Mechanisms underlying the attenuation of chronic inflammatory diseases by aged garlic extract: Involvement of the activation of AMP-activated protein kinase (Review)

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Abstract. AMP-activated protein kinase (AMPK) is an ubiquitously expressed serine/threonine kinase and an important regulator of energy metabolism. The decreased activity of AMPK induced by low-grade chronic inflammation has been implicated in several diseases, including type 2 diabetes and atherosclerosis. However, the activation of AMPK by natural and synthetic products can ameliorate these diseases through the inhibition of inflammation. For example, aged garlic extract (AGE) has been shown to enhance the phosphorylation of Thr172 of the α-subunit of AMPK in several tissues of disease model animals. In addition, AGE has been reported to suppress the progression of atherosclerotic plaque formation in an animal model of atherosclerosis. Moreover, AGE has been found to decrease the level of plasma glycated albumin and to improve hyperglycemia in an animal model of type 2 diabetes.

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Abbreviations: ABCA1, ATP-binding cassette protein A1; AGE, aged garlic extract; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ApoE-KO mice, apolipoprotein E-knockout mice; ATP, adenosine triphosphate; CaMKKβ, calcium/calmodulin-dependent protein kinase kinase β; CCL2, C-C motif chemokine 2; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; FAS, fatty acid synthase; FFA, free fatty acid; GLUT4, glucose transporter 4; IL, interleukin; IRAK4, interleukin-1 receptor-associated kinase 4; LDLR, low-density lipoprotein receptor; LKB1, liver kinase B1; MCP-1, monocyte chemoattractant protein-1; MyD88, myeloid differentiation primary response 88; PPRs, pattern-recognition receptors; SAC, *S*-allylcysteine; SAMC, *S*-allylmercaptocysteine; SREBP-1c, sterol regulatory element-binding protein-1c; S1PC, *S*-1-propenylcysteine; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; TSOD mice, Tsumura Suzuki Obese Diabetes mice

Key words: aged garlic extract, AMP-activated protein kinase, chronic inflammatory diseases, inflammation, Toll-like receptor signaling pathway

These inhibitory effects of AGE are induced by the suppression of the inflammatory response. In the present review, we discuss the mechanisms through which AGE activates AMPK, as well as the mechanisms through which the activation of AMPK by AGE modulates the inflammatory response in disease models.

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1. Introduction

AMP-activated protein kinase (AMPK) is a master regulator of energy metabolism and forms a heterotrimer consisting of a catalytic α-subunit and two regulatory subunits (β and γ). AMPK is activated via the phosphorylation at Thr172 of the α-subunit by liver kinase B1 (LKB1) through the interaction of adenosine monophosphate (AMP) with the AMPK γ-subunit under nutrient starvation (1-3). The other mechanism of AMPK activation is the calcium-dependent phosphorylation at Thr172 of the α subunit by calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ) (2,3). AMPK contributes to several cellular events, such as protein synthesis, lipid metabolism, glucose metabolism, anti-inflammation, redox regulation and anti-aging (1-3). In addition, AICAR, an AMPK activator, has been shown to suppress several diseases, such as acute and relapsing colitis (4), autoimmune encephalomyelitis (5) and acute lung injury (6). Therefore, the activation of AMPK may ameliorate inflammatory diseases.

Chronic inflammation has been reported to be a key event in the development and progression of several diseases (7-10) and

is triggered by multiple immune cells, including macrophages, T lymphocytes and mast cells (11). Damage-associated molecular patterns (DAMPs), such as proteins, peptides, fatty acids and lipoproteins derived from dead cells are recognized by pattern-recognition receptors (PRRs) expressed on the immune cell surface and induce the secretion of inflammatory molecules, including tumor necrosis factor-α (TNF-α), C-C motif chemokine 2/monocyte chemoattractant protein-1 (CCL2/MCP-1) and C-reactive protein (CRP) (12-14). These molecules damage various tissues and induce chronic inflammatory diseases, such as atherosclerosis and type 2 diabetes.

Aged garlic extract (AGE) is produced by aging garlic (*Allium sativum* L.) in a water-ethanol mixture for >10 months at room temperature and contains several characteristic sulfur compounds, such as *S*-allylcysteine (SAC), *S*-1-propenylcysteine (S1PC) and *S*-allylmercaptocysteine (SAMC) (15,16). AGE has been shown to exert immuno-modulatory effects (17-20), anti-atherosclerotic effects (21-25), anti-hypertensive effects (26-29), antioxidant effects (30-32) and blood flow-improving effects (33) in clinical and animal studies. In addition, recent studies have suggested that AGE and its components can induce the activation of AMPK in several cell types and tissues (19,23,34-37).

In the present review, we summarize the AMPK-activating effects of AGE and its components, and discuss the association between AMPK activation and the ameliorating effects of AGE on several inflammatory diseases.

2. Induction of AMPK phosphorylation by AGE and its constituents

AGE has been shown to trigger the activation of AMPK in the liver, adipose tissues and gastrocnemius muscles in a model of type 2 diabetes (34). In addition, AGE has been shown to induce the phosphorylation of AMPK in the liver in a mouse model of atherosclerosis (23). Accordingly, researchers have demonstrated that AGE enhances AMPK activity in various tissues and animal models. However, the mechanisms underlying AGE-induced AMPK activation are not yet fully understood. Several natural compounds have been shown to activate AMPK. Resveratrol from red grapes, curcumin from the turmeric, and berberine from *Coptis chinensis* trigger the phosphorylation of Thr172 of the AMPK α-subunit by increasing the AMP/ATP ratio (38,39). These compounds decrease ATP production through various mechanisms. Resveratrol and curcumin inhibit the production of ATP by suppressing mitochondrial F1F0-ATPase/ATP synthase, whereas berberine decreases ATP production by blocking respiratory chain complex I (38,39). SAMC has been shown to increase the phosphorylation of LKB1 in the liver (37), whereas SAC promotes the activation of CaMKKβ in human hepatocyte HepG2 cells (35). Therefore, both SAMC and SAC are major constituents of AGE (15,16), and they are involved in the induction of the phosphorylation of AMPK by increasing the AMP/ATP ratio and/or intracellular Ca^{2+} concentration. Consequently, AGE containing these components may induce the phosphorylation of AMPK through these pathways.

3. Inhibition of plaque formation and induction of AMPK activation by AGE

Atherosclerosis is a vascular inflammatory disease, which causes macrophage infiltration, atherosclerotic lesion formation and defective efferocytosis (40). AMPK regulates cell apoptosis, inflammation, cholesterol efflux and efferocytosis via autophagy; however, its function is impaired in atherosclerosis (41-44). AGE has been shown to enhance the phosphorylation of AMPK in the livers of apolipoprotein E knockout (ApoE-KO) mice, a mouse model of atherosclerosis (23). It has previously been suggested that the activation of AMPK improves several processes in atherosclerosis. Li *et al* reported that the administration of the AMPK activator, S17834, reduced lipogenesis and the atherosclerotic plaque region by inhibiting sterol regulatory element-binding protein 1c (SREBP-1c) cleavage and nuclear translocation in low-density lipoprotein receptor (LDLR)-knockout mice (45). In addition, xanthohumol derived from the hop plant lowers plasma lipids and inflammatory chemokine production by activating AMPK in the liver (46). Furthermore, berberine has been shown to suppress plaque formation by inhibiting oxidative stress and vascular inflammation through the activation of the AMPK-nuclear respiratory factor 1 signaling pathway (47). These findings suggest that AMPK inhibits plaque formation by modulating lipid metabolism, as well as by exerting antioxidant and anti-inflammatory effects.

AGE has been shown to suppress lipid deposition in the aorta and to prevent the elevation of serum CRP levels in ApoE-KO mice (22,23). CRP secreted from hepatocytes is a marker of chronic inflammation and systemic inflammation induced by pro-inflammatory cytokines (48,49). PRRs, including TLRs trigger the production of pro-inflammatory cytokines by recognizing not only foreign pathogens, but also cellular components, such as proteins, peptides, fatty acid and lipoprotein, that are derived from dead cells. Accordingly, chronic inflammation is caused by the continuous stimulation of these components (12-14). AGE has been shown to inhibit the TLR signaling pathway by reducing the phosphorylation of interleukin-1 receptor-associated kinase 4 (IRAK4), which is a key regulator of TLR signaling, in ApoE-KO mice (23). The activation of AMPK also contributes to the inhibition of the TLR signaling pathway via several mechanisms (6,50,51). S1PC induces the degradation of myeloid differentiation primary response 88 (MyD88) by activating AMPK-mediated autophagy (19). SAC increases cholesterol efflux by the induction of ATP-binding cassette protein A1 (ABCA1) expression in THP-1 cells (52). In addition, the pharmacological or genetic activation of AMPK increases ABCA1 expression through transcriptional activator liver X receptor α, and promotes cholesterol efflux (53). Therefore, the activation of AMPK is an important event for the amelioration of atherosclerosis and may be a therapeutic target for this disease (Fig. 1).

4. Suppression of plasma glycated albumin level and induction of AMPK activation by AGE

Type 2 diabetes is characterized by hyperglycemia and dyslipidemia associated with insulin resistance (54-56). In addition, inflammation contributes to the disruption of insulin
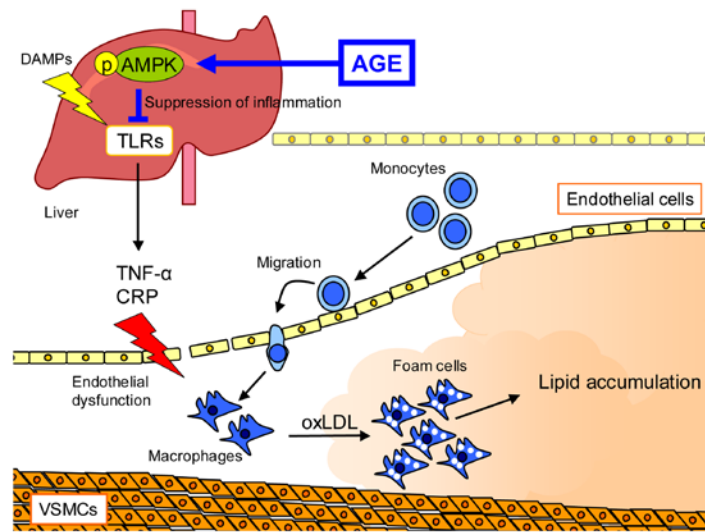
Figure 1. Effect of AGE on plaque formation. AGE inhibits the TLR signaling pathway by activating AMPK and consequently suppresses the production of TNF-α and CRP in the liver. The reduction of pro-inflammatory cytokines decreases the infiltration of immune cells into the artery wall, which in turn suppresses plaque formation. AGE, aged garlic extract; AMPK, AMP-activated protein kinase; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; oxLDL, oxidized low-density lipoprotein; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor-α; VSMCs, vascular smooth muscle cells.
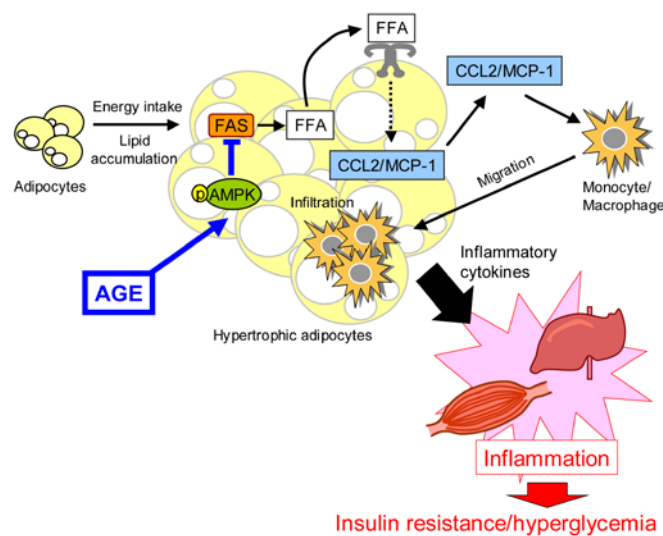

Figure 2. Effect of AGE on hyperglycemia. FFA induces the production of CCL2/MCP-1 via TLR. CCL2/MCP-1 recruits monocytes/macrophages to several tissues. AGE inhibits the production of FFA via the suppression of FAS by AMPK activation, and improves insulin resistance and hyperglycemia by reducing TLR-mediated inflammation in various tissues. AGE, aged garlic extract; AMPK, AMP-activated protein kinase; CCL2, C-C motif chemokine 2; FAS, fatty acid synthase; FFA, free fatty acid; MCP-1, monocyte chemotactic protein-1; TLR, Toll-like receptor.

signaling and the destruction of adipose homeostasis (57,58). Furthermore, monocytes and macrophages infiltrate into adipose tissues and produce inflammatory cytokines, such as TNF-α, interleukin (IL)-1β and IL-18 (59-62). AMPK is a key molecule for the prevention and/or amelioration of type 2 diabetes and insulin resistance (39,63). Metformin has been used for the therapy of diabetes through the activation of AMPK by inhibiting mitochondrial complex I of the respiratory chain (64,65). Treatment with metformin has been shown to reduce blood glucose levels, inhibit hepatic gluconeogenesis and improve insulin sensitivity (66,67). In addition, resveratrol has been shown to increase glucose uptake and mitochondrial biogenesis via the activation of AMPK (68-70). Furthermore, berberine has been shown to improve glucose intolerance, reduce body weight, increase the expression of the insulin receptor and LDLR, lower total and LDL cholesterol levels, and reduce triglyceride levels (71,72). Therefore, the activation of AMPK helps ameliorate type 2 diabetes.

AGE has been shown to increase the phosphorylation of AMPK in Tsumura Suzuki Obese Diabetes (TSOD) mice, a mouse model of type 2 diabetes (34). In addition, AGE suppresses the plasma glycated albumin level and improves glucose intolerance in TSOD mice. The level of glycated albumin is proportional to the amount of glucose in plasma as glucose nonenzymatically reacts with the amino group of proteins in plasma (73,74). Blood glucose is taken up via glucose transporter 4 (GLUT4) in skeletal muscle and adipose tissue (75,76). However, the production of GLUT4 is impaired through the inhibition of insulin signaling by pro-inflammatory cytokines in diabetes (75,76). Accordingly, inflammation induces insulin resistance and hyperglycemia.

Previous studies have suggested that AGE suppresses inflammation in clinical trials and animal studies (23,28,29,34). AGE has been shown to inhibit the expression of *Ccl2*/*Mcp-1* mRNA in adipose tissue and liver of TSOD mice (34). PRRs, including TLRs trigger the production of inflammatory cytokines and chemokines by recognizing antigens, whereas PRRs have been reported to recognize not only foreign pathogens, but also cellular components (12-14). Saturated free fatty acids (FFA) from adipose tissues have been reported to activate TLR4 and trigger the production of inflammatory cytokines in immune cells (57,58). The level of FFA is regulated by fatty acid synthase (FAS), and AMPK negatively regulates the expression of *Fas* mRNA by modulating SREBP-1c (45,77). AGE has inhibited the expression of *Fas* mRNA via the activation of AMPK (34). Therefore, AGE can ameliorate hyperglycemia and insulin resistance by anti-inflammatory effect via the activation of AMPK in TSOD mice (Fig. 2).

5. Conclusions

AGE ameliorates atherosclerosis and type 2 diabetes through the suppression of inflammation. In addition, AGE and its components induce the activation of AMPK in several tissues and cells. AMPK plays an important role in regulating the inflammatory response through the inhibition of the TLR signaling pathway. Thus, AMPK is considered as a possible therapeutic target for inflammatory-related diseases. Therefore, AGE, which has a promoting effect on AMPK activation, may prove to be a useful preparation for the prevention and improvement of various diseases associated with chronic inflammation.

Availability of data and materials

Not applicable.

Authors' contributions

SM, JIS and NM conceived this review. SM, KK and JIS analyzed the relevant literature. SM wrote the manuscript and constructed the figures. JIS, KK and NM critically revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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