Review

Another Player in the Field: Involvement of Glycotoxins and Glycosative Stress in Insulin Secretion and Resistance

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Abstract: The term glycotoxins includes the group of advanced glycation end-products (AGEs) and their precursors, most of them highly reactive intermediary compounds, such as methylglyoxal (MG). Glycotoxins were initially thought to participate in the development of diabetic complications because of their increased formation from glucose. However, they also form and accumulate in tissues since the early stages of disease, such as metabolically unhealthy obesity and prediabetes. Such accumulation has been suggested to result from dysregulated activity of detoxification systems, such as the glyoxalase system, as well as increased dietary consumption, namely from high-glucose and high-fructose foods processed at high temperatures. Although some studies may have used supraphysiological doses, in vitro systems and animal models have shown glycotoxin-induced insulin resistance. Moreover, dietary glycotoxin restriction was shown to improve insulin resistance in humans and glyoxalase (GLO)-1 upregulation improved insulin sensitivity and metabolic function. This review summarizes the current knowledge about glycotoxin involvement in the development of insulin resistance, the mechanisms involved and the usefulness of GLO-1 modulation, and a possible therapeutic strategy to improve insulin sensitivity.

Keywords: glycation; glycotoxins; glycosative stress; insulin resistance; glyoxalase

1. Introduction

The term glycotoxins includes the group of advanced glycation end-products (AGEs) and their precursors, most of them highly reactive intermediary compounds, such as methylglyoxal (MG). MG originated as a byproduct of glucose and fructose metabolism and modifies arginine and lysine residues of biomolecules, namely proteins and DNA, forming AGEs [1–4]. Such reactions may occur intracellularly (cytoplasmic proteins and transcription factors) or with circulating (hemoglobin, albumin, or lipoproteins) and extracellular matrix proteins [1–4]. The AGEs N δ -(5-hydro-5-methyl-4-imidazolone-2-yl)-ornithine (MG-H1) and argpyrimidine are formed after MG-induced arginine modification, whereas lysine modification leads to methylglyoxal lysine dimer (MOLD) and (carboxyethyl)lysine (CEL) formation [5,6], reviewed by [7,8]. MG-mediated modification of intracellular proteins was shown to increase oxidative and nitrosative stress in different cell types,

but also to impair detoxification systems, weakening the activity of the proteasome and protein quality control pathways [1]. Modification of extracellular proteins may lead to AGE-mediated activation of membrane receptors (RAGE), which trigger intracellular inflammatory and oxidative pathways [9]. Extracellular AGEs, namely MG-derived imidazolones (MG-derived) and N ϵ -(carboxymethyl)lysine (CML), are natural ligands of AGE receptors (RAGE), which, when activated (reviewed by [10]), trigger inflammatory and stress signaling pathways such as NF- κ B, responsible for the expression of inflammatory mediators and generation of oxidative stress [11–14]. Besides increasing oxidative stress generation through membrane receptor activation, intracellular AGEs were also shown to induce the formation of superoxide anion, hydrogen peroxide, and peroxynitrite, as well as the depletion of antioxidant defenses in different cell types [15–20]. Moreover, the accumulation of MG-induced misfolded proteins, together with the modification of proteasome subunits and protein quality control pathways, was also shown to increase endoplasmic reticulum stress [21–24]. Glycotoxins may also have originated in the diet, namely foods rich in sugars and cooked at high temperatures. Intestinal absorption of glycotoxins and AGEs has been shown, as well as their deposition in tissues (reviewed by [25]).

The glyoxalase (GLO) system, which is composed of GLO-1 and GLO-2, was discovered at the beginning of the 20th century in several tissues and was described to detoxify ketonic aldehydes, such as MG (reviewed by [1]). In the last decades, downregulation of the GLO system has been described in patients and animal models of diabetes and to be correlated with the progressive development of diabetic complications ([26–28], reviewed by [1]). The activity of the GLO system is glutathione (GSH)-dependent, so increased oxidative stress generation and depletion of antioxidant defenses lead to a self-perpetuating cycle of reactive oxygen species (ROS)/AGE formation. Intriguingly, normalization of glycemia does not completely prevent diabetic complications, from which originated the new concept of “metabolic memory”, based on a self-perpetuating cycle of AGE and reactive oxygen species (ROS) production sustained even after glucose normalization [3–29].

Insulin-independent cells (endothelial and glial cells, podocytes, and neurons) are more susceptible to AGEing (progressive accumulation of AGEs and its consequences), which is associated with the traditional complications of diabetes (retinopathy, nephropathy, and peripheral neuropathy) (reviewed by [1,5]). Besides, AGEing has been involved in a myriad of other complications, from the cardiovascular and neurometabolic spectra, such as cardiac apoptosis, reduced NO bioavailability, impaired Ach-dependent relaxation, blood–brain barrier changes, or increased neurotoxic effects of beta-amyloid (reviewed by [1,5]).

Diverse studies mainly from the last decade have raised the hypothesis that, indeed, glycotoxins may also be implicated in the process of loss of metabolic homeostasis itself, and particularly in the impairment of insulin secretion and sensitivity. Such studies rely on the fact that MG formation and AGE accumulation may occur since the early stages of disease such as prediabetes [30]. Glycotoxins have been shown to reduce long-term beta-cell viability, despite some evidence of increased insulin secretion when acutely exposed to MG [31,32]. Moreover, MG was shown to bind to and modify plasma insulin, compromising its binding to the receptor [33,34]. Even after binding to the receptor, innumerable studies have shown glycotoxin-induced insulin resistance in cell lines, animal models, and humans, which will be discussed in the following sections. Although some findings in lean animal models were controversial because of the high doses used, insulin resistance was consistently observed in obese animal models with increased glycosative stress, while AGE-restricted diets have been shown to improve insulin sensitivity in normal, overweight, and diabetic patients (reviewed by [1]). Altogether, such mechanisms may contribute to the progressive deterioration of metabolic homeostasis observed in metabolic syndrome/prediabetes and later in type 2 diabetes. The next sections will discuss the impact of glycotoxins on the mechanisms governing insulin secretion and sensitivity.

2. Regulation of Insulin Secretion by Glycotoxins

Recent evidence supports the thesis that AGE deposition may occur since the early stages of disease such as prediabetes or even earlier, as a result of glucose metabolism or increased consumption of glycotoxins in the diet. Their progressive accumulation in the tissues since such early stages has been suggested to be involved in the onset of type 2 diabetes, namely insulin resistance and β -cell damage. In fact, the impact of MG on insulin secretion has been described in several studies. MG was shown to transiently activate insulin secretion under basal glucose concentrations, but to impair its secretion under hyperglycemic conditions or in the presence of acetylcholine [31,32]. Moreover, it was shown to hamper beta-cell survival and long-term insulin synthesis and secretion. Long-term deleterious effects of MG on β -cell lines (Ins-1 and RIN-m5F) have been shown in vitro, namely, redox-independent inhibition of insulin receptor substrate (IRS) 1 and PI3K/Akt pathway, generation of oxidative stress, mitochondrial damage through decreased membrane potential and ATP, and mitochondria-induced apoptosis [32,35–41]. Moreover, He et al. (2020) have demonstrated β -cell dysfunction and impaired glucose-stimulated insulin secretion after co-culture with AGE-pretreated macrophages, which was attributed to increased expression of proinflammatory cytokines [42]. Altogether, such mechanisms were demonstrated to be involved in MG-induced decrease of cell viability and insulin secretion.

2.1. Glycotoxins Involvement in the Development of Insulin Resistance

Reduction of insulin action in the sensitive tissue may be attributed to the inactivation of insulin receptor signaling pathway (insulin resistance) or to decreased insulin intrinsic activity. These two conditions have been shown in diabetic patients. Although most of the studies have focused on insulin resistance, reduction of insulin intrinsic activity due to glycation of the insulin molecule was recently shown to impair its ability to bind and activate the receptor, possibly contributing to systemic insulin resistance (Figure 1) [33,34].

2.2. In Vitro Studies

Insulin receptor inactivation has been shown in vitro after MG exposure in the most relevant insulin-sensitive cells. MG was shown to inhibit the insulin receptor substrate (IRS)-1 and PI₃K/Akt pathway in muscle cells and 3T3 adipocytes [43–45]. Interestingly, impairment of GLUT4 trafficking to the cell membrane and glucose uptake were also shown in L6 myoblasts exposed to exogenous MG or following GLO-1 knockdown [43,44,46,47]. The authors showed that this was also associated with increased activation of apoptotic pathways. In hypoxic adipocytes, Tang et al. (2020) have demonstrated RAGE/NF- κ B involvement in the development of insulin resistance [48]. Additionally, in cultured hepatocytes, Gaens et al. have shown increased expression of inflammatory markers after CML incubation [49]. In endothelial cells, insulin-mediated endothelial nitric oxide synthase (eNOS) activation and NO release were also shown to be impaired by MG in vitro [50].

Thus, the current body of evidence based on cell systems studies supports the idea that exposure to glycotoxins leads to the upregulation of proinflammatory pathways, which may be possibly involved in downregulation of the insulin receptor pathway (Figure 1). However, such studies rely on possible supraphysiological doses and only some of these results have been proven in animal models and human studies.

Figure 1. Overview of the mechanisms involved in glycotoxins-associated insulin resistance in adipose tissue (A), liver (B) and skeletal muscle (C). Dysregulation of the angiogenic process in the adipose tissue, with hypoxia and fibrosis, leads to activation of inflammatory pathways consequently to lipolysis and insulin resistance. Increased free fatty acids efflux to the liver and skeletal muscle leads to hepatic and muscular steatosis, which impair mitochondrial function and conduce to the chronic development of oxidative stress and activation of stress-response pathways that impair insulin signalling. Moreover, direct modification of the insulin molecules may also account for their lower binding to the insulin receptor. DNL, de novo lipogenesis; IRS, insulin receptor substrate; NEFA, Non-Esterified Fatty Acids; ROS, reactive oxygen species.

2.3. Development of Animal Models

GLO-1 knock-out in *Drosophila* was recently shown to resemble features of type 2 diabetes development, namely insulin resistance and glucose intolerance [51]. Similarly, Lodd et al. (2019) have shown increased susceptibility to diet-induced insulin resistance in GLO-1 knockout zebrafish [52]. On the other hand, GLO-1 knockout mice have shown a lower susceptibility to MG, due to a compensatory increase of other enzymatic systems, namely Aldo-keto reductases [53]. Despite such differences between models, which may suggest an acquirement of compensatory mechanisms in mammals, we do not know whether such mechanisms occur in physiological conditions or result from the gene knockout. Several animal models with MG administration were observed to develop insulin resistance, but only when supraphysiological doses were used (reviewed by [1]). Insulin resistance was observed after MG i.v. injection (50 mg/Kg) or administration in the drinking water (1%) to Sprague-Dawley rats [54–56]. Moreover, diets enriched with AGEs and MG-BSA were also shown to produce similar results, namely glucose intolerance and lower insulin receptor activation in muscle, liver, and adipose tissue. However, such results were mainly observed in db/db mice, without significant effects on normal mice [57,58]. MG production was observed in adipocytes due to increased Aldolase-A activation and decreased antioxidant defenses [59]. Our group has shown the accumulation of adipose tissue MG at levels similar to diabetic rats following oral administration (75 mg/Kg), but with little effects on adipose tissue insulin signaling [60,61]. MG was only observed to change plasma free fatty acids levels and to induce structural changes in the tissue (fibrosis, hypoxia, macrophage accumulation, and hypoadiponectinemia) and decreased blood supply, but normal insulin signaling and GLUT4 levels [61]. We have also shown that MG accumulation impairs adipose tissue response to hypoxia, leading to higher activation of inflammatory pathways, but insulin resistance was only observed in an experimental model of adipose tissue ischemia [62]. Adipose tissue insulin resistance in the presence of MG was only observed after high-fat diet-induced obesity. In obese rats, MG-induced alterations of the vascular architecture impair adipose tissue blood flow and expandability, conducting to hypoxia and adipose tissue insulin resistance, namely lower insulin receptor phosphorylation and GLUT4 levels [60]. Similar observations were made in the liver of the same animal model, where MG-induced AGE accumulation impairs the lipid metabolism of diet-induced obese rats, changing the hepatic lipidemic profile to less esterification and unsaturation and causing inflammation, oxidative stress, and insulin resistance [63]. Accordingly, the grade of hepatic steatosis was shown to be proportional to liver CML levels in patients with obesity, suggesting a role for glycotoxins in the dysregulation of liver metabolism and development of non-alcoholic fatty liver disease [49].

Fructose is a known inducer of methylglyoxal through Aldolase B and its inhibition results in decreased fructose-induced MG formation [64,65]. In addition, fructose may directly react with aminoacids residues and form fructose-derived AGEs [66]. A high fructose intake was shown to result in MG accumulation in adipose tissue and not in the liver, mainly because of different constitutive expression of GLO-2, although MG was shown to mediate fructose-induced insulin resistance in the liver [67,68]. In the muscle, fructose-induced MG formation was shown in vitro in L6 myotubes and in vivo (20% in drinking water) in Sprague-Dawley, which were associated with decreased glucose homeostasis [69]. The direct involvement of glycation in muscle insulin resistance was shown in rats treated with AGE-albumin (20 mg/Kg/day), displaying insulin resistance and decreased GLUT4 in the muscle. Similarly, normal muscles incubated ex vivo with AGE-albumin (1 mg/mL) resulted in GLUT4 downregulation [70]. The effects of glycation were also suggested to involve increased extracellular matrix glycation [71].

The involvement of glycotoxins in the development of insulin resistance may be deeper than initially proposed, after recent evidence that maternal exposure to glycotoxins predisposes the offspring to insulin resistance in the adulthood. Toop et al. (2017) have shown increased adiposity and altered liver fat content in the offspring of rodents fed a diet rich in high-fructose corn syrup during the prenatal period [30]. Accordingly, using a similar approach, Francisco et al. (2018) have shown that maternal

consumption of methylglyoxal (60 mg/Kg/day) during pregnancy results in glucose intolerance and lower beta-cell function in the offspring at adulthood [72].

Thus, previous studies using in vitro and animal models should be carefully interpreted as most of them used supraphysiological MG doses (Table 1). Most likely, the initial idea that increased endogenous formation of MG or consumption of MG-enriched diets is enough to induce insulin resistance may not be true. On the other hand, depletion of antioxidant and detoxifying mechanisms due to the accumulation of MG adducts and MG-derived AGE may be relevant in impairing lipid and glucose metabolism in obesity (Figure 1). This suggests that glycation may have a role in obesity-associated insulin resistance, but not in lean models.

Table 1. Summary of experimental conditions and outcomes obtained in studies administrating glycotoxins and advanced glycation end-products (AGEs) to in vitro and animal models. MG, methylglyoxal.

Reference	Dose/Concentration	Administration Route	Duration	Model	Main Conclusions
Engelbrecht et al., 2013 [43]	400 uM MG	-	-	L6 myotubes	Impaired GLUT4 trafficking
Deshmuchi et al., 2017 [47]	1–5 mM MG	-	-	L6 myotubes	Impaired insulin signalling
Wei et al., 2020 [50]	0.5–1 mM MG	-	-	HUVECs	Inhibition of insulin-induced NO release
Dhar et al., 2011 [54]	60 mg/kg/day MG	Subcutaneous minipump	28 days	Sprague-Dawley rats	Beta-cell dysfunction Decreased glucose tolerance Lower glucose uptake and GLUT4 levels in AT
Truong et al., 2019 [56]	1% MG	Drinking water	18 weeks	C57BL/6N mice	Lower glucose tolerance Impaired liver insulin signalling
Guo et al., 2009 [55]	1% MG	Drinking water	5 weeks	Sprague-Dawley rats	Insulin resistance Increased renal AGEs excretion
Matafome et al., 2012 [61]	50–75 mg/kg/day MG	Drinking water	14 weeks	Wistar rats	AT glycation, fibrosis, and decreased irrigation Normal glucose tolerance
Rodrigues et al., 2017 [60]	75 mg/kg/day MG	Drinking water	18 weeks	Aged Wistar rats (standard vs. high-fat diet)	Normal glucose tolerance Decreased glucose tolerance and AT insulin signalling in HFD-fed rats
Neves et al., 2019 [63]	75 mg/kg/day MG	Drinking water	18 weeks	Aged Wistar rats (standard vs. high-fat diet)	Decreased glucose tolerance and liver insulin signalling in HFD-fed rats Impaired liver lipidemic profile
Francisco et al., 2018 [72]	60 mg/kg/day MG	Gavage	21 days	Lactating female Wistar rats	Increased milk AGEs Increased body weight, adiposity and beta-cell dysfunction of the offspring
Hofmann et al., 2002 [58]	Diet rich AGEs (3.4-fold)	Oral	20 weeks	C57/BL/KsJ <i>db/db</i> mice	Morphological alterations of the pancreas Insulin resistance in <i>db/db</i> , but not control mice
Cai et al., 2012 [57]	Iso caloric diet rich in MG-derived AGEs	Oral	-	4 generations of C57BL/6N mice	Depletion of antioxidant and anti-stress defenses Susceptibility to insulin resistance
Pinto-Junior, et al., 2018 [70]	Diet rich on AGE-albumin (12.6-fold to albumin of normal diet)	Oral	12 weeks	Wistar rats	Insulin resistance Lower muscle GLUT4 expression

2.4. Evidence in Human Studies

The relation between glycosative stress and insulin resistance has also been shown in humans and increased α -dicarbonyl levels were observed in patients with established type 2 diabetes [73]. Moreover, skin autofluorescence has been demonstrated to be correlated with the development of insulin resistance in patients with type 1 diabetic patients, which, although being attributed to increased AGEs levels, may not solely result from their accumulation [74]. Increased glycotoxins levels were also shown in patients with metabolically unhealthy obesity, when compared with metabolically healthy ones, as well as in patients newly diagnosed with type 2 diabetes. Such observations suggest a link with early stages of metabolic dysregulation such as prediabetes and avoiding the classical idea of glycosative stress being a consequence of chronic hyperglycemia [73,75]. Such a relation was also detailed by Jiménez et al. (2017), who have observed increased probability of developing prediabetes or type 2 diabetes according to the progressively higher serum AGEs levels seven years earlier [76]. In another study in children with obesity, insulin resistance was associated with increased CML levels and lower antioxidant activity [77]. Nevertheless, elevated serum AGEs levels are still to be correlated to the development of specific complications. Serum AGEs and sRAGE levels were not related to vascular complications in patients with prediabetes nor impaired glucose metabolism in patients with type 2 diabetes [78,79]. Although in higher levels, CML and sRAGE were also not associated with obesity or inflammation in unhealthy obese adolescents [80]. It is likely that total AGEs levels are not directly associated with insulin resistance or vascular complications, but modification of specific proteins or accumulation in tissue may be better markers of such complications.

Consumption of AGE-rich diets only causes a marginal increase in weight gain, although they were described to increase the odds of adolescents to develop metabolic syndrome [81,82]. On the other hand, AGE-restricted diets have been shown to improve insulin sensitivity in normal, overweight, and diabetic patients, showing the link between increased glycoxidative stress and impaired metabolic homeostasis [64,74,83–85]. Interestingly, the authors reported the best results in combination with physical exercise [85]. The authors also reported upregulation of endogenous protective mechanisms, such as SIRT1 and AGER1, in peripheral mononuclear blood cells, suggesting that lower consumption of dietary AGEs prevents the depletion of protective pathways against oxidative stress [84]. Nevertheless, most studies were performed with a small number of participants and future studies in larger populations are required.

3. Modulation of the GLO-1 System as a Strategy to Improve Insulin Sensitivity

Diminished GLO-1 activity has been linked with muscle insulin resistance and modulation of its activity has been pointed out as a promising strategy to improve not only muscle, but whole-body insulin sensitivity (reviewed by [86]). Diabetic patients were shown to have decreased levels of GLO-1 and NRF2 and increased Keap1 levels (negative NRF2 regulator) in skeletal muscle biopsies, suggesting a dysregulation of glycosative stress in the muscle of patients with type 2 diabetes [87]. Similarly, we have observed decreased GLO-1 activity in the visceral adipose tissue, not only in patients with type 2 diabetes, but also with prediabetes, suggesting that impaired GLO-1 function may in fact precede adipose tissue dysfunction and may be a good therapeutic target [88].

Several nutraceuticals such as the trans-resveratrol/hesperetin combination (tRES/HESP) have been shown to improve GLO-1 activity and vascular function in humans, but its ability to increase insulin sensitivity is still to be proven [89,90]. Upregulation of GLO-1 has been evaluated following NRF2 activation with several compounds, but sustained GLO-1 activation and protection against complications were still not achieved in most of the cases [91]. Recently, lower levels of glycotoxins were observed in patients with type 2 diabetes following berberine treatment (1.5 g/day during 3 months) and upregulation of GLO-1 activity in mice treated with Brazilian propolis was shown to reduce muscle inflammation [92]. Moreover, our group has recently shown that bariatric surgery and Liraglutide are able to produce a sustained increase of GLO-1 levels and activity in the epididymal

adipose tissue of obese diabetic rats, opening new therapeutic opportunities for improved adipose tissue function [88].

4. Conclusions and Future Perspectives

Glycotoxins are a heterogeneous group of compounds that were initially thought to participate in the development of diabetic complications owing to their increased formation from glucose, mainly in insulin-independent cells. Later data evidenced their increased formation and accumulation in tissues since the early stages of disease, such as metabolically unhealthy obesity and prediabetes. Such accumulation has been suggested to result from dysregulated activity of detoxification systems, such as the glyoxalase system, as well as increased dietary consumption, namely from high-glucose and high-fructose foods processed at high temperatures. Importantly, many studies in in vitro systems and animal models have shown glycotoxin-induced insulin resistance, but they have used supraphysiological doses. Nevertheless, animal models with physiological doses of glycotoxins have shown higher levels of oxidative stress and inflammation, which results in higher susceptibility of adipose tissue and liver to develop insulin resistance in obesity. Moreover, restriction of glycotoxins in the diet was shown to improve insulin resistance in humans, showing their relevance in the process of metabolic dysregulation. However, despite recent evidence of improved metabolic function after GLO-1 upregulation, the usefulness of its modulation to prevent insulin resistance and metabolic dysregulation is still in the first step to be proven and achieved.

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