Sun et al. 2009; Thangarajah, Yao et al. 2009). Pentoxyfylline, drug with chemical name 1-(5-oxohexyl)-3, 7-dimethylxanthine also has inhibitory action on AGEs but its mechanism of action is not known (May and Qu 2000).

Aldose Reductase Inhibitors (ARIs)

ARIs are programmed against the sorbitol pathway, thereby blocking the excessive metabolism of glucose. Intermediates formed during sorbitol pathway (e.g. fructose, fructose-3-phosphate, glyceraldehyde-3-phosphate and 3-deoxyglucosone) have glycating effect on proteins and result in the formation of intracellular AGEs. Fructose-3-phosphate and 3-deoxyglucosone are the major culprits (Kato, Hayase et al. 1989; Szwergold, Kappler et al. 1990). In diabetic patients, epalrestat (an ARI) contributes in decreasing AGE accumulation by lowering the levels of fructose 3-phosphate (Hamada, Odagaki et al. 1995), and also decreases imidazolone and CML (AGEs) due to reduced lipid peroxidation (Tsukushi, Katsuzaki et al. 1999; Hamada, Nakamura et al. 2000). In galactosemic rats, ARI have shown to restrict the accumulation of pentosidine (an AGE) in lens (Nagaraj, Prabhakaram et al. 1994). Although, ARIs possess functional groups (carboxyl, amino, imino, imidazole, and hydroxyl groups) with promising chelating activity, their chelating activities have not been explored thoroughly yet (Ou, Nourooz-Zadeh et al. 1996). Sorbitol pathway is active in lens, nerve and kidney and hence therapeutic intervention by ARI is a novel strategy to prevent toxic effects of AGE accumulation in these cells.

Angiotensin II Receptor Blockers (ARB) and Angiotensin Converting Enzyme Inhibitors (ACEI)

ARB, for example, olmesartan, candesartan, irbesartan, losartan, termisartan and valsartan have common core structure, 5-(4'-methylbiphenyl-2-yl)-1H-tetrazol, which may possibly be the reason for their AGE inhibitory action. ACEI such as, temocaprilat, enalaprilat, captopril, and perinoprilat also have inhibitory effect on AGEs, but lack a common core structure. The possible mechanisms of action of ARB and ACEI are: 1) trapping of carbonyl compounds and/or inhibiting carbonyl production; 2) free radical scavenging action; 3) chelating metal ions (Miyata and van Ypersele de Strihou 2003). Ramipril and valsartan have reduced AGE accumulation in kidneys of STZ-induced diabetic rats (Forbes, Cooper et al. 2002; Forbes, Thomas et al. 2004). The revelation of AGE inhibiting property of ARB and ACEI has opened more avenues for newer therapeutic interventions.

Future outlook

Formation of AGEs and their role in the pathogenesis, of diabetes and various autoimmune diseases, and in the development of complications have been well established, and still attract the attention of many researchers. Extensive studies have been carried out in the past decade in search and development of drugs, which can inhibit AGEs formation and accumulation, and counteract their pathological effects. The need of the hour is to continue these studies and clinical trials to develop the ideal AGE inhibitor. The inhibitor should be stable, easily absorbed and excreted with little or no adverse effects. Long term clinical studies are essential, so that the results of the work done so far can be finally channelized into the development of effective, marketable, newer class of drugs to treat these complex autoimmune diseases.

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