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REVIEW ARTICLE

New mechanisms of metformin action: Focusing on mitochondria and the gut

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ABSTRACT

The most well-known mechanism of metformin action, one of the most commonly prescribed antidiabetic drugs, is adenosine monophosphate-activated protein kinase activation; however, recent investigations have shown that adenosine monophosphate-activated protein kinase-independent pathways can explain some of metformin's beneficial metabolic effects as well as undesirable side-effects. Such novel pathways include induction of mitochondrial stress, inhibition of mitochondrial shuttles, alteration of intestinal microbiota, suppression of glucagon signaling, activation of autophagy, attenuation of inflammasome activation, induction of incretin receptors and reduction of terminal endoplasmic reticulum stress. Together, these studies have broadened our understanding of the mechanisms of antidiabetic agents as well as the pathogenic mechanism of diabetes itself. The results of such investigations might help to identify new target molecules and pathways for treatment of diabetes and metabolic syndrome, and could also have broad implications in diseases other than diabetes. Accordingly, new antidiabetic drugs with better efficacy and fewer adverse effects will likely result from these studies.

INTRODUCTION

Metformin (1, 1-dimethylbiguanide hydrochloride) has been widely used to treat type 2 diabetes since the 1950s[1], and is currently the drug of choice recommended by the American Diabetes Association and the European Association for the Study of Diabetes[2]. Although the detailed mechanisms underlying the metabolic effects of metformin have not been completely elucidated, the most commonly accepted mechanism is activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK; Figure 1)[3,4]. AMPK is a highly conserved serine/threonine protein kinase composed of a catalytic α subunit and two regulatory β and γ subunits, and is activated by an increased AMP : adenosine triphosphate (ATP) ratio in metabolic stress conditions, such as hypoxia or glucose deprivation[5]. Thus, AMPK can act as a sensor of cellular energy levels. However, recent studies have also suggested AMPK-independent pathways as important mechanisms of action of metformin[6]. For example, it has been reported that metformin-induced suppression of glucose production is more pronounced in *AMPKα1α2*-null hepatocytes compared with control cells[7].

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In the present review, we summarize recent findings on the new mechanisms of metformin, focusing especially on AMPK-independent mechanisms, such as alterations of mitochondria and the gut. We also discuss the recent 'hot' issue of intestinal microbiota as it relates to metformin activity.

MITOCHONDRIAL STRESS AND METFORMIN

Metformin and phenformin, another biguanide drug, both have been reported to inhibit the activity of mitochondrial complex I[8]. The inhibition of mitochondrial complex activity by metformin might be a mechanism of metformin-induced AMPK activation[9], as intracellular ATP levels are decreased by the inhibition of mitochondrial complex activity and AMP levels are increased by the action of adenylate kinase converting two molecules of adenosine diphosphate (ADP) to ATP and AMP (Figure 1). AMP molecules can then bind to the γ subunit of AMPK and activate AMPK activity directly or by inhibiting dephosphorylation of AMPK phosphorylated by liver kinase B1 (LKB1) or calcium/calmodulin-dependent protein kinase kinase-β (CAMKKβ)[10].

Mitochondrial stress can affect tissue metabolism independent of AMPK. Specifically, mitochondrial stress has been shown to initiate an integrated stress response (ISR)[11] through activating transcription factor 4 (ATF4) to induce fibroblast

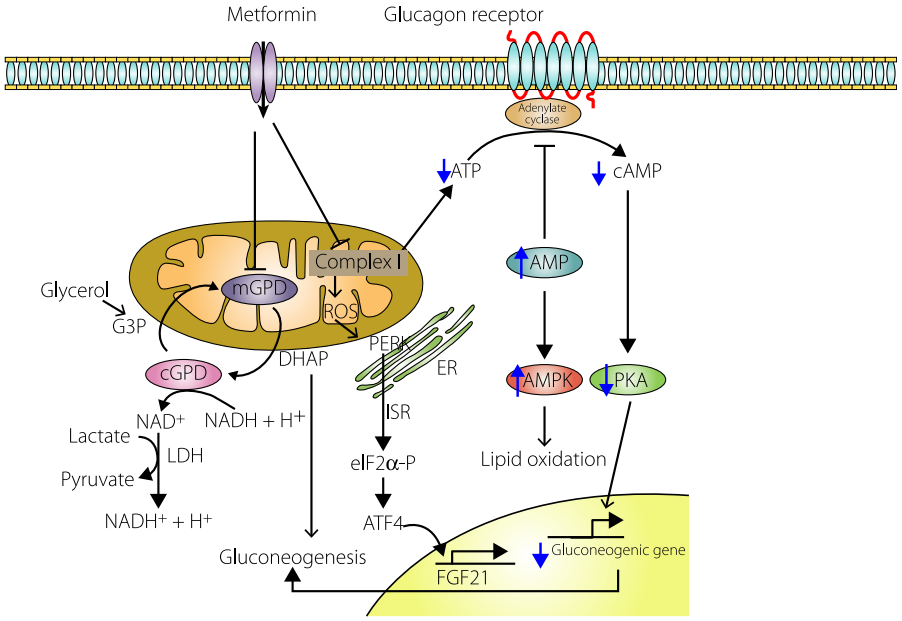

Figure 1 | Metformin inhibits mitochondrial complex I, mitochondrial shuttle and glucagon signaling. Metformin diminishes mitochondrial complex I activity. Decreased adenosine triphosphate (ATP) and increased adenosine monophosphate (AMP) content by metformin as a result of decreased mitochondrial complex activity contributes to adenosine monophosphate-activated protein kinase (AMPK) activation. Mitochondrial reactive oxygen species (ROS) production as a result of mitochondrial complex I inhibition leads to integrated stress response (ISR) through activation of double-stranded ribonucleic acid-activated protein kinase-like endoplasmic reticulum (ER) kinase at the mitochondria-associated membrane site between mitochondria and ER[94], followed by eukaryotic translation factor 2α (eIF2α) phosphorylation and activating transcription factor 4 (ATF4) induction. ATF4 induces fibroblast growth factor 21 (FGF21). Metformin inhibits mitochondrial glycerophosphate dehydrogenase (mGPD), but not cytosolic glycerophosphate dehydrogenase (cGPD). Inhibition of mGPD impedes conversion of glycerol-3-phosphate (G3P) to dihydroxyacetone phosphate (DHAP), and blocks gluconeogenesis from glycerol that needs to be converted to G3P and then to DHAP for gluconeogenesis. Decreased cytosolic oxidized form of nicotinamide adenine dinucleotide (NAD^+) leads to the accumulation of lactate, which is frequently observed during metformin treatment. Increased AMP after metformin treatment inhibits adenylate cyclase and reduces 3′-5′-cyclic adenosine monophosphate (cAMP) content, which attenuates glucagon-induced gluconeogenic gene expression mediated by protein kinase A (PKA).

growth factor 21 (FGF21), which in turn improves the metabolic profile associated with obesity or lipid injury as a 'mitokine'[12]. A recent investigation examined whether metformin could induce a similar ISR by inducing mitochondrial stress. As hypothesized, metformin was able to induce the expression of FGF21 through the double-stranded ribonucleic acid-activated protein kinase-like endoplasmic reticulum (ER) kinase (PERK)-eukaryotic initiation factor 2α–ATF4 axis in hepatocytes, which was attributed to the inhibition of mitochondrial complex I activity (Figure 1)[13]. Metformin-induced FGF21 expression was still observed in AMPKα1-dominant negative transfectants or *AMPKα1α2*-null mouse embryonic fibroblast cells, suggesting an AMPK-independent ISR leading to FGF21 induction. Treatment with (2-(2,2,6,6-tetramethylpiperidin-1-oxyl-4-ylamino)-2-oxoethyl) triphenylphosphonium chloride monohydrate (MitoTempo), a mitochondrial reactive oxygen species (ROS)-specific quencher not only reversed mitochondrial ROS production by metformin, but also attenuated FGF21 induction after metformin treatment, supporting the role of mitochondrial stress or mitochondrial ROS in the induction of FGF21. Serum levels of FGF21 were increased by *in vivo* administration of metformin in mice, suggesting the contribution of FGF2 in the metabolic effect of metformin administration *in vivo*. Finally, serum FGF21 levels were increased in patients with type 2 diabetes after metformin therapy for 6 months, supporting the possible role of FGF21 induction in metabolic improvement by metformin administration to human patients with diabetes[13].

Mitochondrial stress induced by metformin or other measures might have broad implications in addition to FGF21 induction. Indeed, several recent investigations have examined the relationship between mitochondrial stress response, metabolism and longevity in the *Caenorhabditis elegans* model[14,15]. Specifically, these studies showed that imbalances between mitochondrial and nuclear protein synthesis by genetic manipulation, nicotinamide adenine dinucleotide (NAD^+) supplementation or sir-2.1 expression activates the mitochondrial unfolded protein response and increases longevity. Such a relationship between mitochondrial stress and longevity might also be involved in the increased life span of experimental mice

following metformin administration[16], although it is still unclear whether the relationship between mitochondrial stress and longevity observed in *C. elegans* also extends to the vertebral system[17].

MITOCHONDRIAL SHUTTLE AND METFORMIN

One of the main metabolic features of metformin is its ability to reduce hepatic glucose production[18]. A recent study suggested that inhibition of mitochondrial glycerophosphate dehydrogenase (mGPD), a critical enzyme in the glycerophosphate shuttle, could be the primary mechanism of metformin-induced inhibition of gluconeogenesis (Figure 1)[19]. Specifically, the glycerophosphate shuttle together with the malate-aspartate shuttle allows a cytoplasmic reduced form of nicotinamide adenine dinucleotide (NADH) generated by glycolysis to enter mitochondria for production of ATP and regeneration of cytoplasmic NAD^+. The inhibition of the mitochondrial shuttle leads to the increased cytosolic redox state and decreased mitochondrial redox state. Thus, an increased cytosolic redox state could impair conversion of lactate to pyruvate by lactate dehydrogenase, leading to decreased gluconeogenesis and accumulation of lactate. The latter effect is frequently observed in animals and humans treated with metformin, and could be the cause of lactic acidosis, a well-known side-effect of metformin. Gluconeogenesis from glycerol can also be impaired, as conversion from glycerol-3-phosphate to dihydroxyacetone phosphate by mGPD in the mitochondrial matrix, a necessary step for gluconeogenesis from glycerol, is inhibited by metformin (Figure 1)[19]. This finding could represent a novel mechanism of metformin that can explain its ability to inhibit gluconeogenesis and lactate overproduction, although it is not clear whether the inhibition of the glycerophosphate shuttle, which represents only a small portion of ATP production, can lead to significant changes in the cellular redox state[20]. These results might also potentially contribute to the identification of new molecular targets for development of a novel class of antidiabetic agents.

GLUCAGON AND METFORMIN

Another novel mechanism explaining decreased gluconeogenesis by metformin was recently proposed. Metformin was shown to inhibit glucagon signal transduction by decreasing 3′-5′-cyclic adenosine monophosphate (cAMP) production in hepatocytes[21]. Decreased cAMP content leads to decreased activity of both cAMP-dependent protein kinase A, an important signal transducer of glucagon action and glucagon-induced gluconeogenesis (Figure 1). Decreased cAMP was attributed to the direct inhibition of adenylate cyclase by increased intracellular AMP content after metformin treatment rather than AMPK activation. Increased AMP content could be a result of the aforementioned inhibition of mitochondrial complex I activity and reduced hepatic energy charge by metformin treatment (Figure 1). Together, these results suggest a novel mechanism of metformin action related to glucagon signaling, and a potential role of adenylate cyclase as a new therapeutic target for the treatment of type 2 diabetes.

INTESTINAL MICROBIOTA AND METFORMIN

Accumulating data suggest that gut microbiota play an important role in the control of energy balance by extracting energy from ingested food[22]. Intestinal microbiota also play a crucial role in the maturation of gut immunity and maintenance of immune homeostasis[23]. The human gut microbiota comprises 10–100 trillion microorganisms of more than 1,000 species[24,25]. Furthermore, recent studies have shown that changes in gut microbiota could be important in the pathogenesis of the obese and diabetic phenotypes. For example, germ-free mice are protected against diet-induced obesity, which is accompanied by increased levels of AMPK activity in the liver or muscle tissue and derepression of fasting-induced adipose factor (Fiaf)[22,26]. As Fiaf is an inhibitor of lipoprotein lipase, Fiaf could inhibit the storage of lipid in adipose tissue in germ-free mice. In addition, obesity and high-fat diets are associated with a significant increase in the relative abundance of the Firmicutes phylum and decrease in the Bacteroidetes phylum[27,28]. Furthermore, transplantation of gut microbiota from obese mice to germ-free mice leads to a significant increase in body fat content and insulin resistance compared with those from lean mice[29].

Previous studies have shown that the intestines play a significant role in the glucose-lowering effect of metformin by facilitating uptake and utilization of glucose[30,31] (Figure 2). The concentration of metformin reaches a higher level in the intestinal mucosa compared with other tissues[30,31], which might be related to the adverse effects of metformin on the gastrointestinal tract. Based on the significant potential impact of metformin on the intestine, whether metformin affects the gut microbiota was investigated, and also if the metabolic effects of metformin are related to changes in the gut microbiota. When microbiota abundance was studied using 16S ribosomal ribonucleic acid pyrosequencing, marked changes in microbiota composition by metformin treatment were observed, particularly in high-fat diet (HFD)-fed conditions, suggesting a possible interaction between HFD, metformin and intestinal microbiota. Nearest shrunken centroid analysis showed significant changes of 29 genera of six phyla, with *Akkermansia* belonging to the *Verrucomicrobia* phylum representing one of the genera showing the most conspicuous changes[32]. *Akkermansia muciniphila* is a recently identified Gram-negative anaerobic bacteria that can enhance mucin production by degrading mucin[33]. When cultured *Akkermansia* was administered instead of metformin, the metabolic profile of HFD-fed mice was improved, similar to the metabolic changes induced by metformin. The numbers of mucin-producing goblet cells were also increased similarly by metformin or *Akkermansia* administration (Figure 2). These data are supported by another study showing that metformin treatment induces intestinal mucin 2 and mucin 5 expression, and that *Akkermansia* is enriched by metformin in an *in vitro* culture system[34]. Improvement of the metabolic profile by met-

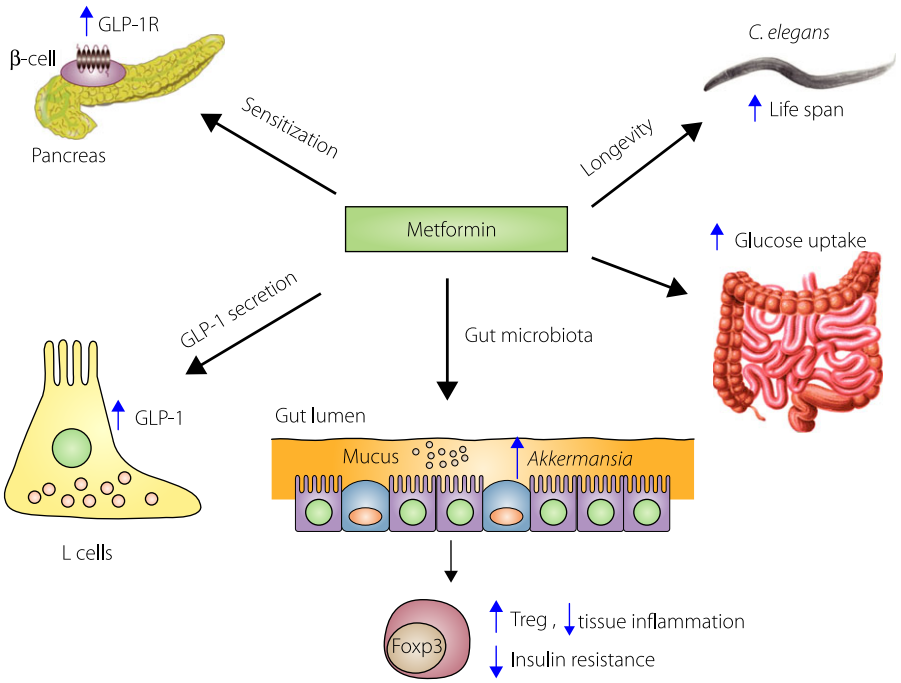

Figure 2 | Effects of metformin on the gut. Metformin induces glucagon-like peptide 1 (GLP-1) release from intestinal L cells, and also GLP-1 receptor expression on pancreatic β-cells. Metformin increases the abundance of *Akkermansia*, a mucus-degrading Gram-negative bacteria, in the gut, which is associated with restoration of reduced regulatory T (Treg) cells and amelioration of low-grade tissue inflammation in the adipose tissue of obese animals. Increased life span of *Caenorhabditis elegans* by metformin has also been attributed to changes in intestinal microbiota. The intestine is a major organ responsible for uptake and utilization of glucose after metformin administration.

formin or *Akkermansia* administration was also associated with the reversal of diminished regulatory T cell number and downregulation of elevated interleukin (*IL*)*-1*β and *IL-6* messenger ribonucleic acid expression in visceral adipose tissue of mice fed a HFD (Figure 2). These results suggest that metformin or *Akkermansia* improves the metabolic profile of diet-induced obesity by ameliorating low-grade tissue inflammation, a cause of insulin resistance associated with obesity.

Consistent with the studies aforementioned, *Akkermansia* has been shown to upregulate the intestinal expression of several endocannabinoids controlling inflammation, barrier function and peptide secretion in the gut[35], which in turn lead to improvement of diet-induced metabolic deterioration[36]. Metformin has also been reported to restore impaired gut barrier function in animals with fructose-induced liver steatosis, supporting the beneficial effects of metformin or *Akkermansia* in the intestine[37]. The role of *Akkermansia* as an agent contributing to the improvement of the metabolic profile was substantiated by several other studies that showed increased abundance of *Akkermansia* after gastric bypass surgery[38], and in a 'high gene count' group characterized by lower adiposity and less insulin resistance among the general population[39]. In contrast, a metagenome-wide association study reported enrichment of *Akkermansia* in samples from patients with type 2 diabetes[40]. It is possible that such differences could be a result of patient selection, because composition of the gut microbiota can change during the course of treatment with antidiabetic agents, such as metformin. The molecular mechanism of the restoration of regulatory T cells and downregulation of tissue inflammation by metformin or *Akkermansia* remains unclear. However, a recently reported role of mucin in the tolerization of intestinal dendritic cells and inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells signaling might contribute to this process[41].

The effect of metformin on gut microbiota has also been studied using non-vertebrate *in vivo* models. Intriguingly, metformin was reported to increase the healthspan and lifespan of both mice and *C. elegans*[16,42]. A recent paper provided evidence that retardation of aging of *C. elegans* by metformin is a result of the altered folate and methionine metabolism of intestinal microbiota of *C. elegans*, leading to reduced methionine availability and calorie restriction-like effects in the host (Figure 2)[43]. These results suggest that metformin influences the microbiota of both nematodes and mammals, which might be involved in metabolic improvement and possibly lifespan extension[44].

INCRETIN AND METFORMIN

Incretins are a group of gastrointestinal hormones that increase insulin release after food ingestion, and comprise glucagon-like

peptide 1 (GLP-1) and gastric inhibitory peptide. Incretin-based therapies have recently been introduced in clinical practice, where they are used to achieve improved glycemic control without weight gain. Additionally, those therapies have potential long-term beneficial effects on islet β-cell mass and function[45,46]. In particular, incretin + metformin combination has become a popular treatment. In this regard, a study exploring the relationship between the action mechanisms of metformin and incretin was undertaken[47], which was based on the previous observation of increased plasma GLP-1 levels in obese individuals and diabetic patients treated with metformin[48,49]. That study confirmed that metformin administration increases plasma levels of GLP-1, but not that of gastric inhibitory peptide or peptide YY, which co-localizes with GLP-1 in intestinal L cells (Figure 2). Increased GLP-1 levels after metformin treatment were not related to the inhibition of dipeptidyl peptidase-4 that degrades incretins or induction of proglucagon gene expression. Furthermore, metformin might not be a direct secretagogue of GLP-1 from intestinal L cells[50]. With respect to the mechanism of the increase of plasma GLP-1 level in response to metformin, a role of muscarinic acetylcholine receptor has been suggested[50]. In that study, pretreatment with a specific antagonist of the muscarinic M3 receptor significantly reduced the increase in GLP-1 levels after administration of metformin, whereas other muscarinic receptor antagonists or vagotomy were ineffective, suggesting the involvement of a non-vagal M3 muscarinic pathway in metformin-induced GLP-1 elevation[50]. In contrast to these results, a direct effect of metformin in GLP-1 expression on an L cell line through Wnt signaling has been reported[51].

Intriguingly, metformin has been reported to increase GLP-1 receptor expression on islet cells, which was dependent on peroxisome proliferator-activated receptors pathway, but not on AMPK activation[47] (Figure 2). These results provide a theoretical basis for combination therapies using metformin and incretins (or dipeptidyl peptidase-4 inhibitors that increase incretin levels), as induction of GLP-1 receptor expression by metformin can have synergistic effects with administered incretins.

AUTOPHAGY AND METFORMIN

Although metformin has AMPK-independent mechanisms for the improvement of the metabolic profile[6], most investigators agree that metformin activates AMPK[4]. Then, metformin can enhance autophagy, as AMPK activation is known to upregulate autophagic activity through direct phosphorylation of unc-51-like kinase and Beclin 1, key molecules involved in the initiation of autophagy (Figure 3)[52–54]. Autophagy is a process of subcellular membrane rearrangement to form a double-membraned autophagosome enclosing cytoplasmic constituents and organelles, which is expedited by nutrient deficiency[55]. Thus, autophagy is important for nutrient supply in the case of energy deficiency, and is also critical for the proper turnover and function of organelles, such as mitochondria and the ER.

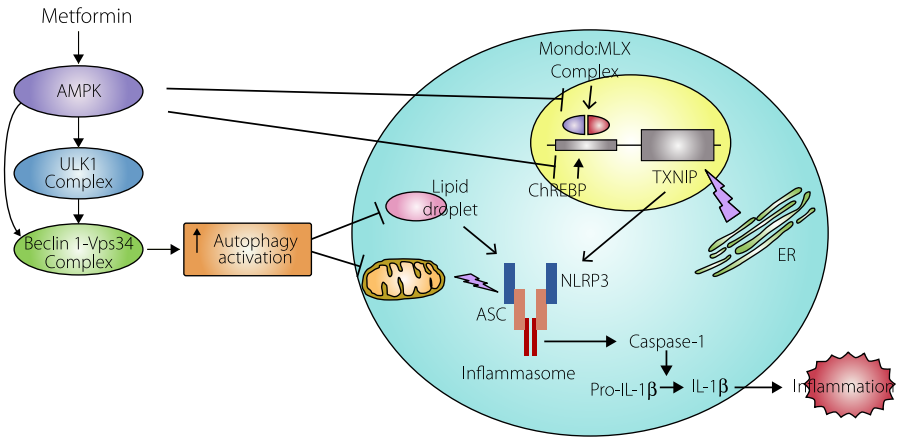

Figure 3 | Effects of metformin on autophagy, inflammasomes and endoplasmic reticulum (ER) stress. Metformin activates autophagy through adenosine monophosphate-activated protein kinase (AMPK) activation and subsequent phosphorylation of unc-51-like kinase 1 (ULK1) and Beclin 1. Autophagy expedites clearance of lipid droplets by increasing lipophagy. AMPK activation can attenuate inflammasome activation, which might involve rejuvenation of 'stressed' mitochondria through mitophagy, as dysfunctional mitochondria accelerate inflammasome activation[83]. Lipids can act as ligands to activate inflammasomes[75]. Thus, autophagy activation downregulates inflammasome activation through effects on both lipid content and mitochondria[61]. AMPK attenuates thioredoxin-interacting protein (TXNIP) induction through inhibition of the recruitment of Mondo: Max-like protein X (MLX) complexes and carbohydrate response element-binding protein (ChREBP) to the TXNIP promoter. TXNIP binds nucleotide-binding oligomerization domain–leucine-rich repeats containing pyrin domain 3 (NLRP3) and contributes to inflammasome activation[78]. TXNIP expression is increased by ER stress, which plays a role in β-cell injury through inflammasome activation[86]. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; IL, interleukin.

As mitochondria and the ER play critical roles in pancreatic β-cell physiology and insulin sensitivity[56,57], autophagy has a significant impact on body metabolism. Although the effects of autophagy deficiency on the body metabolism are distinct, depending on the location and severity of autophagy deficiency[58], a global increase in autophagic activity is likely to improve the metabolic profile under metabolic stress conditions[59–62], which might be related to attenuation of low-grade tissue inflammation associated with obesity by autophagy activation[61], as explained in the next section.

As aforementioned, autophagy induction by AMPK activation is in line with the concept that autophagy is an adaptive process occurring in response to nutrient deficiency, and that AMPK is a sensor of intracellular energy balance. In this way, the activation of AMPK by metformin suggests the possibility that improvement in metabolic profiles by metformin might be related to autophagy induction through AMPK activation (Figure 3). Consistent with this possibility, protection of pancreatic β-cells against lipoapoptosis by metformin has been attributed to activation of autophagy[63,64]. In addition, metformin has been shown to enhance disposal of accumulated autophagic vacuoles in β-cells[65]. Likewise, metformin has been reported to enhance autophagic activity in cardiac tissue by facilitating dissociation of the B-cell lymphoma 2 (Bcl-2)-Beclin 1 complex through AMPK activation[66] and ameliorating ultrastructural abnormalities associated with diabetes in an animal model of diabetic cardiomyopathy[67].

In contrast to these reports showing AMPK-dependent autophagy activation by metformin, a recent paper reported amelioration of hepatic steatosis by metformin through autophagy activation via sirtuin 1 pathway rather than AMPK pathway[68].

The target organelles of autophagy include not only the mitochondria and ER, but also peroxisomes and lysosomes. Additionally, lipid droplets can be the target of autophagy in a process called lipophagy[69]. Thus, accelerated disposal of lipids by lipophagy could be another mechanism of autophagy-mediated amelioration of obesity-induced metabolic derangements and tissue inflammation associated with obesity[61] (Figure 3). Indeed, a recent paper reported that metformin can expedite lipophagy through forkhead box O1-mediated induction of lysosomal acid lipase (Figure 3)[70].

INFLAMMASOMES AND METFORMIN

Although type 2 diabetes has been categorized as a metabolic disorder, the etiological role of low-grade tissue inflammation in insulin resistance and β-cell dysfunction is widely accepted[71–73]. Among diverse innate immune receptors, nucleotide-binding oligomerization domain–leucine-rich repeats containing pyrin domain 3 (NLRP3), a member of NLRP subfamily of the Nod-like receptor (NLR) family, plays a crucial role in the tissue inflammation associated with lipid overload or obesity[74,75]. NLRP is critically involved in the activation of the inflammasome complex, which is an essential component in the maturation of pro-IL-1β to IL-1β[76]. Potential effector molecules that can activate NLRP3 in metabolic disorders include high glucose, lipids such as free fatty acids, and human islet amyloid polypeptide[75,77,78].

A recent paper reported that metformin inhibits IL-1β production from macrophages of diabetic patients through AMPK activation *in vitro*[79]. Administration of metformin to diabetic patients for 2 months also increased AMPK activity and decreased IL-1β maturation in macrophages of diabetic patients. Although the molecular mechanism of the inhibition of inflammasome activation by metformin has not been elucidated, a recent paper suggested a potential role of autophagy activation through AMPK. Specifically, it was reported that metformin can increase β-amyloid clearance and decrease IL-1β production from microglia after treatment with extracellular β-amyloid fibrils by inducing autophagy (Figure 3)[80]. These results are consistent with previous reports showing that autophagy deficiency is a pro-inflammatory condition characterized by increased activation of inflammasomes[81], and that activation of autophagy can diminish inflammasome activation[82]. The mechanism of increased susceptibility of autophagy-deficient cells to inflammasome activation could include disturbed mitochondrial homeostasis in these cells (Figure 3), as mitochondrial dysfunction leading to altered spatial arrangement could be crucial in apposition of apoptosis-associated speck-like protein (ASC) containing a caspase recruitment domain on mitochondria and NLRP3 on ER, and subsequent inflammasome activation[81,83].

ER STRESS AND METFORMIN

In addition to mitochondrial stress, ER stress might be affected by metformin. ER stress is important in the development of both insulin resistance and β-cell failure in diabetes[57,84,85]. The mechanism of β-cell failure as a result of ER stress is not completely understood; however, several recent papers have shown that thioredoxin-interacting protein (TXNIP) induced by irremediable ER stress and inositol-requiring enzyme 1α hyperactivation are critical mediators of β-cell death through activation of inflammasomes[86,87]. TXNIP is an endogenous binding partner and inhibitor of thioredoxin, an essential and ubiquitous oxidoreductase. TXNIP expression has been reported to be induced by high concentrations of glucose in pancreatic islet cells, and acts as an upstream activator of the NLRP3 inflammasome after dissociation from thioredoxin by ROS[78]. As such, NLRP3 activation could involve both insulin resistance and β-cell failure[74,75,88]. Intriguingly, metformin has been shown to reduce the expression of TXNIP, probably through AMPK activation, which could be involved in the inhibition of the recruitment of transcription factors, such as carbohydrate response element-binding protein or Mondo: Max-like protein X complex to the TXNIP promoter (Figure 3)[89,90]. Together, these results suggest a possible role of metformin in the protection of β-cells from terminal ER stress, although such a possibility has not yet been fully studied.

CONCLUSIONS

Although metformin is not a new drug in the field of antidiabetic medicine, new mechanisms of action continue to be identified. Furthermore, metformin is attracting the interest of investigators in fields other than diabetes, as metformin has been shown to have anticancer[91], immunoregulatory[92] and anti-aging effects[16], all of which are beyond the scope of the present review. A review article summarizing the therapeutic value of metformin in diseases other than diabetes, such as cancer or cardiovascular disorders, was recently published[93]. The investigations described in the current review and elsewhere continue to broaden our understanding of the molecular mechanisms of metformin action and its wide range of potential applications. Likewise, discovery of new drugs with enhanced antidiabetic activity and reduced side-effects with improved safety profiles will be aided by the identification of new mechanisms of action and novel targets of metformin.

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DISCLOSURE

The authors declare no conflict of interest.

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