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Review Article

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Hypoglycemic Drugs and Advanced Glycation Endproducts

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Abstract

Recent data showed that 9.1% of adults worldwide have diabetes, and 318 million adults have a high risk of developing diabetes in the future. Diabetes and its complications have serious impact on human health. In the early stages of diabetes, excessive advanced glycation endproducts (AGEs) accumulate in the body and bind to its receptor RAGE, which impairs glucose regulation. In the later stages of diabetes, increased blood glucose can accelerate the production of more AGEs. AGEs play a pivotal role in the development of diabetes and its complications. In recent years, AGEs have become one of the research hotspots. The search for potential drug targets that can block or reduce the accumulation of AGEs has attracted increasing attention. This review summarizes the role of AGEs and the effects of various hypoglycemic agents on AGEs from the perspective of mechanisms, in order to provide reference for the further search for targeted drugs against AGEs.

Keywords: AGEs; Diabetes; Complications; Hypoglycemic drugs; Mechanism; Targets

Background

According to the latest report of the International Diabetes Federation Diabetes Atlas, 415 million adults in the world have diabetes, corresponding to an overall incidence rate of 9.1%, and 318 million adults have impaired glucose regulation with a high risk of developing diabetes in the future [1]. China is the country with the largest number of diabetic patients in the world. According to a published national survey, the prevalence of diabetes in China has increased dramatically over the past 30 years: from less than 1% in 1980, to 5.5% in 2001, and 9.7% in 2008. In the 2013 survey, it is estimated that the prevalence of prediabetes in China will reach 35.7% [2].

Advanced glycation endproducts (AGEs) are a series of stable and irreversible covalent compounds (such as carboxymethyl lysine, 3-deoxy glucosanoic acid, pentosidine, pyrroline, glyoxal) produced by the reaction of the aldehyde groups of the reducing sugars with the free amino groups of the macromolecules (proteins, lipids, or nucleic acids, etc.) in non-enzymatic conditions, involving processes of condensation, rearrangement, cleavage and oxidative modification [3].

Several studies have shown that AGEs are involved in the occurrence and development of chronic complications of diabetes, atherosclerosis, uremia, Alzheimer's disease, and cataracts [3-7]. AGEs are important pathogenic factors in the pathogenesis of atherosclerosis, diabetes, diabetic nephropathy, cataract and neurodegenerative diseases (including Alzheimer's disease) [8-12]. Unreasonable dietary structures, increased oxidative stress in the body, decreased deglycosylation ability, and long-term hyperglycemia can all lead to accelerated accumulation of AGEs. In the early stage of diabetes, excessive accumulation of AGEs *in vivo* and the interaction of AGE and its receptor RAGE can lead to apoptosis and necrosis of islet β cells, insulin resistance, and impaired glucose regulation [13]. In the middle and later stages of diabetes, the continuous increase in blood glucose can accelerate non-enzymatic chemical reactions in the body and produce more AGEs. Therefore, there is a higher level of serum AGEs in diabetic patients and this excess AGE will accumulate in the body and attach to cells. The level of diabetic AGEs in the vascular endothelial cells, nerve cells, kidney tissue, lens and other body tissues is also higher than that in the normal population [14-17]. AGEs can cause the development of diabetic complications through direct or indirect actions.

AGEs Mechanism of Action

Three Main Mechanisms for AGE-Mediated Tissue Effects

Cross-linking with extracellular (matrix) proteins affects the mechanical properties of tissues [18]. The formation and accumulation of cross-linked extracellular matrix proteins with AGE is a chronic process. Extracellular matrix proteins, especially the long-lived protein type IV collagens of basement membrane are more susceptible to glycosylation [19, 20]. Advanced glycosylation and cross-linking make other extracellular matrix proteins (such as collagen I and elastin) stiffer and less susceptible to degradation [18]. This mechanism may contribute to increased diabetes and vascular stiffness in the elderly [18, 19, 21]. The structure of low-density lipoprotein (LDL) can also be altered by the glycation of AGE, preventing normal elimination pathways from removing

them from the circulation. Instead, they are taken up by blood mononuclear cells to form foam cells, resulting in the development of atherosclerosis [5, 22].

Cross-linking with intracellular proteins, altering the physiological properties and functions of the cells [23, 24]. For example, AGEs cross-link the domains of Ryanodine receptor and SERCA2a in cardiomyocytes, leading to altered calcium homeostasis in diabetic cardiomyopathy [25, 26].

Binding to cell surface receptor RAGE to induce multiple intracellular signal transduction cascades [27]. It has been shown that there is a nuclear factor kappa B (NF-kappa B) binding site on the promoter of RAGE gene, thus linking RAGE expression with the inflammatory cascade [28].

RAGE

RAGE is a multi-ligand receptor for AGEs. RAGE is upregulated in a ligand-rich environment of diabetes or aging. The expression of RAGE is even more elevated in monocytes, smooth muscle, and endothelial cells at the diabetic vasculature [29]. It has been shown that circulating AGEs bind to endothelial RAGE and activate many signaling pathways, such as activation of nicotinamide adenine dinucleotide phosphate oxidase leading to increased reactive oxygen species (ROS) production and impaired endothelial function [30]. ROS have been shown to play a key role in causing significant cardiovascular damage in diabetes by altering the structure of cellular nucleic acids, proteins, and lipids, thereby altering their physiological function [31]. It has been reported that AGE-RAGE is involved in the process of increasing the phosphorylation of mitogen-activated protein kinase, extracellular signal-regulated kinase 1/2 and p21ras, p38, activating the GTPases Rac and Cdc42. These effects ultimately induce the activation and the nucleus translocation of NF-κB and subsequently initiate the transcription of cytokines and adhesion molecules that play a major role in inflammation and atherosclerosis (including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, vascular endothelial growth factor (VEGF), endothelin-1, tissue factor, E-selectin, thrombomodulin, and proinflammatory cytokines, such as interleukin (IL)-1α, IL-6, and tumor necrosis factor-α.) [30, 32-35].

SRAGE

The interaction of AGEs-RAGE results in oxidative damage and the production of matrix metalloproteinases (MMPs), whereby cell-bound RAGE is cleaved to produce soluble RAGE (sRAGE) [36]. SRAGE competes with RAGE for RAGE ligands (AGEs, HMGB1, and S100b) through binding or trapping, thus reducing inflammation mediated by RAGE [36, 37]. Studies have shown that RAGE signaling pathway is blocked by sRAGE, suggesting sRAGE as a potential therapeutic agent for preventing atherosclerosis [38]. To support this idea, the decrease in plasma sRAGE concentrations is a predictor of cardiovascular events and it is speculated that sRAGE may be a potential protective agent against vascular complications [39].

AGEs and Diabetes

AGEs are considered to be the main cause of different diabetic complications [40]. AGEs accumulate in most sites of diabetic complications including atherosclerotic plaque, kidney, and retina [41].

AGEs and Diabetic Nephropathy

Diabetic nephropathy is characterized by the accumulation of ECM (extracellular matrix) proteins in the glomerular mesangium and tubulointerstitium. AGEs may induce imbalances in the metabolism of ECM components, resulting in increased accumulation of collagen, fibronectin, and laminin [42]. After AGE modification, the affinity of type IV collagen and heparan sulfate proteoglycans with laminin and fibronectin decreases [43]. The saccharification reaction inhibited the process of polymer self-assembly for collagen type IV and laminin [44]. Studies have shown that AGEs can stimulate angiotensin II (Ang II) type 1 receptor (AT1R) and induce DNA damage and partial detachment of podocyte [45]. These changes may be particularly pronounced in the glomerular basement membrane, where the induction of chemical cross-linking between amines leads to increased protein permeability [46]. In cultured human mesangial cells, it has been demonstrated that soluble AGE containing carboxymethyllysine induces the upregulation of CTGF (connective tissue growth factor; also known as IGFBP-2) and fibronectin, which may promote the occurrence of renal fibrosis [47, 48].

AGEs and Diabetic Peripheral Neuropathy

RAGE is expressed in endothelial cells and Schwann cells of the perimysial and endoneurial vessels in rat peripheral nerves. A study showed that AGEs could cause death of neuronal cells and Schwann cells in vitro, resulting in changes in the structure and function of peripheral nerves [49]. In addition, neurofilaments and tubulin are modified by AGEs, which may interfere with axonal transport and lead to the development of atrophy and degeneration of nerve fibers [50]. AGEs-modified P0 protein may induce demyelination of nerve fibers [51]. Moreover, glycosylation of collagen and laminin alters the charge of basement membrane and leads to an increase in the permeability of blood vessels and thickening of the basement membrane. It has also been reported that AGEs can quench the vasodilatory mediator nitric oxide (NO) and inhibit the expression of NO synthase, thereby reducing neuronal blood flow and inducing hypoxia in peripheral nerves. Furthermore, the interaction between AGEs and RAGE on the endothelial cells of the peripheral and intimal blood vessels promotes the development of peripheral neuropathy [53, 54].

AGEs and diabetic retinopathy, cataract

AGEs lead to various retinal cell dysfunction and death [55]. Some studies have shown that the accumulation of AGEs is associated with dysfunction of glial cells in rat diabetic retinal Müller cells [56]. RAGE up regulates the pro-inflammatory response of retinal Müller glial cells [57]. AGEs can induce increased expression of ICAM-1 (intercellular adhesion molecule-1) in cultured bovine retinal endothelial cells and promote the reduction of diabetic retinal microvascular leukocytes [58, 59]. Studies have shown an increase in AGEs formation in the vitreous in patients with diabetic retinopathy. AGEs induce the expression of VEGF (basic fibroblast growth factor) gene in retinal cells by stimulating IL-6 secretion in human retinal Müller cells, inducing local hypoxia and increasing reactive oxygen species [60, 61]. This leads to increased mitogen and increased vascular endothelial growth factor (VEGF), which in turn stimulates neovascularization and induces proliferative retinopathy [62]. Local increases in VEGF concentrations are associated with increased vascular permeability [63]. In addition, recent studies have shown that AGEs are key regulators of non-proliferative retinopathy in patients with type 2 diabetes mellitus [64]. Therefore, AGEs are

involved in the development of diabetic retinopathy.

The severity of diabetic cataracts is related to the rate of AGEs accumulation. Long-term hyperglycemia leads to progressive saccharification oxidation of lens proteins. The accumulation and cross-linking of AGEs with external capsules gradually nucleizes the lens and increases the thickness and stiffness, promoting the formation and development of cataracts. In the lens, AGEs induce the aggregation of lens proteins, forming high-molecular-weight aggregates that cause vision loss and astigmatism [65]. AGEs can also change the surface charge of proteins, resulting a conformational change that may subsequently affect the protein-water interaction and reduce the transparency of the lens [66, 67]. Saccharification of lens proteins may be induced by elevated levels of glucose in the aqueous humor, resulting in increased production of AGEs and superoxide radicals [11]. AGE-RAGE in the lens epithelium further increases the production of O_2- and H_2O_2 [68]. In diabetic patients, reduced anti-oxidation capacity of the lens leads to increased level of free radicals and the sensitivity to oxidative stress [69].

AGEs and Diabetic Cardiomyopathy

Mitochondrial membrane depolarization is associated with AGE-induced cardiomyocyte dysfunction [70]. AGEs increase the cross-linking of matrix proteins such as collagen, laminin, vitronectin, and elastin [71]. As a result, matrix proteins have reduced pliable properties and become stiffer, which lead to decreased cardiac contractility and diastolic dysfunction. Increased cross-linking of collagen and elastin also leads to more ECM surface area, resulting in stiffer vasculature [19, 72]. Another pathway for diastolic dysfunction is activation of RAGE through AGEs [73]. In transgenic mouse models, over expression of human RAGE in the heart was found to reduce contractile and diastolic intracellular calcium concentrations [74]. AGEs may also promote the development of heart failure [75].

AGEs and Diabetes Proinflammatory State

AGEs have high affinity to cysteine in lysozyme and lactoferrin molecules, thereby reducing their antibacterial activity, which potentially contributes to the fact that the diabetic patients have declined anti-infectious abilities [76]. AGE-RAGE interaction inhibits phosphatidylinositol 3 (PI3) kinase activity, increases protein kinase C (PKC) activity and proinflammatory cytokine levels, and promotes diabetes mellitus inflammation state [77].

AGEs and diabetic Macroangiopathy

A large number of clinical studies have shown that AGEs are closely related to diabetic macroangiopathy. AGEs can impaire endothelial cell function and accelerate the progression of atherosclerosis [78]. AGEs reduce the release of vasoactive substances (such as NO, SDF-1, PGI2, TPA, etc.), promote apoptosis of late endothelial progenitor cells (EPCs) and inhibit their migration and adhesion [79]. Accumulated AGEs also accelerate atherosclerosis by cross-linking endothelial matrix proteins leading to platelet aggregation and abnormal metabolism of lipoproteins [80-82]. Therefore, AGEs may be one of the pathological mechanisms of diabetic macro vascular complications.

AGEs and Diabetic Bone Metabolism Abnormalities

Patients with poorly controlled diabetes have increased AGE-modified collagen, affecting osteoblast differentiation and function *in vitro*, and leading to osteopenia [83]. Through the NF-κβ non-dependent mechanism, AGEs promote the apoptosis of human osteoblasts and mesenchymal stem cells, which further reduces bone formation.

Hypoglycemic Drugs and AGEs

Hypoglycemic agents can be broadly classified into oral hypoglycemic agents and injectable hypoglycemic agents. Current oral hypoglycemic drugs commonly used in China include insulin secretagogues, metformin, α-glycosidase inhibitors, thiazolidinedione derivatives, dipeptidyl peptidase 4 (DPP-4) enzyme inhibitors, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors and the like. Among these drugs the insulin secretagogues are further classified into sulfonylureas and non-sulfoureas (glinides). Injectable antidiabetic drugs include insulin and similar drugs, and glucagon-like peptide-1 (GLP-1) receptor agonists. They have different effects on AGEs in many ways.

α-Glucosidase Inhibitors

In diabetic animals, since acarbose reduces the mean blood glucose area under the curve, the non-enzymatically saccharified protein and the formation of AGEs are reduced [84, 85]. Patients with type 2 diabetes treated with acarbose have reduced serum levels of glyceraldehyde-derived AGEs [86]. Acarbose treatment can significantly reduce the level of some inflammatory factors that are present in higher levels in diabetes patients than healthy individuals including AGEs [87]. In addition, acarbose has been shown to inhibit the formation of aortic collagen glycosylation in diabetic rats [88].

Glinides

Glyceraldehyde reacts rapidly with the amino groups of proteins to form glyceraldehyde-derived AGEs, causing vascular inflammation and endothelial dysfunction, and accelerating the atherosclerotic process in diabetic patients. Studies have found that nateglinide reduces glyceraldehyde-derived AGE levels in GK (Goto-Kakizaki) rats after 6 weeks of treatment [89].

In ZF (Zucker fat) rats, an animal model of insulin resistance and obesity, studies have shown that combination therapy of nateglinide (NAT) and telmisartan (TEL) improves postprandial metabolic disturbances and mitigate insulin resistance, with reduced AGEs levels in serum, RAGE expression levels, and AGE-RAGE index, probably due to the suppression of the AGE-RAGE signal in the liver [90].

Thiazolidinedione insulin sensitizer

Since thiazolidinediones have PPARγ agonist activity, they have been shown to play a role in anti-AGE therapy by up regulating sRAGE expression and being inversely related to atherosclerosis [91]. Circulating soluble RAGE (sRAGE) and endocrine RAGE (eRAGE) compete with RAGE to bind AGEs. Binding of AGEs to their receptors (RAGE) results in the production of oxygen free radicals, nuclear factor kappa-beta, pro-inflammatory cytokines, and cell adhesion molecules that are involved in the pathophysiological process of triggering cardiovascular disease (CVD). Rosiglitazone has been used to increase sRAGE levels [92]. A randomized placebo-controlled study of 111 patients with type 2 diabetes and high-risk coronary heart disease who had undergone rosiglitazone in the year of 2013 tested increased levels of sRAGE after 6 months of rosiglitazone treatment [93]. The PPARγ agonist rosiglitazone can reduce AGE levels, improve arterial injury, and mitigate AGEs-induced EPCs dysfunction [94, 95]. In human neural stem cells (hNSCs) exposed to AGEs, two neuroprotective factors (Bcl-2 and

PGC1α) are down-regulated, and inflammatory response factors (TNF-α and IL-1β), NF-κB (p65) and inflammatory genes (iNOS and COX-2) are upregulated. Aosiglitazone can rescue these effects in hNSCs via activation of PPARγ and inhibits the activity of caspase 3, thereby increases the viability of hNSC. This neuroprotective effect of rosiglitazone can be effectively blocked by a PPARγ-specific antagonist (GW9662), indicating that the above-mentioned effects of rosiglitazone are mediated by the PPARγ-dependent pathway [96].

A study conducted in 2010 showed that pioglitazone significantly increased sRAGE levels in diabetic patients at 12 weeks of follow-up [97]. In the 24-week follow-up period of PioRAGE trial, pioglitazone inhibited RAGE expression and increased plasma sRAGE levels, independent of plasma glucose or insulin resistance levels. In patients with type 2 diabetes, pioglitazone treatment has a good overall efficacy by significantly affecting the level of serum adiponectin, AGEs, human normal T cells, and secreted factors RANTES, endothelin ET, and homocysteine Hcy [98, 99].

Sulfonylureas secretagogues

One of the sulfonylurea derivatives, GP, inhibits ATP-dependent K + channels therefore can completely reverse the inhibitory effects of AGEs on ATP production and insulin secretion [100].

Gliclazide can reduce the expression of RAGE mRNA, which may have a protective effect on renal tissue damage in diabetic rats [101]. AGEs promote the binding of NF-κB to the motif at the VEGF promoter region in the bovine retinal capillary endothelial cells (BRECs), leading to the proliferation of these cells. Gliclazide blocks AGE-induced DNA binding activity of NF-κB and inhibits AGE-induced VEGF expression and PKC activation. Treatment with anti-VEGF antibodies or gliclazide inhibited the above-mentioned cell proliferation effects [102].

AGEs significantly inhibited the expression of megalin and cubic protein, cubulin, and the uptake of albumin by HK-2 cells *in vitro*. In glomerular cells of GK rats, Gliconeone can inhibit the expression of RAGE and PKC-β, upregulate the expression of PKA, megalin and cubilin, promote the secretion of C-peptide, and increase the albumin uptake. Treatment with gliquidone alleviated the injury of glomerular basement membrane and podocytes, promoted renal tubular reabsorption, and effectively reduced urinary protein and proteinuria in diabetic nephropathy GK rats [103, 104]. Gliquidone also inhibited AGEs-induced expression and secretion of RANTE (regulated on activation, normal T cell expressed and secreted) in human mesangial cell (HRMC) [105].

Glimepiride may reduce toxic glyceraldehyde-derived AGEs (glycerol-AGEs) levels and increase colony-stimulating factors to potentially repair tissue damage [106].

Metformin

MG (methylglyoxal) is the major precursor of AGE and is directly toxic to tissues. Metformin binds MG and inactivates it, reducing MG-related AGEs [107]. Metformin inhibits the production and accumulation of AGEs, thereby inhibiting the development of adverse myocardial structural and functional changes [108]. AGEs-induced proliferation of VSMCs was inhibited by metformin [109, 110]. Thiazolidine-derived metformin reduces AGE levels in patients with polycystic ovary syndrome and reduces arteriosclerosis in young women with polycystic ovary syndrome [111].

Metformin can reduce the accumulation of AGEs and down-regulate the expression of RAGE in the kidney of diabetic rats [112]. Metformin inhibited AGEs-induced growth of SW-480 cells [113]. Metformin reduced the serum AGEs level in postmenopausal osteoporosis rats, which in turn improves bone metabolism [114].

Dipeptidyl peptidase-4 inhibitor

Sitagliptin reduced the levels of RAGE and angiotensin II type 1 receptors in spontaneously hypertensive rats [115]. Sitagliptin significantly inhibited AGEs-induced viability of mesangial cells and downregulated the level of collagen IV (Col IV) in the supernatant, which may exert renal protective effects by causing autophagy of mesangial cells [116].

In db/db mice, cilizytin can downregulate serum AGEs, inhibit glycosylation *in vivo* and in cells cultured *in vitro*, and alleviate AGE-related diabetic complications [117]. Treatment with vildagliptin can downregulate the levels of AGEs, RAGE and oxidative stress marker 8-OHdG (8-hydroxydeoxyguanosine) in thoracic aorta of diabetic rats, and the above-mentioned increase in levels of substances with MCP-1 (mononuclear) Cell chemokine-1), VCAM-1, and PAI-1 (type I plasminogen activator inhibitor) gene expression were associated with decreased expression [118]. Linagliptin significantly inhibited AGE-induced ROS production and downregulated the expression of RAGE, ICAM-1 and PAI-1 genes in HUVEC cells, and reduced AGEs, RAGE gene expression, and 8-OHdG levels in the kidneys of diabetic rats [119, 120]. Another study found that alogliptin can block the AGEs-RAGE axis in patients with type 2 diabetes, thereby reducing proteinuria [121].

GLP-1 receptor agonist

GLP-1 inhibits AGEs-induced RAGE gene expression, protein arginine methyltransferase-1 (PRMT-1) gene expression and ROS production [122]. In addition, GLP-1 binds to RAGE and inhibits RAGE activation [123]. GLP-1 is also reported to inhibit AGEs-induced apoptosis of EC cells, increase the ratio of anti-apoptosis Bcl-2/pro-apotosis Bax, downregulate cytochrome C levels, and inhibit caspase-3 and caspase-9 activities [124]. Moreover, recent studies have shown that GLP-1 can directly act on GLP-1R of ECs, which may play a role in anti-AGEs by reducing RAGE expression [125]. GLP-1 can reduce the levels of RAGE, ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) in human retinal pigment epithelial cells [126]. Continuous intraperitoneal injection of the GLP-1 analogue exendin-4 inhibits renal RAGE gene expression [122]. In rat mesangial cells RMC, PPARδ and GLP-1 receptor agonists significantly inhibited AGE-induced production of IL-6 and TNF-α, down-regulated AGE-induced RAGE expression, and decreased mesangial cell death [127]. Liraglutide reduced aortic RAGE expression and atherosclerosis in a diabetic ApoE-/- mouse model [128, 129].

Sodium-glucose Cotransporter-2 (SGLT-2) Inhibitors

Treatment with SGLT-2 inhibitors down regulates increased AGE / RAGE signaling in ZDF rats (Zucker diabetic rats), animal models for type 2 diabetes. Serum level of AGE precursor methylglyoxal is reduced, thereby reducing AGE formation and RAGE-dependent signal transduction. In ZDF rats, treatment with engliflozin can prevent oxidative stress, AGE/RAGE signaling, and inflammation development by reducing glucose levels, restoring insulin sensitivity and signal transduction, increasing glucose utilization, and partially

improving endothelial function. In addition, improvement of the redox state contributes to decreased apoptosis of beta cells and increased insulin production [130]. Treatment with high-dose SGLT2 inhibitors in STZ rats reduced both transcription and translation of RAGE gene, AGE-positive protein levels in the aorta, and serum level of AGE precursor methylglyoxal [131]. Furthermore, studies have shown that application of engliflozin for 4 weeks significantly reduced the expression of AGEs, RAGE, 8-OHdG, and F4/80 in kidneys of streptozotocin-induced diabetic rats. This suppression of AGE-RAGE axis partly inhibited the oxidation, inflammation and fibrosis in the kidneys of diabetic rats [132].

Insulin

Studies have confirmed that circulating levels of AGEs are associated with insulin resistance, indicating an association of RAGE gene polymorphisms and insulin resistance [133]. In addition, glycated albumin (a source of AGEs) may be involved in the regulation of insulin signaling. In adipose tissue of insulin-resistant rat models, an increase in methylglyoxal (a precursor of AGEs) impairs insulin signaling by reducing insulin-induced glucose uptake [134]. AGEs are involved in several mechanisms to contribute to insulin resistance. First, due to direct changes in insulin, glucose uptake is reduced; insulin clearance is suppressed; and insulin secretion is further increased. Second, AGE may increase RAGE expression and promote insulin resistance by decreasing the expression of AGER1 and an insulin receptor substrate—SIRT1—whose depletion leads to changes in insulin signaling and induction of inflammation. Third, AGEs affect insulin signaling and induce inflammation by stimulating PKCα and upregulating TNFα [135-141].

Conclusion and Future Expectations:

Diabetes is a common chronic disease that severely affects human health. AGEs promote the occurrence and development of diabetes and its complications through multiple mechanisms that involve many signaling pathways. In recent years, research on AGEs has become one of the hot spots. But research in this area is relatively few and not deep enough. Various hypoglycemic drugs, in addition to their role in hypoglycemia, hindered the production and accumulation of AGEs from many aspects, thereby reducing the adverse effects of AGEs on various tissues. This review may provide rationale for the research and development of specific drugs targeting AGEs in the future.

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