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The effect of ampk signaling in type 2 diabetes a literature review

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ABSTRACT

Diabetes is a metabolic syndrome characterized by inadequate blood glucose control and associated with reduced quality of life and various complications that significantly shorten life expectancy. Type 2 diabetes is caused by insulin resistance, in which insulin is well secreted but cells do not respond properly. Increasing evidence reveals the role of molecular pathways in the development of DM and its associated complications. The references of this literature review were collected from PubMed. Studies have attempted to identify signaling networks and therapeutic targeting in DM therapy. As the disease progresses, DM is followed by evidence of the existence of a molecular pathway in the form of AMPK signaling which can coordinate cell metabolism according to specific energy needs. AMPK is a master regulator of metabolism that functions to restore energy balance during metabolic stress at both a cellular and physiological level. Inducing AMPK signaling can provide blood glucose in DM which is important to improve hyperglycemia. The purpose of this literature review was to determine the effect of AMPK signaling on type 2 DM and gives an insight about agents that can enhances AMPK signaling to prevent the further impact of DM.

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INTRODUCTION

Diabetes is commonly divided into two types, type 1 diabetes and type 2 diabetes. Type 2 diabetes is commonly known as diabetes mellitus (type 2 DM). There is a big difference between type 1 diabetes and type 2 diabetes. Type 1 diabetes is thought to be an autoimmune disease that destroys pancreatic β-cells and causes insulin secretion failure. Meanwhile, in type 2 DM, insulin levels are high but cells are resistant to insulin. Other types of diabetes are gestational diabetes and other rare diabetes including monogenic diabetes and diabetes associated with cystic fibrosis (Ashrafizadeh et al., 2019; Yaribeygi et al., 2020).

Type 2 diabetes mellitus has become a public health burden associated with very large treatment costs, and early mortality. Unhealthy dietary habits and lifestyles are the biggest factors causing the increasing cases of type 2 DM throughout the world, especially in developing, low- and middle-income countries (Tinajero & Malik, 2021).

Insulin resistance in target tissues is the main characteristic and factor causing type 2 DM. The liver is an important organ in DM which plays a central role in maintaining glucose homeostasis by balancing gluconeogenesis and glycogen synthesis. Insulin resistance can lead to increased gluconeogenesis and decreased glycogen synthesis in the liver, causing hyperglycemia (Yan et al., 2018). Increasing studies reveals the role of molecular pathways in the development of type 2 DM and its associated complications. Studies have attempted to identify signaling and therapeutic targeting networks in DM therapy (Entezari et al., 2022). AMP-activated protein kinase (AMPK) is a serine/threonine kinase that functions as a cellular energy-sensing protein that is activated by reducing the availability of glucose or adenosine triphosphate (ATP) in cells (Entezari et al., 2022; X.-D. Wang et al., 2021).

In the case of diabetes, glucose uptake triggers energy-forming processes in cells, so that when AMPK is activated, glucose uptake is increased and energy-producing pathways in target cells are activated (Chung et al., 2021). Further investigations revealed a role for AMPK signaling in improving insulin sensitivity and reducing inflammation for the treatment of diabetic patients. Clinical studies in diabetic patients have demonstrated a role for AMPK signaling in ameliorating diabetic complications such as brain disorders. AMPK can also improve neuropathy, nephropathy, liver disease and reproductive changes that occur during DM (Entezari et al., 2022).

This article describes how AMPK signaling can modulate glucose uptake, metabolism and inflammation which play an important role in the treatment of DM. It also can give an insight to find a therapeutic agent that can increase AMPK signaling to prevent the further impact of DM.

RESEARCH METHOD

The method used in this literature review was systematically carried out according to the keywords "type 2 diabetes" and "AMPK" and "insulin resistance" through the PUBMED search engine with inclusion criteria including articles in the last 5 years from 2018-2023, full text access, original articles or article reviews in English. The procedures carried out in this study were: (1) Search for articles using the keywords and criteria above, (2) Eliminate duplicate articles, (3) Screen the substance of the article by looking at the title and abstract, (4) Perform extraction data with the suitability of the title of the article with the research objective in order to obtain relevant articles (5) Perform analysis and synthesis of the substance of the article. The total number of final literatures used to review AMPK signaling that have the potential to improve insulin resistance in type 2 diabetes is 10 articles.

Table 1. Summary of research articles about AMPK signaling to improve type 2 diabetes

Researcher and year of publication	Types of research	Research conclusion
Morrow et al., 2020	Experimental using mice model	Nobiletin increases AMPK and Acetyl-CoA carboxylase (ACC) phosphorylation in mouse hepatocytes. In rats fed a high-fat diet, nobiletin is effective in preventing obesity, hepatic steatosis, dyslipidemia, and insulin resistance.
Karunakaran et al., 2021	Experimental using mice model	Pioglitazone activates AMPK independent of PPARγ. Pioglitazone selectively protects beta cells against high glucose toxicity through AMPK activation, regulates TRAP1/HSP75-Glutaminase 1 (GLS1) interactions, leading to an increase in the GSH/GSSG ratio as well as inhibiting

		mTORC1-mediated maladaptive ER stress in beta cells.
J. Li et al., 2020	Experimental using HepG2 cells	Sesquiterpene glycosides (SG) can stimulate AMPK signaling to enhance glucose metabolism and uptake in insulin-resistant HepG2 cells.
Rao et al., 2021	Experimental using mice model	AMPK was able to induce phosphorylation of Serine 168 residue from TBC1D17 to increase Rab5 expression. Then, Rab5 mediates GLUT4 translocation in myoblasts and skeletal muscles to increase glucose uptake and reduce serum glucose levels which are important targets of DM treatment.
Qiu et al., 2020	Experimental using mice model	Amyloid beta (Aβ) induces inflammation through upregulation of NLRP3. Administration of lychee seed polyphenols induces the AMPK/autophagy axis to improve inflammation.
Xu et al., 2021	Experimental using human periodontal ligament tissues	Simvastatin has anti-inflammatory activity through inducing AMPK signaling, upregulating MAPK and inducing a significant decrease in NF-κB expression. NF-κB is one of the most well-known AMPK signaling targets in the inflammatory process.
S. Wang et al., 2020	Experimental using mice model	Hesperetin has anti-inflammatory activity through the regulation of AMPK. By stimulating the AMPK/CREB axis, hesperetin induces SIRT1 expression which prevents RelA/p65 acetylation in suppressing NF-κB signaling and reducing inflammation.
X.-D. Wang et al., 2021	Experimental using mice model	Metformin induces AMPK signaling which then induces SIRT1 expression resulting in a significant reduction in serum IL-6 and TNF-α levels.
Shamshoum et al., 2021	Experimental using mice model	Rosemary extract has been shown to play a role in increasing glucose uptake by muscle cells, even though these cells are insulin resistant. The mechanism is by inducing AMPK phosphorylation which then increases GLUT4 levels to stimulate glucose uptake by muscle cells.
Lee et al., 2020	Experimental using mice model	Ganoderma lucidum extract induces AMPK signal phosphorylation to increase the expression levels of GLUT1, GLUT4, protein kinase-B (Akt), IR substrate 1 (IRS1), insulin receptor (IR) and acetyl-CoA carboxylase (ACC).

RESULTS AND DISCUSSIONS

The islets of Langerhans, liver and muscles play an important role in glucose homeostasis in the body. Glucose is produced by the liver and low consumption of glucose by muscle and adipose tissue contributes to hyperglycaemia. These factors together can cause DM. Up to 90% of the glucose produced in the body is produced in the liver tissue. Thus, dysregulation of glucose metabolism in the liver can cause type 2 DM (Entezari et al., 2022).

It is generally recognized that AMPK is a key player in regulating energy metabolism. Liver AMPK controls glucose homeostasis through inhibition of gluconeogenesis. AMPK also regulates liver glycogen metabolism which can promote glycogen synthesis. Thus, dysregulation of

AMPK contributes to the onset and development of type 2 DM. Previous studies have shown that activation of AMPK can activate the hepatic Phosphatidylinositol 3-kinase (PI3K)/AKT signaling pathway and increase hepatic insulin sensitivity. Therefore, AMPK activation in the liver is expected to be useful in improving type 2 DM. Recent studies have shown that AMPK activation is very important for suppressing ROS production and oxidative stress (Yan et al., 2018).

PI3K/AKT pathway plays an important role in the insulin signaling pathway, which is considered a key regulator of gluconeogenesis and glycogen synthesis. Hepatic insulin resistance is often associated with inhibition of the PI3K/AKT pathway. Oxidative stress is thought to increase the onset and development of liver disease in diabetic patients. Increased production of reactive oxygen species (ROS) has been shown to be associated with hepatic insulin resistance. In addition, disruption of the PI3K/AKT pathway in diabetes is one of the main mechanisms of insulin resistance caused by increased ROS levels. The production of ROS derived from the enzyme NADPH oxidase is an important factor in oxidative stress in diabetes. And among the NADPH oxidase enzymes, NADPH oxidase type 4 (NOX4) has been reported to be overexpressed in streptozotocin (STZ)-induced rat liver. In addition, NOX4 inhibitors can increase insulin sensitivity, which has implications for the potential effect of NOX4 inhibition in preventing hepatic insulin resistance (Yan et al., 2018). Further investigations revealed a role for AMPK signaling in improving insulin sensitivity for the treatment of diabetic patients. Clinical studies in diabetic patients have demonstrated a role for AMPK signaling in ameliorating diabetic complications such as brain disorders. Furthermore, AMPK can improve neuropathy, nephropathy, liver disease and reproductive changes that occur during DM (Entezari et al., 2022).

AMPK is a serine/threonine kinase that functions as a cellular energy-sensing protein that is activated to reduce the availability of glucose or adenosine triphosphate (ATP) in cells (Entezari et al., 2022). AMPK restores energy balance by inhibiting anabolic processes that consume ATP and encouraging catabolic processes that produce ATP (Entezari et al., 2022; X.-D. Wang et al., 2021). AMPK is a trimeric complex consisting of a catalytic subunit (α subunit) and two regulatory subunits (β and γ subunits). In mammals, the α subunit is encoded by two isoforms, and the β and γ subunits are encoded by two and three isoforms, respectively (Chung et al., 2021; Garcia & Shaw, 2017). The expression level of this AMPK isoform varies across tissues, leading to diverse subunit combinations in different cell types. Although the different complexes are largely functionally repeatable, they can exhibit somewhat different biochemical properties. AMPKα1, AMPKβ1, and AMPKγ1 are expressed in various tissues, but the other isoforms show a more restricted expression pattern. AMPK α2 is abundantly expressed in skeletal and cardiac muscle, where it is the predominant α subunit, it is also expressed in the liver and to a lesser extent in other tissues. Similarly, AMPKβ2 is the predominant β subunit in skeletal and cardiac muscle, but is found at lower levels in many other tissues. AMPKγ2 and AMPKγ3 expression appears to be limited to skeletal and cardiac muscle (Garcia & Shaw, 2017).

AMPK is activated under conditions of increased AMP: ATP ratio, such as exercise and metabolic stress. Studies of the effects of exercise, hypoxia, and ischemia have shown that when the AMP:ATP ratio increases, AMPK is activated by AMPK kinases and then binds to AMP to induce a conformational change that blocks the ATP consumption pathway and activates the ATP generation pathway (Chung et al., 2021; Garcia & Shaw, 2017). Once activated, AMPK suppresses lipid and sterol synthesis by inhibiting acetyl-CoA carboxylase activity, causing reduced glycogen storage by glycogen synthase (Chung et al., 2021).

AMPK signaling activation occurs under stress conditions, when energy is low. The α subunit has catalytic activity and its phosphorylation of threonine 172 (T172) induces activation of AMPK signaling. Calcium/calmodulin-dependent protein kinase kinase (CaMKK) β, transforming growth factor-β-activated kinase 1 (TAK1), and liver kinase B1 (LKB1) are thought to be upstream mediators of AMPK signaling and induce T172 phosphorylation in AMPK signaling stimulation capable of triggering signaling AMPK through increasing AMP levels and decreasing ATP levels.

The AMPK signaling process appears to be of interest, as increased levels of AMP and ADP under metabolic stress result in activation of AMPK by binding to the γ subunit and inducing T172 phosphorylation. Of note, AMPK can be activated independently of AMP levels, so that calcium and its accumulation in cells can induce T172 phosphorylation, leading to CaMKKβ-dependent upregulation of AMPK (Entezari et al., 2022).

In addition, AMPK can regulate glucose transporter 4 (GLUT4) and free fatty acids to improve insulin resistance (Chen et al., 2021). AMPK phosphorylates proteins involved in the translocation of glucose transporters and promotes the translocation of GLUT4 to the cell membrane, thereby increasing glucose uptake. AMPK also activates lipase and promotes fatty acid release, thus increasing β-oxidation. β-oxidation and blood glucose uptake are representative pathways responsible for energy generation. In the case of diabetes, glucose uptake eventually triggers energy-generating processes in cells, so that when AMPK is activated, glucose uptake is enhanced and pathways that create energy in target cells are also activated (Bai et al., 2018).

Other studies have also reported that AMPK is able to induce phosphorylation of Serine 168 residue from TBC1D17 to increase Rab5 expression. Rab5 is a small GTPase that functions as an essential regulator for endosome fusion, transport, and biogenesis. Rab5 is also important for modulating metabolic events, including autophagy, and for the sorting of GLUT4-containing vesicles. Then, Rab5 regulates GLUT4 translocation in myoblasts and skeletal muscle to enhance glucose uptake and decrease serum glucose levels. This plays an important role in the treatment of DM (Entezari et al., 2022; Rao et al., 2021).

The identification of AMPK has helped explain how AMPK improves energy homeostasis in cells. The therapeutic potential of AMPK is widely recognized for the treatment of metabolic diseases such as diabetes, obesity, inflammation, and even cancer. Moreover, recently studies discovered crystal structure of AMPK has elucidated how the nucleotide activates AMPK down to the site bound by the small molecule activator, thereby providing avenues for better therapeutic management (Garcia & Shaw, 2017). AMPK plays an important role in energy metabolism. Many studies found this role can make a potential target for the treatment of type 2 DM. Hepatic gluconeogenesis is increased in type 2 DM while AMPK controls hepatic glucose homeostasis primarily through inhibition of gluconeogenesis. In HFD/STZ mice, hepatic AMPK phosphorylation at T172 was decreased while phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6pase) increased (Yan et al., 2018).

Mice with DM show lipid accumulation and insulin resistance. Administration of ligustilide and catalpol increased AMPK phosphorylation to mediate insulin sensitivity in rats with DM(Guo et al., 2021; Yan et al., 2018). Therefore, AMPK signal activation can be considered as a protective mechanism in the treatment of DM.

AMPK turns out to be involved in the mechanism of action of metformin, and thiazolidinediones or pioglitazone which play a role in clinical anti-diabetic responses, where these two drugs have become the main treatment options for type 2 DM to date (Stumvoll et al., 2005). In addition to drugs that have been clinically proven, there are also several compounds from various studies that are known to activate AMPK. Compounds derived from herbal plants, namely catalpol also affect AMPK signaling in improving insulin resistance in type 2 DM. Giving catalpol increases AMPK expression to reduce NOX4 and oxidative stress. NOX4 down-regulation leads to stimulation of the PI3K/AKT axis which inhibits insulin resistance (Yan et al., 2018).

Another compound discovered in herbal research, Dieckol, a phlorotannin isolated from Ecuronia cava, significantly reduced blood sugar, serum insulin, and body weight in a rat model of type 2 diabetes. This phenomenon was observed to increase the activities of the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-px) in liver tissue and levels of AMPK and Akt phosphorylation in muscle tissue. This study shows that Dieckol can be used as a diabetes drug due to its role in AMPK activation (Kang et al., 2013).

Hsu et al. evaluated the anti-diabetic properties of Pterosin A, a natural product isolated from several fern plants. Administration of pterosin A for 4 weeks dramatically improved hyperglycaemia and glucose intolerance in a mouse model with no observed side effects. This phenomenon is accompanied by a significant increase in AMPK and Akt phosphorylation in muscle. In addition, Pterosin A increases glucose uptake and AMPK phosphorylation in cultured muscle cells. These results indicate that the anti-diabetic effect of pterosin A is achieved through AMPK activation (Hsu et al., 2013).

Crocin is another agent that can regulate insulin sensitivity in type 2 DM. Administration of crocin increases AMPK expression to suppress the CDK5/PARPγ axis which will increase insulin sensitivity (Fang & Gu, 2020). Naringenin prevents insulin resistance, enhances glucose uptake and reduces inflammation and oxidative stress through activation of AMPK signals (S. Li et al., 2019). Overall, studies show that insulin resistance in DM significantly increases serum glucose levels and to correct this condition, activation of AMPK signaling is recommended.

AMPK signaling reduces NF-κB expression to prevent inflammation. Furthermore, AMPK regulates the PI3K/AKT axis to influence inflammation and reduce apoptosis in the kidney to prevent nephropathy in type 2 DM (Su et al., 2021; Zhao et al., 2021). Therefore, understanding these interactions can provide new insights in improving insulin resistance in type 2 DM.

CONCLUSION

Based on the discussion from this literature review, various variations of AMPK signaling have been obtained with regard to its regulatory function related to its activity in the development of type 2 DM. AMPK is a key regulator of metabolism whose function is very relevant not only for physiological, but also for pathological conditions. Recent research into the regulatory mechanisms of AMPK signaling continues to increase as understanding of AMPK activity and of how cells manage their energy requirements. Many studies have identified compounds that can activate AMPK, especially in the role of AMPK in improving insulin resistance and hyperglycaemia in type 2 DM. Future researchers are expected to be able to investigate more about various therapeutic agents that can enhance AMPK signaling up to the clinical trial stage.

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